Remington

An Introduction to Pharmacy

Edited by Loyd V Allen Jr

Pharmaceutical Press

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Edited by **Loyd V Allen Jr,** PhD, RPh
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Preface

There has been a long-time need for a book that introduces the first year pharmacy student to all the different aspects of pharmacy and one that would serve as an introduction to the content of the courses involved in the making of a pharmacist. When this Editor entered pharmacy school, the purchase of a full size Remington's *Practice of Pharmacy* was mandatory. It was not used much the first year of pharmacy school but was extensively used later in the curriculum. A volume such as this would have been a great addition to the first-year experience in pharmacy school.

Today, *Remington: An Introduction to Pharmacy* for the first time provides the student with an easy-to-use volume that gives a preliminary view into the course content to which they will be exposed over the next few years along with a thorough discussion of the various types of pharmacy practice that will be available to them upon graduation.

The book is organized in such a way that a team of faculty members can cover the various sections and emphasize their areas of expertise with the pharmacy students. The content parallels both Volumes I and II in *Remington: The Science and Practice of Pharmacy*. This book uses the Sections as the major divisions in the book; starting in Volume 1 and progressing through Volume 2. The sections include the (1) Introduction, (2) Pharmaceutical Chemistry, (3) Pharmaceutical Analysis and Quality Control, (4) Pharmaceutics, (5) Pharmaceutical Dosage Forms; Manufacturing and Compounding, and (6) Pharmacokinetics and Pharmacodynamics. Next, comes (7) Fundamentals of Pharmacy Practice, (8) The Scope of Pharmacy Practice, (9) Social, Behavioral, Economic, and Administrative Sciences, and (10) Patient Care.

This new book contains the information of interest to early pharmacy students; it is extracted from the two-volume set. It contains the new chapters along with the long-standing parts of *Remington*.

What is the advantage of this book? It introduces early pharmacy students to the scope of pharmacy practice and the course content that is required to practice as a pharmacist. With this very valuable resource used as an early-on introduction, pharmacy students should be able to confirm their career choice early in their curriculum.

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Scope of pharmacy

Pharmacy has historic roots as the art and science of preparing and dispensing medications. While this traditional role is still a viable role for pharmacists, the preparation of medicines has transitioned in large part to the pharmaceutical industry. Dispensing of medicines has increasingly become more centralized and automated, with many of the tasks formerly performed by pharmacists being done using technology or delegated to pharmacy technicians. The provision of drug-related information to other healthcare professionals and the public and disease-state management programs to assure the proper use of medicines has become a more important role for pharmacists. It is now recognized that medication-use is a complex and problem-prone process, in which errors that result in injury to patients can occur at each step. This process includes prescribing, transcribing, interpretation of the order, preparation and dispensing, and administration and monitoring. It has been estimated that more than 2 million hospitalized patients per year experience an adverse drug reaction, two thirds of which were the cause of hospital admission and more than 100 000 of which are fatal.[1] For pharmacists to contribute to improving the value of medicines, they must have a role in every aspect of medication use, from preparation to monitoring the outcome of drug therapy. Pharmacy practice therefore involves the review and interpretation of prescription orders; the compounding, labeling, and dispensing of drugs and devices; drug product selection and medication-use evaluation (MUE); patient monitoring and intervention; and the provision of information related to use of medications and non-pharmacological modalities. The American Pharmacists Association (APhA) describes the mission of pharmacy as serving society as "the profession responsible for the appropriate use of medications, devices, and services to achieve optimal therapeutic outcomes." The Report of the Commission of Pharmacy, Pharmacists for the Future (often referred to as the Millis Report), states that "pharmacy should be conceived basically as a knowledge system that renders a health service by concerning itself with understanding drugs and their effects."

Pharmaceutical care holds that the important role of the pharmacist is "the responsible provision of drug therapy for the purpose of achieving definite outcomes that improve a patient's quality of life." Pharmacists are experts on medications. They are also the most accessible member of today's healthcare team, and often they are the first source of assistance and advice on many common ailments and healthcare matters.

Education

The Doctor of Pharmacy (PharmD) is the entry level degree in pharmacy. This is a graduate professional degree at the doctoral level with a clinical focus, much like medicine (MD), dentistry (DDS), optometry (OD), and veterinary medicine (DVM). The PharmD curriculum requires at least six academic years to complete and in some cases, where a BS degree is required for entry into a PharmD program, eight academic years. For the six-year program, coursework often commences in the third academic year that is considered the first professional year (PY 1). For all programs, the final professional year (PY 4) consists entirely of experiential education. There are 122 colleges and schools of pharmacy in the United States (see Table 1.1; http://www.aacp.org[2]). Colleges of Pharmacy are accredited by the Accreditation Council for Pharmacy Education (ACPE). Accreditation is the public recognition accorded a professional program that is judged to meet established qualifications and educational standards through initial and subsequent periodic evaluations (see: https://www.acpe-accredit.org/[3]).

Pre-professional courses

Mathematics and the physical and biological sciences teach the principles, the application of which find their way into many of the upper-level professional pharmacy courses. Courses in chemistry, including general and organic chemistry, are of particular importance in preparing for the pharmacy curriculum. Courses in mathematics, including calculus, are also important. Courses in the social sciences, humanities, arts, history, and literature provide the broad general education required of a professional in today's society.

Professional Courses

Basic to most pharmacy curricula are courses in pharmacology, medicinal chemistry, pharmaceutics, biopharmaceutics, therapeutics, and the clinical-pharmacy externships. Courses in social and administrative pharmacy, as well as pharmacy law, also are found in this sequence.

Opportunities for students to specialize in certain professional areas have become more available and increasingly popular. Most prominent are hospital/institutional pharmacy, nuclear pharmacy, management, and various research specialties.

Licensure requirements

The practice of pharmacy is regulated by each individual state through the Board of Pharmacy within that state. The law in all states, including the District of Columbia, Puerto Rico, and US Territories, requires applicants for licensure to be of good moral character, have graduated from an ACPE accredited first professional degree program, have passed an examination given by the Board of Pharmacy, and be 21 years of age.

All states require that candidates for licensure have a record of practical experience or internship training acquired under the supervision and instruction of a licensed practitioner. Some jurisdictions grant licensure by licensure transfer. Requirements vary from state to state. Information about licensure transfer is available from the National Association of Pharmacy (http://www.nabp.net/programs/licensure/licensure-transfer/index.php[4]).

The vast majority of the states have established continuing education requirements for re-licensure. This requirement has been adopted as a way to reassure the public that licensed pharmacists are keeping up-to-date to maintain their professional competence. The types of programs that are recognized and the prescribed range of acceptable content matter are fairly uniform. The ACPE also has responsibility for accrediting providers of professional continuing education programming.

A list of the governmental agencies that license pharmacists in the various states is available from the National Association of Boards of Pharmacy, 700 Busse Highway, Park Ridge, IL 60068–2402 (see http://www.nabp.org[5]).

Careers

Job opportunities for pharmacists are expected to continue to be strong because of the increased use of medications by a growing and aging population[6]. There are other factors that may increase the demand for

Table 1.1 Pharmacy professional degree programs

The following colleges and schools offering professional degree programs in pharmacy hold membership in the AACP.

Alabama	Auburn University, Harrison School of Pharmacy, Auburn University, AL 36849 Samford University, McWhorter School of Pharmacy, Birmingham, AL 35229
Arizona	Midwestern University, College of Pharmacy-Glendale, Glendale, AZ 85308 University of Arizona, College of Pharmacy, Tucson, AZ 85721
Arkansas	Harding University, College of Pharmacy, Searcy, AR 72149 University of Arkansas for Medical Sciences, College of Pharmacy, Little Rock, AR 72205
California	California Northstate College of Pharmacy, Rancho Cordova, CA 95670 Loma Linda University, School of Pharmacy, Loma Linda, CA 92350 University of California, San Diego, Skaggs School of Pharmacy and Pharmaceutical Sciences, La Jolla, CA 92093 University of California, San Francisco, School of Pharmacy, San Francisco, CA 94143 University of the Pacific, Thomas J. Long School of Pharmacy and Health Sciences, Stockton, CA 95211 University of Southern California, School of Pharmacy, Los Angeles, CA 90089 Touro University, College of Pharmacy California, Vallejo, CA 94592 Western University of the Health Sciences, College of Pharmacy, Pomona, CA 91766
Colorado	Regla University, School of Pharmacy, Denver, CO 80221 University of Colorado, Skaggs School of Pharmacy, Denver, CO 80262
Connecticut	St. Joseph College School of Pharmacy, Hartford, CT 06103 University of Connecticut, School of Pharmacy, Storrs, CT 06269
District of Columbia	Howard University, College of Pharmacy, Washington, DC 20059
Florida	Florida Agricultural and Mechanical University, College of Pharmacy and Pharmaceutical Sciences, Tallahassee, FL 32307 Nova Southeastern University, College of Pharmacy, Fort Lauderdale, FL 33328 Palm Beach Atlantic University, Lloyd L. Gregory School of Pharmacy, West Palm Beach, FL 33416 University of Florida, College of Pharmacy, Gainesville, FL 32610 University of South Florida, College of Pharmacy, Tampa, FL 33612
Georgia	Mercer University, College of Pharmacy and Health Sciences, Atlanta, GA 30341 Philadelphia College of Osteopathic Medicine School of Pharmacy, Suwanee, GA 30024 South University, School of Pharmacy, Savannah, GA 31406 University of Georgia, College of Pharmacy, Athens, GA 30602
Hawaii	University of Hawaii at Hilo, College of Pharmacy, Hilo, HI 96720
Idaho	Idaho State University, College of Pharmacy, Pocatello, ID 83209
Illinois	Chicago State University, College of Pharmacy, Chicago, IL 60628 Midwestern University, Chicago College of Pharmacy, Downers Grove, IL 60515 Roosevelt University, College of Pharmacy, Shaumburg, IL 60173 Rosalind Franklin University of Medicine and Science, North Chicago, IL 60064 Southern Illinois University Edwardsville, School of Pharmacy, Edwardsville, IL 62026 University of Illinois at Chicago, College of Pharmacy, Chicago, IL 60612

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Table 1.1 *(continued)*	
Indiana	Butler University, College of Pharmacy and Health Sciences, Indianapolis, IN 46208 Purdue University School of Pharmacy and Pharmacal Sciences, West Lafayette, IN 47907
Iowa	Drake University, College of Pharmacy and Health Sciences, Des Moines, IA 50311 University of Iowa, College of Pharmacy, Iowa City, IA 52242
Kansas	University of Kansas, School of Pharmacy, Lawrence, KS 66045
Kentucky	Sullivan University, College of Pharmacy, Louisville, KY 40205 University of Kentucky, College of Pharmacy, Lexington, KY 40536
Louisiana	University of Louisiana at Monroe, School of Pharmacy, Monroe, LA 71209 Xavier University of Louisiana, College of Pharmacy, New Orleans, LA 70125
Maine	Husson University, School of Pharmacy, Bangor, ME 04401 University of New England, College of Pharmacy, Portland, ME 04103
Maryland	Notre Dame of Maryland University, School of Pharmacy, Baltimore, MD 21210 University of Maryland, School of Pharmacy, Baltimore, MD 21201 University of Maryland Eastern Shore, School of Pharmacy, Princess Anne, MD 21853
Massachusetts	Massachusetts College of Pharmacy and Health Sciences - School of Pharmacy - Boston, Boston, MA 02115 Massachusetts College of Pharmacy and Health Sciences - School of Pharmacy - Worcester, Worcester, MA 01610 Northeastern University, School of Pharmacy, Boston, MA 02115 Western New England University, College of Pharmacy, Springfield, MA 01119
Michigan	Ferris State University, College of Pharmacy, Big Rapids, MI 49307 University of Michigan, College of Pharmacy, Ann Arbor, MI 48109 Wayne State University, Eugene Applebaum College of Pharmacy and Health Sciences, Detroit, MI 48202
Minnesota	University of Minnesota, College of Pharmacy, Minneapolis, MN 55455
Mississippi	University of Mississippi, School of Pharmacy, University, MS 38655
Missouri	St Louis College of Pharmacy, St Louis, MO 63110 University of Missouri-Kansas City, School of Pharmacy, Kansas City, MO 64110
Montana	University of Montana, School of Pharmacy and Allied Health Sciences, Missoula, MT 59812
Nebraska	Creighton University, School of Pharmacy and Health Professions, Omaha, NE 68178 University of Nebraska Medical Center, College of Pharmacy, Omaha, NE 68198
Nevada	Roseman University of Health Sciences, College of Pharmacy, Henderson, NV 89014
New Jersey	Rutgers, The State University of New Jersey, Ernest Mario College of Pharmacy, Piscataway, NJ 08854
New Mexico	University of New Mexico, College of Pharmacy, Albuquerque, NM 87131

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Table 1.1 *(continued)*

New York	Albany College of Pharmacy and Health Sciences, Albany, NY 12208 D'Youville College, School of Pharmacy, Buffalo, NY 14201 Long Island University, Arnold and Marie Schwartz College of Pharmacy and Health Sciences, Brooklyn, NY 11201 St. John Fisher College, Wegmans School of Pharmacy, Rochester, NY 14618 St John's University, College of Pharmacy and Allied Health Professions, Jamaica, NY 11439 Touro College of Pharmacy - New York, New York, NY 10027 University of Buffalo, The State University of New York, School of Pharmacy and Pharmaceutical Sciences, Buffalo, NY 14260
North Carolina	Campbell University, School of Pharmacy, Buies Creek, NC 27506 University of North Carolina at Chapel Hill, School of Pharmacy, Chapel Hill, NC 27599 Wingate University, School of Pharmacy, Wingate, NC 28174
North Dakota	North Dakota State University, College of Pharmacy, Fargo, ND 58105
Ohio	Northeast Ohio Medical University, College of Pharmacy, Rootstown, OH 44272 Ohio Northern University, R.H. Raabe College of Pharmacy, Ada, OH 45810 The Ohio State University, College of Pharmacy, Columbus, OH 43210 University of Cincinnati, College of Pharmacy, Cincinnati, OH 45267 The University of Findlay, College of Pharmacy, Findlay, OH 45840 University of Toledo, College of Pharmacy, Toledo, OH 43606
Oklahoma	Southwestern Oklahoma State University, School of Pharmacy, Weatherford, OK 73096 University of Oklahoma, College of Pharmacy, Oklahoma City, OK 73190
Oregon	Oregon State University, College of Pharmacy, Corvallis, OR 97331 Pacific University Oregon, Hillsboro, OR 97123
Pennsylvania	Duquesne University, Mylan School of Pharmacy, Pittsburgh, PA 15282 Lake Erie College of Osteopathic Medicine, School of Pharmacy, Erie, PA 16509 Temple University, School of Pharmacy, Philadelphia, PA 19140 Thomas Jefferson University, Jefferson School of Pharmacy, Philadelphia, PA 19107 University of Pittsburgh, School of Pharmacy, Pittsburgh, PA 15261 University of the Sciences, Philadelphia College of Pharmacy, Philadelphia, PA 19104 Wilkes University, Nesbitt School of Pharmacy, Wilkes-Barre, PA 18766
Puerto Rico	University of Puerto Rico, School of Pharmacy, San Juan, PR 00936
Rhode Island	University of Rhode Island, College of Pharmacy, Kingston, RI 02881
South Carolina	Presbyterian College, School of Pharmacy, Clinton, SC. 29325 South Carolina, College of Pharmacy – MUSC Campus, Charleston, SC 29425 South Carolina, College of Pharmacy – USC Campus, Columbia, SC 29208
South Dakota	South Dakota State University, College of Pharmacy, Brookings, SD 57007
Tennessee	Belmont University, School of Pharmacy, Nashville, TN 37212 East Tennessee State University, Bill Gatton College of Pharmacy, Johnson City, TN 37614 Lipscomb University, College of Pharmacy, Nashville, TN 37204 Union University, School of Pharmacy, Jackson, TN 38305 University of Tennessee, College of Pharmacy, Memphis, TN 38163

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Table 1.1 *(continued)*

Texas	Texas AandM Health Sciences Center, Kinsville, TX 78363 Texas Southern University, College of Pharmacy and Health Sciences, Houston, TX 77004 Texas Tech University Health Sciences Center, School of Pharmacy, Amarillo, TX 79106 University of Houston, College of Pharmacy, Houston, TX 77204 University of the Incarnate Word, Feik School of Pharmacy, San Antonio, TX 78209 The University of Texas at Austin, College of Pharmacy, Austin, TX 78712
Utah	University of Utah, College of Pharmacy, Salt Lake City, UT 84112
Virginia	Appalachian College of Pharmacy, Oakwood, VA 24631 Hampton University, School of Pharmacy, Hampton, VA 23668 Shenandoah University, Bernard J Dunn School of Pharmacy, Winchester, VA 22601 Virginia Commonwealth University, School of Pharmacy, Richmond, VA 23298 University of Washington, School of Pharmacy, Seattle, WA 98195 Washington State University, College of Pharmacy, Pullman, WA 99164
West Virginia	University of Charleston, School of Pharmacy, Charleston, WV 25304 West Virginia University, School of Pharmacy, Morgantown, WV 26506
Wisconsin	Concordia University Wisconsin, School of Pharmacy, Mequon, WI 53097 University of Wisconsin-Madison, School of Pharmacy, Madison, WI 53705
Wyoming	University of Wyoming, School of Pharmacy, Laramie, WY 82071

pharmacists. Scientific advances, including genomics, will result in the discovery of more drugs for the prevention, diagnosis, and treatment of disease. A better understanding of how drugs work will result in personalized medicine. There will be new developments in how medications are administered. The increased availability of information about medicines by well-informed consumers, who are sophisticated about healthcare, will create a need to help them understand how to make use of this information.

Community pharmacy

Community pharmacy is a hybrid practice requiring well-developed professional skills and, in many cases, management abilities. Success in community pharmacy practice depends on business management skills because a pharmacy is a business, and on clinical and therapeutic knowledge because a pharmacist is also a healthcare provider. People skills are also important because of the direct patient contact in a community pharmacy. In addition to dispensing pharmaceuticals, pharmacists in community pharmacies answer questions about prescription and over-the-counter (OTC) drugs and give advice about home healthcare supplies and durable medical equipment. Of an estimated 200 000 pharmacists now in practice, the majority are in community pharmacy practice. Pharmacy technicians and pharmacy interns are also important members of the community pharmacy workforce. While there are still independent community pharmacies in smaller communities and those that provide specialty services such as compounding, an increasing number of community pharmacies are chain drug stores or located in larger retail settings, including grocery stores.

Health-systems pharmacy

Health-systems pharmacy is the practice of pharmacy in private and government-owned hospitals, health maintenance organizations (HMOs), clinics, walk-in

health centers, and nursing homes. This has become a significant setting for pharmacy practice over the past 50 years. In these settings pharmacists, with the assistance of pharmacy technicians, pharmacy interns, and automated technologies, prepare and dispense medications, compound nonsterile and sterile preparations, advise other professionals and patients on the use of drugs, monitor drug regimens, and evaluate drug use. They advise other professionals on the selection and effects of drugs and, in some cases, make patient rounds with them or provide direct patient care. Hospital pharmacy practice involves working extensively with other members of the healthcare team, including physicians, nurses, and other health professionals and workers.

Nuclear pharmacy

Nuclear pharmacy applies the principles and practices of pharmacy and nuclear chemistry to produce radioactive drugs used for diagnosis and therapy. Some of these pharmacists work in hospitals and others work for private nuclear pharmacies that provide radioactive drugs to hospitals.

Industrial pharmacy

Industrial pharmacy offers opportunities to pharmacists of all educational levels. The largest number of pharmacists is involved in marketing, sales, and administration. Some pharmaceutical manufacturers employ pharmacists as their professional service representatives, to educate physicians and pharmacists about the manufacturer's products. This can be a rewarding career for persons with the right personality and motivation, and it is often a stepping-stone to supervisory positions in sales and a path toward integration into the administrative and sales structure of a pharmaceutical firm. Pharmacists with master's degrees in business or additional degrees in law find additional opportunities in the pharmaceutical industry in the marketing, sales, and legal departments. Pharmacists can also serve the industry as professional communications managers and clinical research scientists; research and development personnel often have advanced degrees, although this is not always the case. Production and quality-control (or quality-assurance) supervisory positions often are held by pharmacists.

Government service

Government service offers opportunities to pharmacists in various capacities. They may serve as noncommissioned or commissioned officers in the Army, Navy, Air Force, and Coast Guard. They also serve as commissioned officers in the United States Public Health Service, which furnishes pharmacists for the Food and Drug Administration, Bureau of Prisons, and the Indian Health Service. Appointments are available for pharmacists in the Drug Enforcement Administration of the Department of Justice, and in the National Institutes of Health, the Center for Medicare and Medicaid Services, the Health Resources and Services Administration, and various other agencies.

Pharmaceutical education

Pharmaceutical education offers opportunities to pharmacists with advanced degrees in any of the professional specialties. Expanding enrollments and changes in the curricula at colleges to meet the employment needs of the future result in an increased need for college-level instructors. Potentially higher salaries, more freedom for research and writing, independence of action, and the cultural surroundings in pharmaceutical education make teaching attractive.

Pharmaceutical journalism

This offers rewarding experiences for a limited number of pharmacists with writing and editing skills.

Organizational management

Organizational management careers are available for those with pharmacy education who wish to serve in national and state associations and on state boards of pharmacy. The increasing number of pharmacists and the interface of pharmacy with insurance carriers and health and welfare agencies mean the responsibilities of associations and boards must expand accordingly and be complicated by the greater involvement of state and federal governments in healthcare. Thus, pharmacists who have organizational interests and talents will be in great demand and will play important roles in the future of pharmacy in the United States.

Postgraduate training

More than 20% of graduating pharmacists enter pharmacy residency programs.[2] An increasing number of hospitals require the completion of a pharmacy residency as a requirement for employment. Pharmacists interested in advanced clinical roles almost always need to have completed a pharmacy practice residency and often a second specialty residency. Pharmacy practice residencies (post-graduate year (PGY) 1 residencies) are 12-month programs with a general focus on all aspects of practice in a defined area, such as a health-system, community pharmacy or managed care. Specialty residencies (PGY 2 residencies) are 12 months or longer, require a PGY 1 residency as a prerequisite, and focus on a particular area of practice, such as pediatrics, psychiatry, hematology-oncology, transplant, critical care, nutrition support, or infectious diseases. The American Society of Health-System Pharmacists (ASHP) accredits pharmacy residency programs. The increase in the knowledge about medicines and the advanced roles that pharmacists play in medication-use management increasingly requires formal postgraduate training beyond an entry level degree and licensure in pharmacy.

Fellowship programs in similar specialty practice areas focus on research and are usually 24 months or longer. Pharmacists interested in an academic career often have a graduate degree and/or fellowship training, in addition to an entry level degree in pharmacy.

Graduate education

Areas of graduate study include pharmaceutics, industrial pharmacy, pharmacology, pharmaceutical/medicinal chemistry, pharmacognosy, and social and administrative pharmacy. A master's or PhD degree in the pharmaceutical sciences or a related field usually is required for research positions, and a PharmD, MS, or PhD degree is necessary for administrative or faculty positions.

Organizations

American Pharmacists Association (APhA)

The APhA is the national professional organization of pharmacists representing pharmacy practitioners, and pharmaceutical scientists and students. Since its founding in 1852, the APhA has been a leader in the professional and scientific advancement of pharmacy. Membership in one of the three academies of the APhA – the Academy of Pharmacy Practice and Management (APPM), the Academy of Pharmaceutical Research and Science (APRS), and the Academy of Student Pharmacists (ASP) – offers members specialized benefits and the opportunity to influence their practice areas.

American Society of Health-System Pharmacists (ASHP)

The ASHP is the professional association of pharmacists who practice in organized healthcare settings. The ASHP endeavors to create an environment in which pharmacists can focus the full potential of their knowledge and expertise on patient care. The mission of the ASHP is to represent its more than 30 000 members, providing leadership that will enable pharmacists in organized healthcare settings to provide high-quality pharmaceutical services that foster the efficacy, safety, and cost-effectiveness of drug use; contribute to programs and services that emphasize the health needs of the public and the prevention of disease; and promote pharmacy as an essential component of the healthcare team. Members can participate in seven Sections and Forums, including the Pharmacy Student Forum, New Practitioner Forum, Section of Ambulatory Care Practitioners, Section of Clinical Specialists and Scientists, Section of Inpatient Practitioners, Section of Pharmacy Informatics and Technology, and Section of Pharmacy Practice Managers.

American Society of Consultant Pharmacists (ASCP)

The ASCP promotes the development and advancement of pharmaceutical care activities directed at elderly patients, particularly those in long-term care institutions. The ASCP has more than 7000 members and 4500 student members. There are 23 ASCP chapters that are defined by geographic region.

National Community Pharmacists Association (NCPA)

Membership in the NCPA, formerly known as the National Association of Retail Druggists (NARD), is

open to independent community pharmacy owners, managers, and employees, as well as pharmacy students and corporations. The NCPA is dedicated to the continuing growth and prosperity of the 23 000 independent community pharmacies in the United States.

American Association of Pharmaceutical Scientists (AAPS)

The AAPS serves an advocacy role for the pharmaceutical sciences, promotes the economic viability of the pharmaceutical sciences and its scientists, and represents scientific interests within academia, industry, government, and other research institutions. AAPS members are eligible for membership in one of several sections: Analysis and Pharmaceutical Quality; Biotechnology; Clinical Pharmacology and Translational Research; Drug Design and Discovery; Formulation Design and Development; Manufacturing Science and Engineering; Physical Pharmacy and Biopharmaceutics; Pharmacokinetics, Pharmacodynamics, and Drug Metabolism; and Regulatory Sciences. There are 12 000 members of the AAPS.

American College of Clinical Pharmacists (ACCP)

The ACCP is a professional and scientific society that provides leadership, education, advocacy, and resources, enabling clinical pharmacists to achieve excellence in practice and research.

ACCP's membership is composed of practitioners, scientists, educators, administrators, students, residents, fellows, and others committed to excellence in clinical pharmacy and patient pharmacotherapy.

American Association of Colleges of Pharmacy (AACP)

Founded in 1900, the AACP is the national organization representing pharmacy education in the United States. The mission of the Association is to both represent and be an advocate for all segments of the academic community in the profession of pharmacy. The AACP comprises all colleges and schools with pharmacy degree programs accredited by the Accreditation Council for Pharmacy Education, including approximately 57 000 professional degree students, 5700 students enrolled in graduate studies, and more than 5600 full-time faculty.

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Evolution of pharmacy

The drug-taking animal

Among the several characteristics unique to *Homo sapiens* is our propensity to treat ailments, physical and mental, with medicines. From archeological evidence, this urge to soothe the burdens of disease is as old as humanity's search for other tools. Like the nodules of flint used to make knives and axes, medicines rarely occur in nature in their most useful (or palatable) form. First, the active ingredients or *drugs* must be collected, processed, and prepared for incorporation into medicaments. This activity, done since the dawn of humanity, is still the central focus of the practice of *pharmacy*. Put another way, pharmacy is, and has been, the art (and later science) of fashioning one of our most important tools – medicines.

For today's pharmacists it is imperative that this deep-seated role of medicines in human history is understood. As with other tools, drugs have been used to gain increased control over our lives, to make them better and longer. Over the millennia the understanding of how drugs work has changed dramatically, in part influencing how they are used (and abused). As is often the case with knowledge, however, common wisdom about medicines is a mixture of myth and science, folklore, and demonstrated fact. Old ideas meld with new concepts to produce a faulty jumble that can lead patients into trouble.

A basic introduction to the development of ideas concerning drugs, as well as the evolution of the profession, increases the ability of pharmacists to adjust to the challenges presented as professional roles expand. Pharmacists have much to gain from a basic appreciation of the complex role that drugs and medicines have played in the past and of pharmacy's part in this development.

A complete world history of how drug knowledge, medical progress, commerce, technology, and professional development came together to produce modern pharmacy would fill an entire volume. Instead, this short chapter will tell two parallel stories: how the concept of *drug* evolved over time and how a separate profession arose to prepare drugs into medicines in the West.

Throughout history, drugs have held a special fascination. Beyond sensational stories of the part drugs have played in exploration, commerce, political intrigue, scientific discovery, and the arts, they have directly influenced the lives of millions. Drugs such as insulin have kept thousands alive, and antibiotics and chemotherapeutic agents have saved thousands more. The simple fact that all drugs become useful through pharmacy bears repeating, and the safe and effective use of such medicines has developed recently into a primary concern for this relatively young profession. Although pharmacy as a skill is perhaps as old as the making of stone implements, the practice of this singular art by a recognized specialist is only about 1000 years old. For this specialization to occur a need had to arise – but that is getting a bit ahead of the story.

Prehistoric pharmacy

Since humanity's earliest past, pharmacy has been a part of everyday life. Excavations of some of mankind's oldest settlements, such as Shanidar (*ca* 30,000 BC), support the contention that prehistoric peoples gathered plants for medicinal purposes. By trial and error, the folk knowledge of the healing properties of certain natural substances grew. Although tribal healers or *shamans* often guarded this healing knowledge closely, the recognition of medicinal plants, which were sometimes used as food, spices, or charms, apparently was so widespread that it hindered any necessity for a special class of drug gatherers and keepers. The arts of primitive pharmacy probably were mastered by all who practiced the domestic medicine of the household.

When healers at Shanidar or other prehistoric settlements approached disease, they placed it within the context of their general understanding of the world around them, which was alive with good and evil spirits. Early peoples explained illness in supernatural terms, as they did the other changes and disasters surrounding them. Treatments followed suit, in that beneficial medicines worked through supernatural means. The spells of sorcerers, sometimes cast with the aid of magical substances, could be combated with the same remedies.

The magical potions for curing were part of the duty of the shaman. Usually in charge of all or most things supernatural in a tribe, the shaman diagnosed and treated most serious or chronic illness. He or she compounded the remedies needed to stave off the influences of evil spells or spirits. This basic pattern, common among ancient peoples, held sway over nearly the full span of human existence. The substances of healing potions, connected for thousands of years with the supernatural world, continue to hold a special place, a fascination for all. Thus, out of these origins a dual heritage has been derived: drugs as both simple tools and substances with nearly supernatural powers.

The discovery that certain natural substances such as opium or myrrh could ease the suffering of human existence, however, should not be trivialized. Even though early peoples discovered only a small number of effective drugs, the very concept of influencing bodily functions via an outside force must be considered one of humanity's greatest advances. The further development of this concept required the environment of civilization. To flourish, rational medical therapy needed the tools provided by settled cultures – writing, systems of exchange, and weights and measures.

Antiquity

When organized settlements arose in the great fertile valleys of the Nile, the Tigris and Euphrates, the Yellow and Yangtze, and the Indus Rivers, changes occurred that gradually influenced the concepts of disease and healing. As men and women learned how to control aspects of nature through farming, permanent shelter, and large-scale building projects, the powers of the gods in day-to-day life started to decline. These changes are evident among the remains of the great civilizations of Mesopotamia and Egypt of the second millennium BC, whose clay tablets and papyri document the beginnings of rational drug use.

An examination of these ancient records reveals a gradual separation of empirical healing (based on experience) from the purely spiritual. For the Babylonians, medical care was provided by two classes of practitioners: the *asipu* (magical healer) and the *asu* (empirical healer). The *asipu* relied more heavily on spells and used magical stones far more than plant materials; the *asu* drew upon a large collection of drugs and manipulated them into several dosage forms that are still basic today, such as suppositories, pills, washes, enemas, and ointments. The *asipu* and the *asu* were not in direct competition and sometimes cooperated on difficult cases. Apparently the ill often went back and forth between the two types of healers looking for a cure.

The extensive records that survive of Egyptian medical practices demonstrate a high level of pharmaceutical sophistication with a wider range of dosage forms compounded from detailed recipes. The Egyptian medical texts, like those from Babylon, show a close connection between supernatural and empirical healing. Suggested recipes usually began with a prayer or incantation. Plant drugs, of which laxatives and enemas were the most prominent, were the main vehicle of healing power. As was the case with healing practices in Mesopotamia, certain individuals specialized in the preparation and sale of drugs. Were these early medicine makers the forebears of today's pharmacists? No, because physicians and other healers again took on the duties of medicine preparation as these two great river civilizations declined. A fully separate pharmaceutical calling would be centuries away.

During the millennium that followed, the roots of the modern medical profession in the West arose out of the flowering of Greek civilization in the basin of the Aegean Sea. In the earliest records of ancient Greece, one finds a similar mixed concept of drug or *pharmakon*, a word that meant magic spell, remedy, or poison. In the *Odyssey*, Homer (*ca* 800 BC) refers to the esteemed medical wisdom of Egypt, thus illustrating the ebb and flow of ancient knowledge long before the printed word. The early Greek physicians described by Homer, the *demiourgoi*, had advanced to where they diagnosed *natural* causes for illness, while still not rejecting the use of supernatural healing in conjunction with empirical remedies. Some people beset with persistent afflictions traveled to a temple of the god Asklepios, where they would sleep with the hope of being visited during the night by the god or his daughter Hygeia, who carried a magical serpent and a bowl of healing medicine.

The rational tradition within Greek medicine that was evident in Homer's work was refined and codified in the body of literature connected with the name of Hippocrates of Cos (*ca* 425 BC). Building on the foundations laid by previous natural philosophers such as Thales (*ca* 590 BC), Anaximander (*ca* 550 BC), Parmenides (*ca* 470 BC), and Empedocles (*ca* 450 BC), the Hippocratic writers constructed a rational explanation of illness. They accomplished this by forging a conceptual link between the environment and humanity by connecting the four elements of earth, air, fire, and water to four governing humors of the body: black bile, blood, yellow bile, and phlegm. The Greek physician (*iatros*) who followed the Hippocratic method favored dietary and life-style adjustments over drug use. If these conservative methods failed, the physician prepared his own medicines or left prescriptions behind for family members to compound and administer.

Most Greek medicines were prepared from plants, and the first great study of plants in the West was accomplished by Theophrastus (*ca* 370–285 BC), a student of Aristotle. His example of combining information from scholars, midwives, root diggers, and traveling physicians was emulated 300 years later by Dioscorides (*ca* 65 AD). The latter Greek physician's summary of the drug lore of his times, the *Materia Medica*, became, in its various forms, the standard encyclopedia of drugs for hundreds of years to follow.

Through the teachings and writings of Galen, a Greek physician who practiced in Rome in the second century AD, the humoral system of medicine gained ascendancy for the next 1500 years. Setting aside the conservative drug use of the orthodox Hippocratists, Galen devised an elaborate system that attempted to balance the humors of an ill individual by using drugs of a supposedly contrary nature. For example, to treat an external inflammation, a follower of Galen might apply cucumber, a cool and wet drug. The same Galenist also might have tried bleeding, a favorite treatment to remove the apparent excess of blood that caused the illness. In addition to the practice of bleeding, Galen advocated the use of polypharmaceutical preparations (what would be

termed "shotgun prescriptions" today). He argued that a patient's body pulls out the substances that it needs to restore humoral balance from a complex prescription.

Medicine in classic antiquity reached its pinnacle with Galen, and the writers who followed tended to be compilers and commentators on his work, not original thinkers. Galen's influence was so pervasive among medical practitioners that the basics of his healing approach – the balance of the body's four humors through contrary drugs – mixed with folklore and superstition to guide common people in their own treatment of ailments. In the Western half of the Roman Empire, such medical knowledge became especially valuable as civilization crumbled in the years following 400 AD.

The Middle Ages

Traditionally, the Middle Ages are defined as the period from the first fall of Rome (*ca* 400 AD) to the fall of Constantinople (1453). The first half of this millennium was once referred to as the "Dark Ages" by historians because of the political and social chaos that existed in the lands that had once been part of the western half of the Roman Empire. Modern historians have revealed, however, that many advances were made during the centuries between 400 and 900, including a new, independent calling that emerged out of the flourishing Islamic civilization – pharmacy.

The story of how Greco-Roman philosophy, science, and art returned to western Europe and sparked the creative period known as the Renaissance is one of the most fascinating of human history. It began with the crumbling of civil authority in the western half of the Roman Empire during the fourth and fifth centuries. Greco-Roman culture survived in the Eastern (Byzantine) half of the empire, but with less creative energy. With Roman authority gone in the West, the Church became the stabilizing cultural force, and local feudalism arose to replace centralized government.

The use of drugs to treat illness underwent another shift, as pagan temples, some of which had operated in conjunction with Greco-Roman healing methods, were closed. Rational drug therapy declined in the West, to be replaced by the Church's teaching that sin and disease were related intimately. The stories of miracles connected with Saints Cosmas and Damian, twin brothers who healed the sick in *ca* AD 300, exemplifies this attitude. Monasteries became centers for healing, both spiritual and corporal, because the two were not viewed as essentially separate. Cast to their own devices, monks put together their own short versions of classical medical texts (epitomes) and planted gardens to grow the medicinal herbs that were no longer available after the collapse of trade and commerce. Strong in their faith, these amateur healers tended to ascribe their cures to the will of God, rather than to their meager medical resources.

As western Europe struggled, a new civilization arose among those who followed the teachings of Mohammed (570–632). The formerly nomadic peoples who united into the nations of Islam conquered huge areas of the Middle East and Africa, eventually expanding into Spain, Sicily, and eastern Europe. Because their faith taught them to respect the written word and those who studied it, they tolerated the scholarship of the Christian sectarians who had fled persecution in the eastern Roman Empire; the Nestorians, for example, established a famous school in Gondeshapur in the sixth century.

At first the Arabs accepted the authority of Greek medical writings totally, especially those of Galen and Dioscorides. But as their sophistication grew, Islamic medical men like Rhazes (860–932) and Avicenna (980–1063) added to the writings of the Greeks. The far-flung trading outposts of the conquering Arabs also brought new drugs and spices to the centers of learning. Moreover, Arab physicians rejected the old idea that foul-tasting medicines worked best. Instead, they devoted a great deal of effort to making their dosage forms elegant and palatable through the covering of pills with gold or silver leaf (gilding or silvering) and the use of sweetened vehicles.

The new, more sophisticated medicines required elaborate preparation. In the cosmopolitan city of Baghdad of the ninth century, this work was taken over by specialists, the occupational ancestors of today's pharmacists. In places such as Spain and southern Italy where the Islamic world interacted most with recovering western Europe, several of the institutions and developments of the more highly developed Arabic culture – such as the separation of pharmacy and medicine – passed over to the West.

By the mid-thirteenth century, when Frederick II, the ruler of the Kingdom of the Two Sicilies, codified the separate practice of pharmacy for the first time in Europe, public pharmacies had become relatively common in southern Europe. Practitioners of pharmacy had joined together within guilds, which sometimes included dealers in similar goods, such as spicers or grocers or physicians. These protopharmacists usually called themselves "apothecaries" after the Latinized Greek term "apotheca," which meant storehouse or repository. Like bakers (bakeries) and grocers (groceries), apothecaries were identified closely with their shops.

Arabic culture had returned classical scientific and medical knowledge to Europe. At centers such as Toledo and Salerno, the writings of the Greeks, which had been translated into Arabic centuries before on the fringes of the old eastern half of the Roman Empire, were translated into Latin for the use of European scholars. Thus, at the emerging universities of Europe such as Paris (1150), Oxford (1167), and Salerno (1180), scholars discussed the works of medical authorities such as Dioscorides, Galen, and Avicenna.

However, the debates on medicine among European academics were based on speculation, not observation. Theirs was a philosophical pursuit, with no great impact on medical practice. For significant change to occur in the use of drugs, the scholastic approach had to be set aside and a more skeptical, observational methodology adopted. This new, experimental age we now call the Renaissance.

The Renaissance and early modern Europe

The Renaissance, simply put, was the beginning of the modern period. Changes that had begun during the European Middle Ages, and were stimulated further by contacts with other cultures, gained momentum. The burst of creative energy that would result in our present shared culture of the West stemmed not from a single episode but from a series of events.

In 1453 Constantinople (current Istanbul) fell to the conquering Turks, and the remnants of the Greek scholarly community there fled west, carrying their books and knowledge with them. About that same time, Johann Gutenberg began printing with movable type, starting an information revolution. Within a half century, Columbus discovered the New World, Vasco da Gama found the sea route to India that Columbus had sought, commerce based on money and banking was established, and syphilis raged through Europe. It was a time for new ideas through reinterpretation of the old classical themes, and through exploration on the high seas and in the laboratory.

The time was ripe for casting off the old concepts of diseases and drugs of Galen. The new drugs that were arriving from far-off lands were unknown to the ancients. Printers, after fulfilling the demand for religious books such as bibles and hymnals, turned to producing medical and pharmaceutical works, especially those that could benefit from profuse and detailed illustrations. On the medical side, for example, this trend is exemplified in the anatomical masterworks of Andres Vesalius (1514–1564).

For pharmacy, printing had a profound effect on the study of plant drugs, because illustrations of the plants could be reproduced easily. Medical botanists such as Otto Brunfels (1500–1534), Leonhart Fuchs (1501–1566), and John Gerard (1545–1612) illustrated their works with realistic renditions of plants, allowing readers to do serious field work or to find the drugs needed for their practices. Among the most gifted of these investigators was Valerius Cordus (1515–1544), who also wrote a work in another popular genre – formula books. His *Dispensatorium* (1546) became the official standard for the preparation of medicines in the city of Nuremberg and generally is considered the first pharmacopeia.

Although they were critical to the advancement of medical science, the nearly modern, precise works of Fuchs and Vesalius did not influence the treatment of disease as much as the speculative, mystically tinged writings of an itinerant Swiss surgeon who dubbed himself "Paracelsus." Born Philippus Aureolus Theophrastus Bombastus von Hohenheim in 1493, the year Columbus went on his second trip, this medical rebel represents well the combined attitudes of the common man, the scholarly physician, the practical surgeon, and the alchemist. The battles of Paracelsus against the static ideas of Galen, Avicenna, and other traditional authorities opened a window into the complicated mind of the Renaissance. As Erwin Ackerknecht observed in *A Short History of Medicine*,

> Paracelsus is one of the most contradictory figures of a contradictory age. He was more modern than most of his contemporaries in his relentless and uncompromising drive for the new and in his opposition to blind obedience to authoritarianism and books. On the other hand, he was more medieval than most of his contemporaries in his all-pervading mystic religiosity. His writings are a strange mixture of intelligent observation and mystical nonsense, of humble sincerity and boasting megalomania.

Paracelsus was the most important advocate of chemically prepared drugs from crude plant and mineral substances, yet he believed firmly that the collection of those substances should be determined by astrology. He stated, again and again, his total faith in observation while at the same time preaching the "doctrine of signatures," a belief that God had placed a sign on healing substances indicating their use against disease (e.g., liverwort resembles a liver, thus it must be good for liver ailments).

An outspoken enemy of university-educated physicians, Paracelsus denigrated their scholasticism and wrote his own works in his native language rather than in the traditional Latin. He harshly criticized pharmacy practitioners as well, even though his advocacy of chemically prepared medicines was to spark the growth of the modern pharmaceutical sciences. Chemical processes, especially distillation, empowered disciples of Paracelsus to isolate the healing principles of a drug, its *quintessence*. Eventually, as the efficacy of some of these drugs became known, they entered professional medical practice and appeared in books on medicines. Largely by this path, chemistry became an important part of pharmacy's pursuit of more effective and palatable medicines.

Paracelsus and his followers, who chastised practitioners of pharmacy, soon took a position on the forefront of chemistry during the sixteenth century. The apothecary Johann Hartmann (1568–1631), for example, was the first professor of chemistry at a European university. This trend continued through the seventeenth, eighteenth, and into the beginning of the nineteenth century as chemistry emerged as a separate profession. For a period of about 300 years, a small minority of practicing pharmacists made significant investigations into the chemistry of drugs, and along the way isolated many drugs that are still used today and contributed much to general chemical knowledge. During that same period, when men and their ships sailed the seas looking for new lands, and returned with new drugs, practitioners of pharmacy explored a much smaller, but equally exciting, world in their laboratories.

Much of the stimulation for the early research came out of the discovery of drugs in recently explored lands. Just as Galen did not know all the diseases in the world, Dioscorides and his Arab elaborators did not know all the drugs in the world. Tobacco, guaiac, cascara sagrada, ipecac, and cinchona bark were among the scores of new plant drugs from the New World.

Cinchona bark, from which quinine was extracted in 1820, first came to Europe around 1640, at which point it created a crisis within scholastic medicine. Galen's elaborate system of balancing humors by using drugs of opposite qualities could not explain cinchona bark's efficacy against malaria. Not only did the bark cure malarial fevers, but also it had little effect on other fevers. Here was something Galen said could *not* exist, but Paracelsus insisted *must* exist – a specific remedy for a disease. This conceptual crisis, plus the efforts of those advocating chemical medicines, displaced the therapeutic agreement of Galenism, which had lasted nearly 1500 years. The following period, about 250 years, was a time of therapeutic chaos that lasted until the present era of modern pharmacology.

During the time of turmoil for therapeutics while the followers of Paracelsus and Galen argued, the calling of pharmacy established the legal and scientific foundations of the modern profession. Out of the medieval complex of guilds on the European continent grew organizations that represented pharmacy.

As the occupational division from medicine spread north, pharmacy practitioners joined together or aligned themselves with similar groups, such as the sellers of spices or physicians and surgeons. The guilds of the late Middle Ages and early Renaissance wielded considerable power, setting up training requirements, examinations, and restrictions on the number and locations of shops. Conflicts within guilds of pharmacists and near competitors often led to government intervention and new laws that

clarified the professional role of pharmacy. Eventually, however, inter-professional friction would lead to the separation of pharmacists into their own organizations, often under governmental authority (e.g., the French Collége de Pharmacie in 1777).

The cooperation between pharmaceutical guilds and governmental bodies also led to the standardization of medicines through the publication of books called *pharmacopeias*. Because of greater pharmaceutical sophistication, the increased number of herbals and distillation books, and the availability of new drugs, physicians wanted assurance that their prescriptions would be prepared uniformly within their city or state. To this end, in 1499 the guild of physicians and pharmacists of Florence sanctioned the *Nuovo receptario* as their book of standards. Historians, however, generally credit the *Dispensatorium* of Valerius Cordus as the first pharmacopeia, which was adopted by the government of Nuremberg, Germany, in 1546.

It is a bit ironic that from the mid-1600s to the mid-1800s, when controversy raged within medicine regarding the proper use of drugs, pharmacy made its greatest contribution to science as well as becoming firmly established as a profession on the European continent. As chemical medicines became more prevalent in medical practice, pharmacists were forced to learn the new methods of preparation and manipulation. To do so they turned to the most popular textbooks on chemistry, which were composed by pharmacists such as Nicaise LeFebvre (*Traité de chymie*, 1660) and Nicolas Lemery (*Cours de chymie*, 1675).

The volume of chemical discoveries made by pharmacists would fill a chapter twice this size. Carl Wilhelm Scheele (1742–1786), for example, discovered oxygen in 1773, a year before Priestley, as well as chlorine, glycerin, and several inorganic acids. Martin Klaproth (1743–1817) was a pharmacist who pioneered the field of analytical chemistry. Like Scheele, he made his discoveries using the equipment of the pharmacy in which he worked. Other pharmacists, such as Andreas Marggraf (1709–1782), became such proficient chemists that they pursued chemical work full-time. Along the way pharmacists contributed much to the development of chemical apparatus, especially analytical chemists such as Klaproth, Marggraf, Antoine Baumé (1728–1804) (modern hydrometer), Carl Freidrich Mohr (1806–1879) (improved burette), and Henri Moissan (1852–1907). Moissan, a French pharmacist, received the Nobel Prize in Chemistry in 1906 for his isolation of fluorine.

Because most drugs before 1900 were derived from the plant kingdom, it is not surprising that pharmacists dominated the investigation of botanical drugs during the 1700s and 1800s. In collaboration with interested physicians, pharmacists documented the sources of plant drugs around the globe, making significant contributions to the nascent science of botany. Combining this proficiency with their skills in manipulative chemistry, pharmacists continued the search begun by the Paracelsians to find pure healing principles within medicinal plants.

Approaching pharmacy with a more modern viewpoint, these men sought to isolate pure, crystalline chemicals that could be measured accurately and identified chemically. Medicinal preparations of crude drugs, no matter how carefully made, fluctuated considerably in potency because of the natural variation of active constituents in botanicals. Thus, the pursuit of active principles was no easy task, and it fascinated pharmaceutical investigators for nearly 300 years. To search, separate, characterize, and identify the scores of chemicals contained in the simplest plant drug was a challenge as great as any exploration.

Discoveries came gradually through hit-and-miss research until the late 1700s, when Scheele, for example, extracted several plant acids including citric acid (1784). The single, most important breakthrough occurred during the first decade of the nineteenth century when the pharmacist Friedrich Sertürner extracted morphine from crude opium. The announcement of his method opened up the era of alkaloidal chemistry, which resulted in the isolation of several pure drugs from crude preparations. The French pharmacists Joseph Pelletier and Joseph Caventou isolated several alkaloids, notably quinine in 1820. Not only were these new, pure drugs rapidly adopted by physicians because their potency was assured, but their existence allowed physiologists to administer drugs accurately during their research, which became the wellspring for modern pharmacology.

Much later, after 1850 or so, the scientific disciplines of pharmacy began to become more professionalized in colleges and manufacturing concerns with a

subsequent decline in *drug shop science*. Pharmacists interested in research left the shop behind for the institutional laboratory.

Despite the impressive achievements of a few pharmacy practitioners, most pharmacists of the early modern period viewed science as secondary to professional and financial success. European pharmacists achieved these goals through strict internal controls on the profession and relatively cordial relations with physicians. In some states on the European continent, laws limited the number and location of pharmacies, and dictated the requirements for education and licensure. Lists of standard prices softened competition. By the nineteenth century, the combination of the fame generated by scientific contributions and solid upper-middle-class credentials had elevated pharmacists throughout much of Europe to a social position similar to that of physicians.

Such conditions did not hold for England, however, where the position of the pharmaceutical profession within the hierarchy of healing did not become established firmly until the mid-nineteenth century. The original class of pharmacy practitioners, the apothecaries, had evolved during the 1600s and 1700s into a second group of medical practitioners, servicing those who could not afford the high fees demanded by the small cadre of university-educated physicians.

As apothecaries became more and more like general practitioners of medicine, *chemists* and *druggists* (i.e., those who manufactured and sold drugs and medicines for the apothecaries) rose up to take over the open pharmaceutical niche. Conflicts and court cases erupted during these years, and the boundaries between the physicians, apothecaries, chemists, and druggists shifted accordingly. It was during this period of confusion within their health community that the British settled what would become the United States of America, a situation that contributed to the development of the unique American profession of pharmacy.

American pharmacy

The exceptional character of American pharmacy (The discussion on American pharmacy is based in part on data from "Professionalism and the Nineteenth-Century American Pharmacist," *Pharm Hist* 1986; 28: 115.) arises out of its remarkable history. When settlers came to the shores of North America, there was little to attract trained or established medical personnel. Unlike the lands of Central and South America, there were no treasures to confiscate or spices to export. This was a land for toil, not spoils. As the frontier was pushed back slowly, most of the populace relied on domestic or "kitchen" medicine guided by home medical books (if the settler could read). When this failed, the colonist often turned to a nearby figure of authority such as a clergyman or government official to provide medical advice or guidance.

As the colonies grew more prosperous during the early eighteenth century, they attracted ambitious businessmen from England, including apothecaries. In the New World, British apothecaries continued to combine pharmaceutical and medical practice, serving the large segment of the public who could not afford university-trained physicians. In North America, the boundaries between medicine and pharmacy were even cloudier, with most physicians having some sort of shop practice. Most apothecary shops were run either by an attending physician or his apprentice, or by an apothecary hired by the owner-physician. In other words, most men who practiced medicine for their livelihood also had their own pharmacy, either out of their homes or in *doctor shops*.

A few eighteenth-century chemists and druggists – practitioners who limited themselves to drug-selling and medicinal preparation – did practice in the larger cities on the Atlantic coast. These forerunners of today's pharmacists had two main areas of sales. As *druggists* they served as wholesalers of the drugs and medicines used by apothecaries, surgeons, midwives, and physicians. They also undersold the apothecaries in the marketing of so-called patent medicines (trademarked secret remedies originally protected from competition by "letters patent"), which became increasingly popular up through the Revolutionary War. There were few laws that directly involved Anglo-American pharmacy during the colonial period, and no effective laws restricted the practice of American pharmacy until the 1870s. Anyone with luck, pluck, and sufficient capital could open up an apothecary or druggist shop.

The hardships imposed by the Revolutionary War proved to be critical in the development of a separate pharmaceutical occupation in America. Britain had been the source of almost all drugs dispensed

by physicians and apothecaries. In order to meet demand, American druggists, the wholesale distributors of drugs, had to learn how to manufacture their own chemically based drugs and how to make common preparations of the crude drugs previously obtained from Britain. In addition, these druggists had to learn how to imitate the popular British patent medicines that were so much in demand by the public. To meet war needs wholesale drug firms, such as that of the respected Marshall family in Philadelphia, expanded their production capabilities. Out of the war came a network for the production, packaging, and distribution of drugs and medicines.

But a profession of pharmacy, at least as we know it, was not spawned during the period of the Revolutionary War. Pharmacy – the compounding of medicines – still was done almost completely by physicians in their own shops or offices (continuing to practice according to the model of the British apothecary) or by their apprentices. Aside from those wholesale druggists who also had an *out front* business – that is, a retail store that sold their products and filled occasional prescriptions – nonmedical practitioners of pharmacy were rare and without any sort of group identity. Many of those who did practice pharmacy solely were either immigrants from the European continent or former employees in doctor shops who bought businesses from their old physician-employers.

To succeed, these chemists needed prescriptions to dispense. Back in the 1760s, in his famous *Discourse* on medical education, Dr John Morgan, a pioneer in American medical education, had advocated the separation of medicine and pharmacy with physicians writing prescriptions. A few physicians did follow Morgan's lead, but the practice did not become common until well into the nineteenth century. Morgan himself returned to operating a shop to make ends meet.

The years surrounding the War of 1812 brought significant changes in American business and healthcare that strongly influenced pharmacy's professional development. It was not until the early years of the nineteenth century that American physicians began to view the special service of an apothecary as distinct and essential. The first hospitals of the young republic, for instance, employed medical apprentices as staff apothecaries. As described in the *Brief Account of the New York Hospital* (1804), a "house Surgeon and Apothecary constantly reside in the Hospital – these offices are filled by the students of the Physicians and Surgeons belonging to the Hospital, which affords an excellent school for the young men appointed to those places." The staff apothecary practiced both pharmacy and medicine in a manner analogous to the British apothecary of the eighteenth century, going on rounds and treating patients.

By 1811, however, the position of apothecary at the New York Hospital had changed. The person chosen was a full-time pharmaceutical practitioner who was tested, before hiring, on his prowess as a compounder of medicines. Instead of being obligated to go on rounds, he was required to stay in the pharmacy at all times. By 1819 the services of the New York Hospital apothecary were so critical that he was required to put up a $250 bond to guarantee that he would not leave his position with less than a two-month notice.

The war with England cut off trade with the largest suppliers of drugs and medicines to the United States. In contrast with the stopgap measures used during the Revolutionary War, the American drug trade during the War of 1812 developed its own resources for the production of basic pharmaceuticals, including patent medicines. When peace returned, some American firms faltered under English pressure, but others continued and formed the basis for the future American drug industry.

The years following the War of 1812 were transitional. More and more physicians gained their clinical experience in hospitals and dispensaries instead of with preceptors, learning to write prescriptions, rather than compound them. After graduation some of these young physicians continued to write out prescriptions, thereby stimulating the growth of pharmacy. As physicians began writing prescriptions for apothecaries to dispense, concern arose over the consistency with which these medicines were being compounded. In 1808 the Massachusetts Medical Society published a state guide to drug standards, with a national convention of physicians approving a *Pharmacopoeia of the United States of America* (USP) in 1820. Although the USP was not recognized as official by the federal government for years to come, it rapidly became accepted nationally as the primary guide to drugs.

The appearance of these books reflected both the growing amount of prescription writing and the medical profession's increasing reliance on pharmacists. The number of pharmacy practitioners in urban areas reached the critical mass necessary for the establishment of local pharmaceutical societies such as the Philadelphia College of Pharmacy (1821) and the Massachusetts College of Pharmacy (1823). These *colleges* (the term being used in the sense of associated colleagues) established night schools for the instruction of apprentices and discussion groups on scientific pharmacy. The small class of retail apothecaries and wholesale druggists presented no particular threat to urban physicians in the first decades of the nineteenth century, and the situation provided them with several conveniences.

Antebellum America: pharmacy finds its niche

The years prior to the American Civil War were to be the most critical for American practitioners of pharmacy; the boundaries of practice between physicians and pharmacists that were drawn during this period still exist relatively unchanged today. During the 1820s and 1830s, East Coast apothecary shops became more standardized in their appearance and in the stock they carried. Pharmacy followed the trend of specialty retailing and concentrated on drugs, medicines, surgical supplies, artificial teeth and limbs, dyestuffs, essences, and chemicals. Grocers took over the selling of exotic dietary items such as figs, raisins, and citrus fruits. Drugstores in small cities and towns, however, tended to keep in stock more general articles such as glass, paints, varnishes, and oils. Above all, apothecary shops became the main distributors of patent medicines, one of the most profitable lines of merchandise in the history of American business.

The educated elite of Atlantic coast physicians fostered the development of a well-trained, yet subservient, pharmaceutical profession. They welcomed the early pharmaceutical associations and served as faculty for the first American pharmacy schools. Physicians voiced support for the growth of an independent profession of pharmacy as a "necessity for a division of labor" to meet the "growing demands" of their communities. As the quality of drugs imported from Europe declined, physicians began to rely on the expertise of pharmacy practitioners to detect adulterated or low-potency drugs.

The relationship between the physician and the druggist began to sour in the 1840s. Feeling more confident of their social standing, apothecaries began shifting their efforts from pleasing physicians to attending the ills of customers. Consequently, American apothecaries took to refilling prescriptions without physician authorization or directly treating customers, a practice called *counter-prescribing*. In the large cities, doctor's shops were back on the rise after a decline of two decades. Medical schools continued to turn out graduates by the hundreds, most of whom sought their fortunes in urban areas, where they would *open shop*.

As the 1850s progressed, the growth of American pharmacy accelerated. The US Census figures for druggists and apothecaries in 1850 and 1860 illustrate the dramatic growth in the profession, especially when compared with physicians. In 1850 and 1860, respectively, the *per capita* number of physicians did not change significantly (1 : 572 to 1 : 576), while the number of druggists grew by nearly 25% (from 1 : 3778 to 1 : 2850). This trend continued, at a slightly lower rate, through the rest of the nineteenth century.

American pharmacy was caught up both in developments within the healthcare sector and in the larger changes occurring in American commerce. As mass-manufacturers began producing drug preparations in the late 1850s, less-skilled men entered the ranks of pharmacy. With large firms doing much of the complicated work, these *mere shopkeepers* flooded the marketplace. Physicians had supported the growth of the pharmaceutical profession largely because it served their own interests, releasing them from the drudgery of compounding medicines and stocking a shop. Moreover, physicians came to depend upon the expertise of the best druggists and apothecaries. With the development of the pharmaceutical industry, however, this relationship changed. As one physician put it in 1860, "It is an admitted and lamentable fact that many of those now practicing pharmacy are totally incompetent to fulfill the responsibilities of the true apothecary. They know nothing of the science of preparing medicines."

By the late 1850s, while the general economy was in crisis and secession strife was imminent, physicians

and pharmacists indulged in a great deal of finger-pointing in both the professional and popular arenas. Both groups blamed each other for the continued popularity of patent medicines. Moreover, competition had reached such a high level that it threatened the integrity of the boundaries that had developed to separate the two professions. Pharmacists were convinced that dispensing physicians and doctor's shops were the cause of much of their difficulties, whereas physicians complained about counter-prescribing. With no legal restrictions on medical or pharmaceutical practice, the lines of separation between medicine and pharmacy were growing hazy. The onset of the Civil War ended much of the bickering between apothecaries and physicians. After the War, the boundaries between the professions were drawn more clearly, aided in part by new approaches to professionalization.

The search for professionalism

In part to raise the stature of their rapidly growing calling, a small group of elite druggists and apothecaries met in Philadelphia in 1852 to found the American Pharmaceutical Association (APhA). They saw the gains made by pharmacy in the 1830s and 1840s being swept away by a rising tide of destructive competition. For American pharmacists of the mid-nineteenth century, organizations like the Philadelphia College of Pharmacy or the APhA held the promise of increasing their professional stature by fostering individual improvement, not by winning the favor of physicians or government bureaucrats.

The crux of this independent achievement was the mastery of prescription compounding. The growth of large-scale pharmaceutical manufacturing during the Civil War years struck fear in the hearts of pharmacy leaders. As William Procter Jr stated (1869),

> Pharmacy may be defined to be the art of preparing and dispensing medicines, and embodies the knowledge and skill requisite to carry them out in practice. But if the preparation of medicines is taken from the apothecary and he becomes merely the dispenser of them his business is shorn of half its dignity and importance, and he relapses into a simple shopkeeper.

Most American pharmacists, undereducated and under-skilled, took advantage of the growing number of ready-made preparations offered by large firms. This was in spite of the arguments put forth by the leaders of pharmacy since the 1830s that the special ability to produce official preparations successfully in-house was what made the individual pharmacist more than a mere merchant. Moreover, this expertise only could be learned through experience, under the watchful eye of a preceptor. As fewer basic ingredients for compounding were made in the shop, however, apprentices would become preceptors and pass along their ignorance.

Pharmacists, at the conclusion of the Civil War, initially rejected the notion that formal educational requirements would solve the problem. They had no interest in any measures that interfered with their freedom to practice. Moreover, some immigrants from the Continent, where states often restricted pharmaceutical practice, expressed opposition to the legal control of pharmacies. Many had come to North America to open their own shops, rather than wait years in their native lands for permission.

In the late 1860s the academic model of professionalism being worked out by other so-called "new professions" such as engineering attracted the attention of some pharmaceutical leaders. Using university degrees, plus state licensing or institutional certification, these new professions set themselves apart from other occupations as "communities of the competent." They sought to avoid the ordeals of the marketplace by putting a cognitive gap between their work and the public's understanding. Theoretically, by controlling admissions to professional schools and raising examination standards, destructive competition could be reduced or even eliminated.

Legislation

The APhA responded to the movement of the late 1860s toward increased public protection and occupational security through law by publishing a model pharmacy act. Physicians and others concerned with the safe use of poisons and potent drugs had petitioned state legislatures for laws governing pharmacy. Initially, pharmacists took a negative view, reacting to the idea that physicians or bureaucrats would gain

authority over pharmacy practice via state inspectors or licensing boards. To ensure that the profession's best interests would be protected, the APhA empowered a committee to draw up a model law. Reflecting the ambivalent attitude of many pharmacists toward legal regulation, the APhA published and distributed their model law without endorsement. As small businessmen, pharmacists did not want outside restriction on their trade.

During the 1870s state legislatures began considering in earnest pharmacy bills sponsored by non-pharmacists. Reacting to this trend, pharmacists organized statewide associations to coordinate support for their own bills, which were often versions of the APhA model. Although not enthusiastic at first about regulation of their businesses, pharmacists wanted a voice in the process. The eventual success of their efforts in the 1870s, 1880s, and 1890s evinced a changing attitude toward the pursuit of professionalism from the 1860s.

The boundary between masters of the pharmaceutical art and mere store clerks, which had always been flimsy, was disintegrating. Pharmacists sought new ways to demonstrate their competence and to separate themselves from ignorant drug sellers and quacks. The evidence for this expertise, however, shifted away from individual achievement in the marketplace toward group identification and institutional certification.

Transition to a modern profession

The period between 1870 and 1920 was transitional for both pharmacy and pharmaceutical education. Before the Civil War perhaps only 1 in 20 American pharmacists had finished formal schooling in pharmacy, which had consisted of night courses to supplement apprenticeship training. With the passage of state laws requiring the examination and registration of pharmacists from the 1870s on, pharmacy became part of the wave of professionalization sweeping across American society. The new professionals based their claims of status on their diplomas and licenses, not their products.

Pharmacy got caught up in this trend, and even though state laws did not require a pharmacy school diploma for licensure until the early twentieth century, the prestige attached to the sheep-skin attracted students to the burgeoning number of schools, as public expectations increased and "professional" became a coveted title.

Pharmaceutical education around the turn of the century was related closely to practice as pharmacist-educators such as Joseph Remington replaced the physicians and other non-pharmacy practitioners who had dominated the earlier schools. Students also had a wide range of possible educational experiences: Many if not most taught themselves by reading textbooks while working as apprentices. Others attended short-term cram schools that focused only on passing state board examinations. Perhaps one-in-five future pharmacists attended one or two years of serious pharmacy school. Most of these were small, local schools of pharmacy that sprang up in medium-sized cities offering basic instruction and large diplomas for display. A handful of old-line schools, affiliated with local pharmaceutical organizations in larger cities, provided students with excellent practical education, plus an opportunity to explore specialty areas of research, depending on the college's faculty. And lastly, starting with the University of Michigan in 1868, schools of pharmacy affiliated themselves with state colleges and universities, a trend that altered eventually the direction of American pharmaceutical education.

As part of larger university communities, these pharmacy schools aspired to the high standards of scholarship exhibited by established disciplines and other professions. The leaders of the university faculties helped transform pharmaceutical education from a vocational to a scientific orientation through pharmacy programs that emphasized full-time coursework and laboratory study.

During this period pharmacy's part in healthcare solidified, as the dispensing of medicines by physicians declined. However, the rise of the cut-rate drugstore and, more importantly, the chain drugstore, also occurred during these 50 years, which further increased economic pressure on the profession.

Still, most pharmacists worked in their own *corner drugstore*, which became a fixture in American life with its shelves of patent medicines for all ills and a soda fountain for delightful beverages; the proprietor, often called *doc*, attended to the minor aches and pains of customers or made chocolate sodas with equal skill. Although the pharmacist relied on

prescription compounding for his professional identity, this provided only a small fraction of his income. Most drugstore owners received more income from sales at the tobacco counter or the soda fountain. Beginning in the early 1800s, soda water was sold at first in pharmacies for its supposed medicinal value. Masters of natural flavorings, pharmacists added new specialties that became the basis of the American soft-drink industry. (Coca-Cola, Dr. Pepper, and Pepsi-Cola all originated at drugstore fountains.) After the Civil War, soda water concoction sales grew rapidly and stores added elaborate beverage counters of marble, chrome, and glass that became identified with the institution of the American drugstore.

To protect this independent and uniquely American style of practice from the incursion of larger retailers, the National Association of Retail Druggists (NARD) was founded in 1898. At first the APhA welcomed and cooperated with the new national organization, but the split that eventually developed between the APhA, which was oriented to scientific and professional advancement, and NARD, which concentrated on the individual commercial success of owners, weakened the profession's voice in national affairs in the years to come.

It was an exciting time in medicine, with therapeutics undergoing a transformation. The germ theory of disease, championed by laboratory scientists such as Louis Pasteur and Robert Koch, resulted in significant immunological advances in the 1880s and 1890s. Pasteur's rabies vaccine and Emil von Behring's diphtheria antitoxin demonstrated that cures for infectious diseases could arise from the laboratory. Paul Ehrlich transcended the biological efforts of his predecessors when he introduced Salvarsan in 1910, the first chemotherapeutic agent. Although it fell short of Ehrlich's ideal of a *magic bullet*, which could destroy microorganisms selectively without damaging the patient, Salvarsan did inspire others to search for drugs with chemotherapeutic potential. Aside from the biologicals, however, few of the drugs discovered during the late nineteenth and early twentieth centuries had a significant impact on the prevention or cure of disease.

Industrial research on drugs produced several new agents, such as the analgesic and antipyretic aspirin or the sedative chloral hydrate, that reduced the pain and suffering associated with illness. Even though pharmacies served as important outlets for sera, antitoxins, and vaccines, most of the medicines compounded or sold by pharmacists around the turn of the century eased symptoms, rather than treated root illnesses.

As scientific pharmacology explained how drugs worked on a cellular and organ system level, the concept of drugs and their actions held by professionals and laypeople diverged. The public clung to outdated ideas of humoralism augmented by a modicum of germ theory. Such beliefs made consumers susceptible to patent medicine advertising, which misled them into equating the effects of strong laxatives and analgesics with the cure of disease. With far greater understanding of the nature of disease, health professionals joined together with muckraking journalists and politicians of the Progressive Era to attack patent medicine *cure-alls*. The 1906 Pure Food and Drug Act, passed mainly in response to poor food-production methods, also addressed problems in the drug trade. Even though it proved ineffectual against patent medicine fakery, the 1906 act did establish the *United States Pharmacopeia* as well as the *National Formulary* of the APhA as official compendia, providing the United States with truly national drug standards for the first time.

It was during these years that pharmacists finally abandoned the in-shop manufacturing of the ingredients of their prescriptions. The pharmaceutical industry had progressed to the point where they could produce basic preparations of crude drugs more cheaply and reliably than could the individual practitioner. Moreover, industry was the source for the new synthetic drugs such as antipyrine and aspirin that resulted from developments in organic chemistry. As compounding, not the making of stock preparations, always had been the crux of pharmacy practice, this change was lamented only by a few of the profession's old guard. The hands of pharmacists still fashioned the essential tools of medicine.

Pharmacy education adapted gradually to the change. Course-work shifted away from the identification of crude plant drugs and their various preparations to a greater emphasis on the chemical compatibility of the ingredients within each prescription. The professional credentials of American pharmacists were strengthened in 1932 when a four-year BSc degree became standard for licensure. For the

next three decades pharmacy schools graduated pharmacists who could claim to be *chemists on the corner*. Yet at the same time that the profession achieved the goal of a scientifically trained workforce fully capable of carrying out all the steps involved in the making of medicines, the technology of the pharmaceutical industry assumed that responsibility.

The era of count and pour

The middle third of the twentieth century was a time of dramatic change for all of medical care including pharmacy. In therapeutics, many of the great scourges of humanity were conquered through the introduction of antibiotics. Although the phenomenon of antibiosis had been observed by Pasteur in the 1870s, the first significant antibiotic substance was not discovered until Alexander Fleming noticed the effects of a colony of *penicillium* mold on a misplaced petri dish in 1928. Development of penicillin did not occur, however, until a decade later when the threat of war in Europe inspired a British team to pursue the scaled-up production of the drug. Other antibiotics followed shortly, as did new classes of therapeutic agents, such as the corticosteroids, tranquilizers, antidepressants, antihypertensives, radioactive isotopes, and oral contraceptives. The pharmacy, which had served as an outpost for the relief of suffering and the treatment of minor ailments, came to hold preventives and cures for serious disease.

Following World War II American pharmaceutical firms applied high technology to the production of medicines and rapidly became one of the most advanced industries in the world. New drugs, new dosage forms, and new marketing methods reinforced a trend evident from the early 1900s of physicians shifting away from prescribing complex mixtures of ingredients toward ready-made, single-entity medicines mass-manufactured by large companies. In the 1930s about 75% of prescriptions required some compounding by a pharmacist; by 1950 that figure had dropped to about 25%. The movement away from prescriptions "tailor-made" for each individual patient accelerated so that by 1960 only about 1 in 25 prescriptions needed the compounding skills of a pharmacist, with the trend leveling out around 1970 at about 1 in 100.

Pharmacists, however, were not at a loss for work. The number of prescriptions grew even faster as new, effective drugs came onto the market in the 1950s, 1960s, and 1970s. In community pharmacies the income from the sale of prescription drugs increased faster than *out-front* sales of over-the-counter medicines, cosmetics, and other traditional drugstore goods. Chain stores and other large retailers rushed into the drug business in the post-war era, displacing the independent corner drugstore as the typical purveyor of pharmaceutical services, especially in urban areas by the 1980s.

Modifications in pharmaceutical legislation and education reflected these dramatic changes in therapeutics and practice, to varying degrees. Federal laws regulating the production of drugs and pharmacy practice were modernized in 1938, 1952, and 1962, the last set of amendments requiring that medicines be judged both safe and effective to be on the market. Laws regulating drugs of high abuse potential were updated through the Drug Abuse Act of 1970, which was subsequently enforced through the Drug Enforcement Agency. In contrast to the law, educational reform came more slowly.

Proposals for six-year Doctor of Pharmacy degrees to elevate the professional standing of pharmacy gained interest in a few places, with the first such program initiated at the University of Southern California in 1950. But, as a whole, pharmaceutical educators compromised and selected a five-year bachelor of science in pharmacy as the standard degree beginning in 1960. The pharmacy curriculum continued to emphasize the physical sciences that underlie the making of medicines, however, ignoring the fact that compounding was disappearing from American pharmacy practice.

Because of the large growth of prescribing, community pharmacists of the 1950s and 1960s stepped back from soda fountains and cigar counters to practice pharmacy nearly full time. Yet, for all of their education, they did little more than routinely fill prescriptions – placing a small number of dosage units from a large bottle into a smaller, properly labeled one. Despite the added responsibility of distributing the hundreds of new and potent medicines coming on the market, pharmacists had little opportunity to use their four, five, or six years of higher education. The restricted role of the pharmacist is exemplified by the

following statement from the Code of Ethics of the APhA, which was in effect from its adoption in 1952 until its revision in 1969:

> The pharmacist does not discuss the therapeutic effects or composition of a prescription with a patient. When such questions are asked, he suggests that the qualified practitioner (i.e., physician or dentist) is the proper person with whom such matters should be discussed.

In 1969 the APhA revamped its Code of Ethics in the face of the large changes occurring in pharmacy. Instead of deferring to physicians, the APhA advanced this statement as the first section of its Code: "A pharmacist should hold the health and safety of patients to be of first consideration; he should render to each patient the full measure of his ability as an essential health practitioner." This dramatic reversal resulted from a new idea that swept through pharmacy during the mid- to late-1960s called clinical pharmacy.

The emergence of clinical pharmacy

The concept of *clinical pharmacy* sprang from a combination of factors, including the development of the subdiscipline of hospital pharmacy since the 1920s, the growth of clinical pharmacology since the 1940s, innovative teaching programs connected with the new PharmD degree, the decline of pharmacology instruction in medical schools, and the appearance of office-style community pharmacies exemplified by Eugene V. White's practice in Berryville, Virginia. To some extent, pharmacy took over an aspect of medical care that had been partially abandoned by physicians. Overburdened by patient loads and the explosion of new drugs, physicians turned to pharmacists more and more for drug information, especially within institutional settings.

Viewed historically, however, the expansion of pharmacy's role to include patient instruction on proper drug use seems a logical extension of the pharmacist's role as toolmaker. Moreover, clinical pharmacy practice bridged the gap between professional and lay understanding of drug action. During the past century medical science far surpassed the public's comprehension of physiology and disease. The concept of how the tool of medicine works, once shared by both doctor and patient, had been lost. The public's trust in medical practitioners subsequently declined. Pharmacists, by sharing insights into the workings of medicines with their patients, became trusted professionals in American society.

Aside from recent innovations in the relationship between pharmacist and patient, several other notable changes have occurred within American pharmacy that have gone relatively unnoticed by the public. Outwardly, the practice of pharmacy today differs little in appearance from that of 60 years ago. An individual hands over a small slip of paper received from a physician to a pharmacist who then retreats into a work area and appears later with a container of medicine. But on closer examination, the changes seem revolutionary. For example, women, who made up only 4% of the profession in 1950, entered the field rapidly starting in the 1970s. By the year 2007 they were approximately 50% of the pharmaceutical workforce and should remain the majority into the foreseeable future.

Pharmacists, traditionally conservative in the face of technological innovation, adapted computer technology to their work as quickly as any other profession of the late twentieth century. Institutional practice, once viewed as the lowest rung on the profession's ladder, became the work area of choice for graduates during the 1970s and 1980s, a period of unprecedented hospital growth. Just as the division of labor opened up a niche for pharmacists in the early 1800s, pharmaceutical specialties such as radiopharmacy, clinical pharmacotherapy, and nutritional support practice have demonstrated the maturity of the American pharmaceutical profession. Once relegated to counting and pouring, pharmacists headed institutional reviews of drug utilization and served as consultants to all types of healthcare facilities.

The conflicting paradigms of pharmaceutical care and managed care

The 1990s in American pharmacy begin with a clarion call for a paradigm shift to Pharmaceutical Care, a practice model described by Charles D. Hepler and Linda Strand as "the responsible provision of drug therapy for the purpose of achieving definite outcomes that improve a patient's quality of life." The diverse organizations of American pharmacy rallied to this expanded vision of practice. Established schools of pharmacy shifted in earnest to all-PharmD programs

to better prepare graduates for the expected challenges. Governmental regulations, such as those connected with the Omnibus Budget Reconciliation Act of 1990 (OBRA 90), pushed pharmacy in the direction of greater responsibility. OBRA 90 requires pharmacists to provide counseling to Medicaid patients and to participate in prospective and retrospective drug use review (DUR) programs. Eventually, states added rules calling for more pharmacy services. This new path to a greater professional role for pharmacists seemed assured.

As the 1990s moved ahead, it soon became clear that the supposed decade of pharmaceutical care was turning into a decade of confusion, conflict, and controversy. The Clinton Administration tackled the difficult task of reforming the complex American healthcare system. This effort failed, but it did inspire a raft of consolidations throughout the pharmaceutical enterprise, which resulted in a leaner and meaner industry. Third parties turned to the principles of managed care to cut costs. Important new classes of drugs appeared, which when combined with an aging population, led to a rapid rise in prescription volume. Prescribing further increased under the pressure of direct-to-consumer advertising, which was given relatively free rein by the late 1990s. The emergence of Internet pharmacies, building on the established mail-order business of earlier years, added to the turmoil of the pharmaceutical marketplace. Independently owned drugstores closed across the nation, replaced in many localities by pharmacies tucked inside mass merchandisers or grocery stores. As the decade ended with the distractions of the Y2K non-event, far more pharmacists found themselves acting as arbiters of managed care squabbles than as advanced care providers.

The promise of a new century

The American people met the twenty-first century with enthusiasm that turned to wariness and discouragement after the events of September 11, 2001. Pharmacy entered the new century with hope built upon the unifying nature of the single PharmD degree for new pharmacists. Various efforts to expand drug coverage for seniors under Medicare came to fruition in late 2003 when President George W. Bush signed the Medicare Modernization Act. For the first time Medication Therapy Management (MTM) services were included along with the new outpatient drug benefit under Medicare Part D. As defined by the leading pharmaceutical associations, MTM "is a distinct service or group of services that optimize therapeutic outcomes for individual patients." In contrast with the older, more generalized Pharmaceutical Care model, MTM services are geared toward individualized concrete plans that often focus on one or more disease states. In 2005, the Joint Commission of Pharmacy Practitioners (JCCP) adopted a vision statement for 2015: "Pharmacists will be the health professionals responsible for providing patient care that ensures optimal medication therapy outcomes." Convinced of the importance of obtaining optimal clinical pharmacy skills, pharmacy graduates in recent years have flocked to residency programs, a trend that reflects their desire to accept further professional responsibilities. The implications for pharmacy of The Patient Protection and Affordable Care Act signed by President Barack Obama in March 2010 are uncertain, however, because of unresolved legal and legislative challenges.

The future

It is too soon for historians to judge the long-term influence of the emerging practice paradigm of MTM. Two full generations of pharmacists have been educated and trained after the general adoption of the aims of clinical pharmacy. Present day-to-day practice reflects this important shift from the product orientation of previous decades to a practice concerned with patients receiving necessary drug information and professional guidance. In the midst of a harsh economic and political climate, only time will tell if the often divided and divisive pharmaceutical profession will unite and continue its progress toward greater societal responsibility for the ancient tool we call medicines.

History as a discipline

Like the other fields of pharmacy described in this textbook, the history of pharmacy is a distinct discipline that produces a body of research. The following bibliography and chronology, updated from the article by Glenn Sonnedecker,[1] is provided for those interested in pursuing some specific aspect of pharmaceutical history. Readers interested in learning more

about important figures in the history of American pharmacy should consult Osol & Hoover[2]. Additional guidance can be obtained from the American Institute of the History of Pharmacy, University of Wisconsin at Madison, 777 Highland Avenue, Madison, WI 53705. Links to useful websites pertinent to the field are found at http://www.aihp.org.

A chronology for pharmacists

The dating of events often involves uncertainties, approximations, and questions of meaning that are not apparent in a concise table such as that below. Particularly, dates before the eighteenth century often are unverifiable or estimated.

BC	
2000?	**Earliest formulary** known in history (Sumerian).
1500	**Ebers Papyrus**, Egyptian manuscript pertaining to pharmacy and therapy.
460	**Hippocrates**, famous Greek physician, is born.
350	**Diocles** writes an important treatise on materia medica.
372	**Theophrastus** (372–285), the "father of botany," is born.
AD	
50	**Dioscorides** writes an important book on materia medica.
130	**Galen**, a Roman physician who experimented with compounded drugs, is born.
303	**Cosmas and Damian**, patron saints of pharmacy and medicine, are martyred.
857	**Johann Mesue Senior** (777–857), Arabian physician, dies.
925	**Rhazes** (865–925), Persian physician, dies.
1035	**Avicenna** (980–1035), physician and philosopher, dies.
1178	**Pharmacists are mentioned in French records**.
1180	**Guild of Pepperers** is already active in London.
1225	**Apothecary shop** is established at Cologne.
1297	**Guild of Pharmacists** is organized in Bruges (Flanders).
1345	**Apothecary shops** have been established in London.
1348	**The Black Death** (bubonic plague) strikes Europe.
1480	**Poison law** is enacted by James I of Scotland.
1499	**Guild pharmacopoeia** is published in Florence, Italy.
1529	**Paracelsus** (1493–1541) publishes his first treatise.
1546	**The Nuremberg Pharmacopoeia** (Dispensatory of Valerius Cordus) is perhaps the first to become "official."
1589	**Galileo Galilei** demonstrates the law of falling bodies.
1604	**Louis Hébert** becomes first pharmacist to settle in North America.
1617	**Society of Apothecaries** in London is organized.
1618	**First London pharmacopoeia** is published.
1620	**Pilgrims** settle at Plymouth, Massachusetts.
1628	**William Harvey** publishes his book on the **circulation of the blood**.
1646	**William Davis** operates an apothecary shop, possibly one of the first in America (Boston).
1665	**Sir Isaac Newton** describes the law of gravitation.
1680	**Antonie van Leeuwenhoek** discovers **yeast** plants.
1703	**English apothecaries are authorized to prescribe as well as dispense**.
1715	**Bartram's Botanical Gardens** established at Philadelphia.
1718	**Geoffroy Étienne/Saint-Hilaire**, French pharmacist, establishes the first tabulation of relationships between chemical substances.
1736	**First law related to pharmacy** in America is enacted in Virginia.
1752	**First hospital pharmacy** in America is established at Pennsylvania Hospital in Philadelphia; Jonathan Roberts is the apothecary.
1762	**Antoine Baumé** publishes his *Élémens de pharmacie* in France.
1765	**John Morgan**, American medical education pioneer, advocates **prescription writing** in US.

1773	**Karl Wilhelm Scheele isolates oxygen** about 1773.
	Joseph Priestley independently isolates oxygen by 1774.
1774	**Scheele** discovers **chlorine**.
	National Association of Retail Druggists is founded in the US.
1776	**Declaration of Independence** is written, and the position of Apothecary General is created for the Continental Army.
	Christopher Marshall, famous American pharmacist, makes medicines for wounded soldiers.
1777	**Collége de Pharmacie** is established in Paris.
1783	**Pilâtre de Rozier**, a pharmacist, makes **first human flight** in a balloon accompanied by the Marquis d'Arlandes.
1785	**William Withering** publishes his treatise on **digitalis**.
	Thomas Fowler introduces **Fowler's Solution** (potassium arsenite solution).
1787	**Ergot** introduced in obstetrics by **Paullitzsky**.
1790	**First US patent law passed**. Elisha Perkins takes out first medical patent in 1796.
1793	**Yellow fever epidemic** strikes Philadelphia.
	Trommsdorff's *Journal der pharmacie* is founded, the first professional-scientific journal devoted to pharmacy.
1798	**Edward Jenner** publishes his work on **vaccination**.
1805	German pharmacist **Friedrich Sertürner** reports isolation of **morphine**.
1809	***Journal de pharmacie et de chimie*** founded; first published as *Bulletin de pharmacie*.
1811	**Bernard Courtois**, a French pharmacist, discovers **iodine**.
1818	French pharmacist-chemists **Joseph Caventou** and **Pierre Pelletier** isolate **strychnine**.
1820	**Pelletier** and **Caventou** isolate **quinine**.
	First edition of *United States Pharmacopoeia* is published.
1821	**Philadelphia College of Pharmacy** is founded as the first local association and school of pharmacy in the United States.
1823	**Massachusetts College of Pharmacy** founded.
1825	**First American professional journal of pharmacy published**, the *American Journal of Pharmacy*.
1826	**Antoine Balard**, French pharmacist, discovers **bromine**.
	Hennel synthesizes **ethyl alcohol**.
1828	**Friedrich Wöhler** synthesizes **urea**, thus bridging gulf between organic and inorganic chemistry.
1829	**New York College of Pharmacy** is founded.
1831	**Chloroform** is prepared independently by **Justus von Liebig** and by **Eugene Soubeiran**.
1832	**Pierre Robiquet**, French pharmacist, isolates **codeine**.
1834	**Friedlieb Ferdinand Runge**, German pharmacist, prepares **carbolic acid** and **aniline**.
1842	**Crawford Long** performs the first **operation using ether anesthesia**.
1843	**Oliver Wendell Holmes** points out that puerperal fever is contagious.
1848	**First American code of pharmaceutical ethics** prepared by Philadelphia College of Pharmacy.
	First drug import law enacted by Congress to curb adulterations.
1852	**American Pharmaceutical Association is** founded as the first national organization.
1859	**Charles Darwin** publishes his *Origin of Species*.
1865	**First international pharmaceutical conference** is held in Brunswick, Germany.
1868	**University of Michigan** opens pharmacy course that will have far-reaching influence in modernizing American pharmaceutical education.
1883	**First National Retail Druggists Association** founded.
1888	**First National Formulary** issued by American Pharmaceutical Association.
1890	**Emil von Behring** and **Shibasaburo Kitasato** introduce **serum therapy**.
1893	**Felix Hoffmann** and **Arthur Eichengrün** discover **aspirin**.
1895	**Wilhelm Roentgen** discovers **x-rays**.

1898	**Marie** and **Pierre Curie** discover **radium**.
1899	**Walter Reed** proves mosquitoes carry **yellow fever**.
1900	**American Association of Colleges of Pharmacy** is founded.
1902	**First International Pharmacopeial Conference** held at Brussels, Belgium.
	First American PhD supervised in pharmacy granted at University of Wisconsin.
1906	**Federal Food and Drugs Act** passed in the US.
1910	**Paul Ehrlich** and **Sahachiro Hata** introduce **ar sphenamine (also known as Salvarsan or "606") in widespread clinical trial for the treatment of syphilis**.
1912	**First** Assembly of **International Pharmaceutical Federation** at The Hague, Netherlands.
1922	**Sir Frederick Banting** and **Charles Best** isolate **insulin**.
1928	**Sir Alexander Fleming** discovers **penicillin**, the first antibiotic.
1935	**Gerhard Domagk** introduces **prontosil**, the first sulfa drug.
1937	***American Journal of Pharmaceutical Education*** is founded, the first periodical devoted to **pharmaceutical education**.
1938	**League of Nations Commission on International Pharmacopeial Standards** holds conferences.
1938	Important revision of **Federal Pure Food and Drugs Act (US)**.
1940	**Howard Florey** and **Ernst Chain** hold the first **clinical trials of penicillin**.
1942	**American Society of Hospital Pharmacists** is founded.
1944	Antibiotic activity of **streptomycin** is announced.
1945	**Atomic energy** released for use in warfare and medicine.
1947	**Medical Service Corps** created in US Army, with pharmacy represented by special group of commissioned officers.
1948	**First Pan-American Congress of Pharmacy and Biochemistry**.
1949	**Cortisone** and **ACTH** are introduced for rheumatic arthritis.
	Influence for change initiated by analysis and suggested reforms from **Pharmaceutical Survey** (US).
1951	**First International Pharmacopoeia** of the World Health Organization.
1952	**Chlorpromazine** is introduced into psychiatry, thus opening the field of psychopharmacology.
1955	**Salk poliomyelitis vaccine** is released for general use.
1959	**Synthetic modifications of natural penicillin** introduced.
	American Society of Pharmacognosy founded.
1962	Important amendments of the **US Food, Drug, and Cosmetic Act**.
1969	**American Society of Consultant Pharmacists** (ASCP) established.
1973	US Supreme Court decision (No 72–1176) holds that states may require that licensed pharmacists have **ownership-control of pharmacies**.
	Congress enacts **Health Maintenance Organization Act**.
1975	Official **drug standardization program** is unified by US Pharmacopeia absorbing National Formulary. Report by Study Commission on Pharmacy (AACP) gives impetus to trend toward drug information and **counseling role** of pharmacists.
1977	Clinical trials of **adenine arabinoside** against herpes raise prospect of **controlling viral diseases**.
1979	**American College of Clinical Pharmacy** is founded.
1982	**Specialty certification** begins in American pharmacy with the board certification of 63 pharmacists in the field of nuclear pharmacy.
1984	Drug Price Competition and Patent Term Restoration Act **growth of generics**.
1986	**American Association of Pharmaceutical Scientists** is founded.

1989	**American Council on Pharmaceutical Education** (ACPE) announces intent to develop accreditation standards for **Doctor of Pharmacy** programs only.
1990	Omnibus Budget Reconcilation Act (OBRA) requires that **pharmacists counsel Medicaid patients** (effective 1993).
1995	**Pharmacy Technician Certification Board** formed.
1996	National Association of Retail Druggists (f. 1898) changes name to **National Community Pharmacists Association**.
2003	After 150 years, the APhA changes its name to the **American Pharmacists Association**.
2006	Outpatient prescription drug **coverage** becomes part of Medicare.

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3

The new drug approval process and clinical trial design

The research and development efforts needed to ensure the safety and efficacy of new drugs are complex, time consuming, and financially risky. Thousands of compounds undergo extensive testing for every one new chemical that receives marketing approval.[1] Research and development costs for each new drug product are estimated at approximately $1 billion.[2] It has been reported that only 30% of drugs that reach the marketplace generate sufficient revenue to recover the average cost of development.[3] This chapter discusses the stages of new drug development and approval in the United States with a focus on clinical trial design and methodology. Readers are encouraged to refer to specific Food and Drug Administration (FDA) guidance documents for more detailed information (http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm). Note that other countries have similar regulatory authorities that oversee drug approvals.

The Food and Drug Administration

The Food and Drug Administration (FDA) oversees the new drug approval process in the United States. The initial legislation, the Pure Food and Drug Act of 1906, was passed in response to Upton Sinclair's exposé of the meat packing industry, The Jungle, which described deplorable practices resulting in contamination. Over time, the authority of the agency expanded, but it remained relatively powerless to effectively assure the safety and efficacy of medicines. In 1937, a sulfanilamide product containing diethylene glycol as a solvent to enhance the aqueous solubility of the drug was developed. Diethylene glycol, however, is a highly toxic agent used in antifreeze solutions, and numerous deaths resulted from its ingestion. Based on these tragic events, Congress passed the Food, Drug, and Cosmetic Act of 1938, which increased the regulatory authority of the FDA to oversee the development of new drug products.[4] The Act required disclosure of the ingredients and formulation, assay methods, manufacturing processes, and all animal and human testing to the FDA prior to the distribution of drug products.

Although the Act of 1938 required new drug products to be safe, efficacy standards were not established until another tragedy occurred in the early 1960s. Thalidomide, a synthetic sedative/tranquilizer, had been sold in Europe without a prescription and was viewed as a possible alternative to the more

toxic barbiturates.[5] Prior to FDA approval of thalidomide, several incidences of toxicity in Europe were reported. Severe birth defects were noted when the drug was administered to pregnant women, the most common being phocomelia or arrested limb development. These events brought about the Kefauver-Harris Amendments of 1962, which strengthened existing laws and emphasized the need for the safety of approved drugs.[6] These Amendments required manufacturers to establish both safety and efficacy of new drug products prior to approval and required investigators to file Investigational New Drug Applications (INDs) prior to testing drugs in humans. As a side note, thalidomide is currently approved in the United States for the treatment and prevention of painful skin lesions associated with erythema nodosum leprosum and multiple myeloma. Other potential uses of this drug under investigation include several types of cancer, Crohn's disease, and autoimmune deficiency-associated diseases.[5,7]

The role of the FDA is to promote and protect the health of Americans. A multidisciplinary staff, consisting of pharmacists, physicians, pharmacologists, chemists, statisticians, attorneys, and other scientists, as well as administrative personnel, is employed at the FDA to achieve this goal. The FDA consists of several Centers, each designated with specific responsibilities. The Center for Food Safety and Applied Nutrition oversees food and cosmetic products. The Center for Veterinary Medicine is responsible for animal feed and drugs. The Center for Devices and Radiological Health covers the safety and efficacy of medical devices. This Center also oversees radiation-emitting devices, such as lasers, x-ray systems, microwave ovens, and cellular telephones. The Center for Biologics Evaluation and Research (CBER) supervises biologics. Finally, the Center for Drug Evaluation and Research (CDER) is responsible for drugs and drug products. In addition to reviewing the safety and efficacy of all prescription and over-the-counter drug products prior to marketing, the CDER is responsible for monitoring drug safety after initial market approval and has the authority to withdraw drugs posing significant health risks from the market. The CDER provides healthcare professionals and consumers with drug-related information and screens television, radio, and print ads for truthfulness and balance.

Other countries have similar regulatory authorities that oversee the approval of new drug products. For example, the European Medicines Agency (EMA) regulates most European markets. The pharmaceutical industry and regulatory authorities, including the FDA, have been working closely with the International Conference on Harmonization (ICH) to develop standardized regulatory processes for the major markets and allow results of international clinical trials to be used to support approvals across countries.

Overview of the US drug approval process

As mentioned previously, drug discovery and development is a complex and expensive endeavor. The next several sections of this chapter discuss the new drug development and approval processes in the United States. Although focused specifically on the CDER and new drugs/drug products, similar requirements exist for biologics. Medical devices are approved in a different manner, depending on how they are used and their invasiveness on human functions. Devices require an approved Investigational Device Exemption (IDE) prior to beginning clinical studies. The drug approval process is divided into two sections: (1) preclinical testing (lead compound selection and animal testing of new chemicals) and (2) clinical testing (administration of new chemicals to humans). Figure 3.1 shows a schematic of these steps.

Drug discovery and lead compound selection

Pharmaceutical companies begin the discovery process by targeting a broad disease category (for example, cancer or cardiovascular disease) or a specific disease state (for example, breast cancer or hypertension). A chemical with potential therapeutic benefit(s), known as a lead compound, must first be identified, and researchers use various high-throughput assay techniques to rapidly screen large numbers of chemicals for biological activity.

Random screening, as the name implies, requires biological testing of a large variety of diverse compounds from existing chemical libraries. Although less up-front financial investment is needed, thousands of

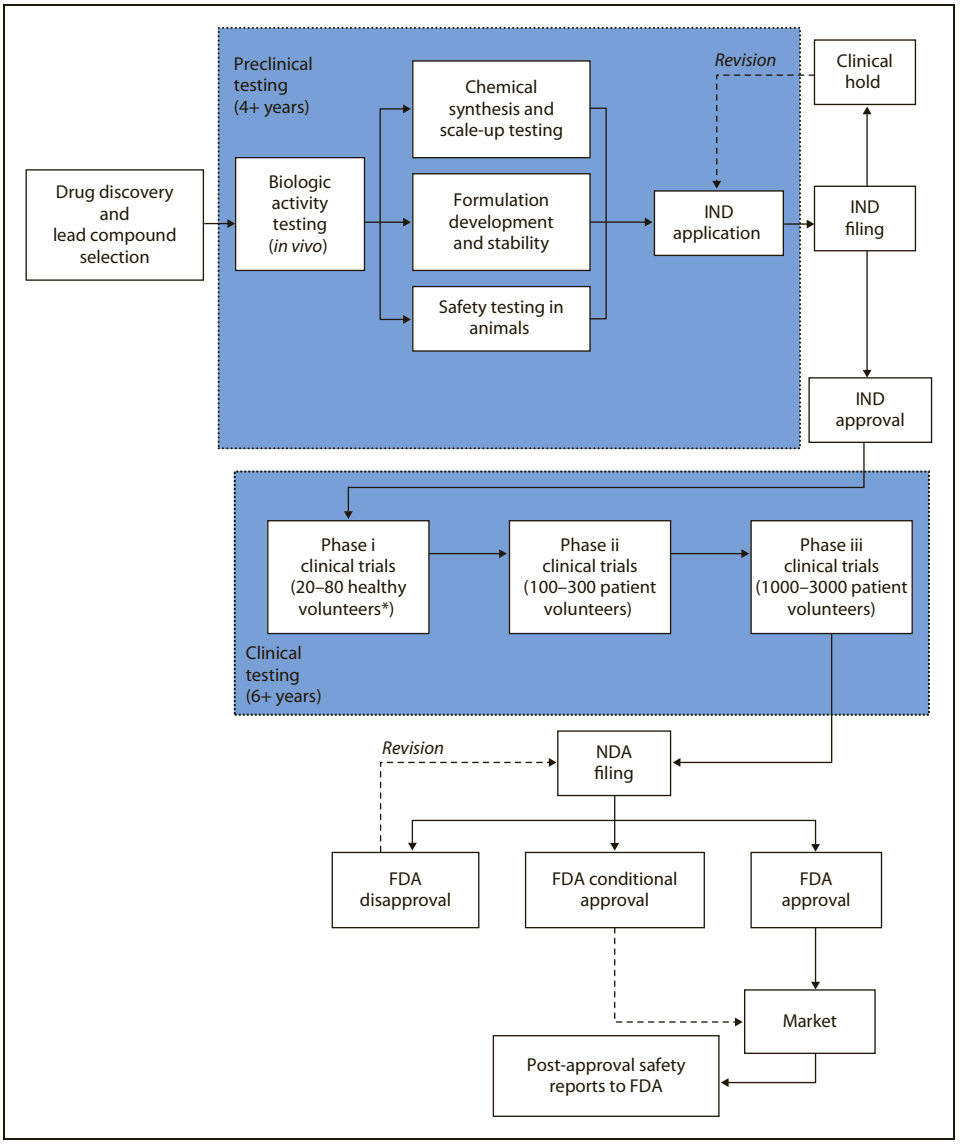

Figure 3.1 Schematic of the new drug approval process in the United States. For life-threatening illnesses such as cancer, patients enrolled in Phase I studies may suffer from the disease.

compounds may be screened and tested before one agent with significant biochemical activity is identified. A more mechanism-based drug design is targeted synthesis, where researchers focus on one step in a disease process as the target for drug intervention. Although an extensive knowledge of the disease state is required, this more directed approach increases the likelihood of successfully identifying a lead compound. In combinatorial chemistry, one compound is used as a base chemical and various functional groups are randomly added to enhance biological activity. This technique is a more expensive, more complex method of identifying potential lead agents. Another method to enhance biological activity is drug modeling, where computers are used to manipulate virtual structures and calculate protein binding capabilities. Although initial costs are significant, drug modeling techniques show a great deal of promise for future drug discovery as more research is conducted to identify biochemical pathways. Generally, these discovery

techniques are used in combination to identify lead compounds.[8–10]

Preclinical testing

A multidisciplinary team of researchers works to determine many of the lead compound's critical properties. This team might continue to work with the compound throughout the entire development process or the development responsibilities might be transferred to another group of scientists during the clinical testing phase. Preclinical testing includes:

- discovery testing to ensure biological activity *in vivo*
- chemical synthesis and scale-up to ensure adequate quantities of high purity can be made
- formulation development and stability testing to characterize various chemical properties, develop the initial drug delivery system, and determine the stability of the compound
- animal safety testing to ensure limited toxicities of the lead agent.

At this stage of the development process, good laboratory practices (GLPs) are followed. These regulations, in the Code of Federal Regulations (CFR) 21 Part 58, provide standards for the design and conduct of preclinical studies. Qualifications of personnel and requirements for standard operating procedures are specified.

During discovery testing, the specifics of the compound's properties, such as the mechanism of action in animal models, compound specificity, duration of action, and structure–activity relationships, are determined. Adequate quantities of the new chemical compound must be produced at a high level of purity. Impurities present at concentrations greater than 0.1% must be characterized and tested for toxicity. The physicochemical properties of the active compound are determined, and development of the drug delivery system to be used in human testing begins. Animal testing provides initial data regarding the absorption, distribution, metabolism, and excretion (ADME) in a living system. Possible side effects and toxicities are noted. Toxicity studies of at least the same duration as the proposed human testing and a minimum of two weeks must be completed. Active and inactive metabolites must be characterized. Often, the most appropriate animal model to predict human response is not known, thus toxicity studies are conducted in at least two animal species, one rodent and one nonrodent, to obtain a comprehensive view of the potential toxicity. Early ADME or toxicity problems may be corrected by slight modifications in the chemical structure of the new entity.

Animals should be given the new drug product by the same route intended for humans. Certain dosage forms, such as aerosol, nasal, or buccal delivery systems, might be difficult to administer to animals. In these circumstances, alternative drug delivery routes may be used, and the selected route of administration should ensure sufficient exposure to the new chemical entity. During animal safety testing, dosing studies are conducted, and the highest no-effect dose is determined. In addition to dose, plasma concentrations of the drug are followed, and noted toxicities are correlated to dose and/or plasma concentration.

Generally, once discovery testing shows therapeutic promise, the chemical synthesis, formulation development, and animal safety testing occur concurrently (see Figure 3.1). Although resources may be wasted on earlier failures, successful candidates will be ready for human testing more quickly. The administration of drugs in humans at the earliest time possible ultimately saves valuable resources, as highly toxic compounds can be eliminated and alternative lead compounds can be developed.

Additional preclinical studies may be conducted during clinical testing to support larger trials and, eventually, the marketing of the drug product. Formulation development continues throughout the process, and the data gained from both animal and human testing allow for optimization of the drug delivery system. It is imperative to identify and resolve formulation problems early in the development process, as unresolved problems will surely re-emerge later, costing the company both time and money as clinical testing is delayed. More chronic animal exposure experiments are conducted to support further clinical testing.

Pre-IND meetings

Pre-IND meetings may be held prior to submission of an Investigational New Drug application (IND) and at the request of the sponsor, during these early stages of development to discuss testing plans and data requirements. These meetings are especially useful

when a drug has been developed overseas and a great deal of preclinical and clinical data is readily available. During pre-IND meetings, the sponsor and FDA should agree on the acceptable phase of the initial clinical investigation. Clinical data from other countries, if obtained following ICH requirements, may eliminate the need for Phase I human safety testing in the United States. FDA guidance documents provide an overview of procedures for requesting formal meetings. These meetings are not intended to replace informal discussions with the FDA.

Investigational New Drug Application (IND)

An IND must be filed with the FDA and approved prior to administering new drug products to humans. The guidelines for preapproval of all clinical testing are specified in 21 CFR Part 312. FDA guidances for INDs can be found on its website. The name and chemical description of the active components, a list of active and inactive components, and the manufacturers of these components must be provided. The method of preparation and the dosage form to be administered are required. The IND includes all preclinical animal data and the names and locations of the investigators performing the planned clinical trials. Data from clinical trials conducted in other countries should also be included. A major component of the IND is the study protocol(s) implemented to evaluate the drug. The protocol must address all aspects of the trial, including study procedures, informed consent, data collection, and analysis, as well as mechanisms for subject selection, follow-up, and safety monitoring to protect the patient. Upon receipt, an IND number is assigned by the FDA, which is used to track all subsequent communication between the study sponsor and the FDA. The IND is assigned to the appropriate division of the Center for Drug Evaluation and Research, and the contents are thoroughly reviewed. The FDA has 30 days from receipt of the IND to decide if the proposed clinical trial should proceed. Rather than "approving" an IND, the FDA must provide notification if the trial is placed on "clinical hold" pending clarifications or changes to the study protocol. If no further communication is received from the FDA, the sponsor is allowed to begin the study by enrolling patients. Each facility's Institutional Review Board (IRB) must approve the protocol(s) conducted under the IND. A subsequent section of this chapter describes this process more fully.

Although the trial may proceed, reviewers at the FDA may place a "clinical hold" on the trial at any time. A "clinical hold" prevents human testing under the IND until FDA concerns have been adequately addressed. Reasons for placing an IND under a clinical hold include unreasonable or significant risk of illness or injury to trial subjects, insufficient information or procedures to assess and minimize patient risks, inadequate qualifications of the clinical investigators, or a misleading, erroneous, or incomplete Investigator's Brochure (a document containing all relevant information about the drug). Revisions to clinical protocols, as well as new protocols or substudies, are submitted to the FDA as amendments to the IND. Progress reports regarding the trial must also be provided annually. The contents of the annual report are specified in the regulations. Furthermore, the sponsor must report any unexpected, serious adverse drug events that occur during the trial to the FDA and the IRB within specified time periods.

Not all clinical trials require INDs. A sponsor proposing a trial with a commercially available, FDA-approved drug product is exempt, if the trial (1) is not intended to be submitted to the FDA to support labeling changes or a new indication; (2) is not intended to support a major change in advertising; and (3) does not involve a route of administration, dose, or patient population that significantly increases the risk of the drug. An IND is not required, if the trial is exempt according to the above criteria, regardless whether a placebo (inert or inactive treatment) is employed as a control group. Independent investigators, rather than pharmaceutical companies, often conduct these types of clinical trials.

Clinical investigations

Clinical investigations involve the administration of a drug product to humans. This segment of the drug development process requires substantial financial and time commitments.[11] Figure 3.2 shows the considerable increase in development costs associated with the initiation of clinical trials. Human testing is divided into four phases, each phase having specific objectives. The following sections discuss the various phases of clinical testing.

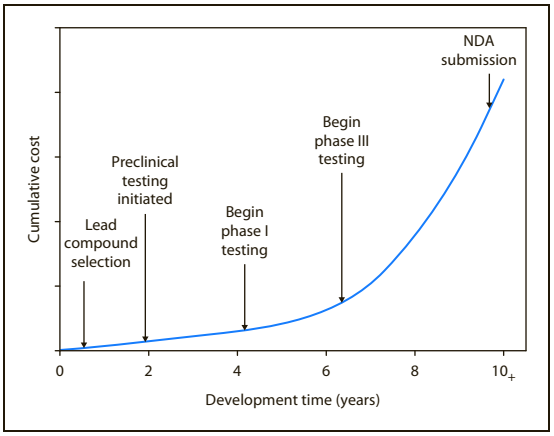

Figure 3.2 Relationship between the time devoted to new drug development and dollars invested.[6]

Phase I clinical trials

The first series of experiments performed in humans occurs during Phase I clinical testing. A small number of healthy volunteers (approximately 20–80 people) are exposed to the new drug product in closely monitored trials primarily to assess the compound's safety. For the investigation of drugs to treat life-threatening diseases, such as cancer or Acquired Immune Deficiency Syndrome (AIDS), patients afflicted with the disease may be enrolled.[12] In Phase I trials, the starting dose is low, often one-tenth of the highest no-effect dose in the animal models. After the initial treatment is completed, additional subjects may be recruited, and higher doses may be administered to determine the maximum dose tolerated without significant side effects. During this phase of testing, preliminary absorption, distribution, metabolism, and excretion data of the parent drug and all metabolites should be evaluated. Data regarding pharmacokinetic and pharmacological effects are used in the design of future Phase II trials.

Phase II clinical trials

Phase II clinical testing shifts the focus of the trials from safety to efficacy. In comparison to Phase I trials, a larger number of people (100–300 patients) are enrolled, and the majority of these participants suffer from the target illness. Side effects from the new drug product are also investigated. These clinical trials are closely monitored and well-controlled (see Clinical Trial Planning and Design section). Failure during Phase II testing is common, as the human body is more complex than a test tube or animal testing. As with any study conducted in humans, clinical protocols for Phase II trials must be sent to the FDA prior to beginning the trial. They may be included as amendments to the IND approved for a Phase I study.

Phase III clinical trials

At the end of Phase II testing, sponsors are encouraged to meet with the FDA personnel who are assigned to the review division for the therapeutic area (for example, Division of Psychiatry Products, Division of Neurology Products, Cardiovascular Renal Products, etc.). These meetings involve review of the acceptability of past trials, the design of future trials, and the general drug development plan. Scientists at the FDA carefully review preclinical and clinical data in evaluating proposed Phase III protocols. Specific areas of the proposed Phase III trials that are scrutinized include the study objectives, informed consent, inclusion/exclusion criteria, dosing regimens, methods and timing of data collection, duration of treatment and follow-up assessment, blinding of the drug products and plans for maintaining the blind, plans to assess compliance with the protocol, identification of primary outcome variables, and methods to account for dropouts. Addressing these key areas of proposed Phase III protocols is expected to limit the bias of trial results. An overall goal of the meeting is a good-faith agreement between the sponsor and the FDA regarding data required for submission of a New Drug Application (NDA), the final regulatory hurdle before the drug product can be marketed.

Phase III clinical trials are the longest and most comprehensive evaluation of new compounds. Significantly larger numbers of patients (1000–3000) who are afflicted with the target illness are tested. Patients are often recruited, tested, and monitored by several major hospitals and clinics throughout the country. Phase III trials may also be conducted internationally. In addition to determining efficacy, these trials monitor adverse reactions. The new drug may be compared to existing therapeutic regimens (that is, comparator products) or a placebo. The final market formulation for the drug product should be optimized prior to the start of Phase III trials. Compounds that successfully complete Phase III testing have a 95% chance of being approved by the FDA.[1]

Prior to the completion of Phase III testing and NDA submission, sponsors are encouraged to meet with the appropriate review division of the FDA again. These meetings help establish the format of the submission, so that the review proceeds smoothly and to determine whether additional animal or human trials are necessary. The meeting should be held sufficiently in advance of the tentative NDA filing date to allow ample time to incorporate recommended changes or perform additional trials.

Phase IV clinical testing

Phase IV trials are post-approval clinical trials designed for one of several reasons. The FDA may mandate Phase IV testing in a specific patient population to further assess efficacy and side effects. Companies may also choose to conduct additional clinical tests to more fully understand how their product compares to other commercially available therapeutic regimens. Since duration of exposure and number of patients treated are often limited during Phase III testing, Phase IV trials may be required to assess long-term safety of the drug.

The New Drug Application (NDA)

Once the Phase III trials have been completed, all preclinical and clinical data are compiled into an NDA, which is submitted to the FDA for review. The FDA also reviews the product's labeling and package insert. The NDA approval process is the last hurdle prior to marketing. An NDA document typically consists of hundreds of thousands of pages and contains highly detailed information. Regulation guidelines, including the information required for an NDA, are provided in 21 CFR Part 314 Subpart B.

Primary items include:

1. safety and efficacy of the drug treatment(s)
2. components of drug product(s)
3. description of methods and controls used in manufacturing the active ingredient and drug delivery system and its packaging
4. proposed labeling.

According to the Center for Drug Evaluation and Research, the time for a standard NDA review has been reduced from a median of 22 months in 1992 to approximately 13 months in 2008 (6 months for priority review).[13] The faster review times have been attributed to the Prescription Drug User Fee Act (PDUFA) of 1992.[14]

When an NDA is submitted, relevant sections of the document are distributed to the appropriate reviewers and evaluated first for completeness. If the document is sufficiently complete, the NDA is accepted for review and assigned a priority status. NDAs for new chemical entities are classified as either "P" for priority review or "S" for standard review. A "P" rating is given to new drug products with improved therapeutic effects, safety, and/or side effects in comparison to currently marketed drugs. NDAs assigned a "P" rating are expected to be reviewed in a more timely manner than those assigned an "S" rating. If the NDA is deemed too incomplete to review, it is not filed. The decision to accept the NDA is made within 60 days of the date of submission.

Once the NDA is accepted, detailed evaluation continues, and the FDA has 180 days from submission to complete the review. Each reviewer submits written comments of his or her assigned section and makes a recommendation. The NDA may also be presented to an Advisory Committee for comment. All documents are then compiled and ultimately submitted to the Director of the Office of Drug Evaluation. The FDA may approve the product for market, approve with specific conditions attached (Conditional Approval), or disapprove the drug product. Primary reasons for disapproval include lack of demonstrated safety and efficacy, issues with the manufacturing/processing procedures, or false/misleading labeling. If not approved, a letter is sent to the sponsor detailing deficiencies in the application. If the NDA is approved, an approval letter, along with a draft of the product labeling, is sent to the sponsor. The label is a combination of the draft submitted by the sponsor and revisions provided by the reviewing section of the FDA. Standardized labeling requirements are provided in 21 CFR Part 201.57.

Prior to NDA approval, the FDA conducts an inspection of the sponsor's facilities to ensure compliance with current Good Manufacturing Practices (cGMPs) as set forth in 21 CRF Parts 210 and 211. These are industry standards to ensure consistent

quality of manufactured drug products. Preapproval inspections are conducted within 45 days of the NDA acceptance. If deficiencies are noted, a letter (FDA Form 483) is sent to the sponsor delineating the problems. Once the deficiencies are resolved, the company must provide written certification, and the FDA will then clear the application within 45 days, if the corrections are adequate. As this step is critical in the approval process, companies often hold mock preapproval audits.

The NDA approval process is complicated and challenging, and may involve several revisions. In 2012, 75 to 80% of reviews were approved. (http://www.pharmalot.com/2012/06/fda-approvals-are-back-on-track/).

In response to the FDA Modernization Act of November 1997, the National Institutes of Health (NIH), in collaboration with the FDA, established the Clinical Trials Website (http://www.clinicaltrials.gov). This website is a searchable database that provides information on clinical trials, including the purpose of the study, recruiting status, criteria for participation, study drug(s), and the location of the trials. Investigators are required by law to provide results on the website once the trial is completed. This process was established to ensure that the results of nonsignificant or negative studies were made public. Most medical journals require proof of registry at http://www.clinicaltrials.gov prior to publication of clinical trial results.

The Abbreviated New Drug Application (ANDA)

In addition to approving new drug products for the United States, the FDA is charged with the approval of generic drug products (21 CFR Part 314). This work is accomplished through the Center for Drug Evaluation and Research's Office of Generic Drugs. A generic drug product must be bioequivalent in comparison to an approved proprietary drug product. The review process for generic drugs is specifically focused on bioequivalence testing rather than safety and efficacy. Thus, conventional clinical testing is not required. To be considered bioequivalent, both the rate and extent of drug absorption must be within established parameters in comparison to the reference drug. *In vivo* (within a biological system) bioequivalence testing is required for most dosage forms. Applicants may request a waiver from performing *in vivo* bioequivalence studies for certain drug products where bioavailability may be established by submitting (1) a formulation comparison for products whose bioavailability is evident (that is, oral solutions, injectables) or (2) comparative dissolution. The FDA provides guidance on establishing bioequivalence. If any portion of the application is not acceptable, a letter of deficiency that details the insufficiencies and requests additional information and data to resolve these concerns is issued. A tentative approval letter delaying the marketing of the generic product may be issued, if approval of the generic occurs prior to the expiration date of patents or exclusivities of the reference drug product.

Rapid access to new drug products

As a result of the demand for more rapid access to new drug products, the FDA has written several regulations and policies specifically designed for drugs intended to treat severely debilitating or life-threatening illnesses. Subpart E (21 CFR 312.80-88) regulations expedite the development and approval process. For example, treatment INDs (21 CFR 312.34) are intended to make drugs relatively far along in the development process available to seriously ill patients and are typically made available during Phase III clinical trials.

Accelerated approval is a mechanism whereby products are approved for marketing based on limited data and exposure of small numbers of patients to the product. Approvals may be granted when studies have been performed using surrogate endpoints, such as laboratory finding or physical signs that may not directly measure patient response yet are considered likely to predict therapeutic benefit or delays in disease progression rather than ultimate endpoints, such as mortality. The process is limited to life-threatening indications, such as HIV and cancer. When a drug is approved via accelerated approval, the FDA requires specific post-approval studies be performed within a predetermined amount of time. However, often, these studies are difficult to perform, because patients may not be willing to participate in trials in which the new treatment may not be given. Thus, completion of these post-approval commitments is often delayed.[15] For example, from December 1992 to July 2010, the

FDA approved 47 new oncology indications for 35 drugs, but only 26 were converted to regular approval, within a median of 3.9 years. Delays in completing post-marketing studies have been as much as 10.5 years.[15] Lack of completion of confirmatory trials was cited as the reason for not moving to regular approval among 14 of the 21 indications. Furthermore, as with other FDA approved products, the use of accelerated approval products often extends beyond the approved indications, because prescribers are allowed to utilize them in off-label settings.

Orphan drug approval

Orphan drugs are drugs used to treat rare diseases or conditions that affect less than 200,000 people in the United States. Orphan drugs go through the same FDA review process previously described. However, the review is expedited, as the majority of orphan drugs are used in the treatment of serious or life-threatening disease. The process by which a company can file an application for orphan drug designation is described in 21 CFR Section 316.20. Due to substantial drug development costs, orphan drugs provide limited opportunities for companies to recoup their investments. The United States federal government, through the Orphan Drug Act of 1983, established tax incentives, reduced user fees, and created exclusivity agreements to encourage research in the orphan diseases.[16] Grants are also available through the FDA to support clinical research, and annual requests for applications may be found in the Federal Register. Thirty nine new products (new chemical entities and new biologic license applications) for orphan diseases were approved in 2012.[17]

Over-the-counter drug approval

The approval process for over-the-counter (OTC) drugs is considerably different from prescription medications, and their review is not held to the same standards as an NDA. The first phase of the approval process involves an advisory panel consisting of a multidisciplinary group of scientists that review data provided by manufacturers and other previously published research. The findings are submitted to the FDA, and these reports are subsequently summarized in the Federal Register. Interested parties are given an opportunity to comment. Next, the FDA reviews all statements and publishes a tentative final monograph. The FDA also publishes the nature of the comments received and provides further opportunity for feedback. Then, the final monograph is published in the Federal Register and goes into effect one year after publication. The monographs establish conditions under which OTC drugs are recognized as safe and effective and are not misbranded. By following a monograph, a company can then market an OTC drug without additional FDA approval. For any unsubstantiated claims that a company wishes to make (that is, claims not approved in the monograph), data must be presented to the FDA to justify revision of the monograph or the sponsor may submit a NDA.

Post-approval activities

Safety monitoring

After an NDA has been granted and marketing is initiated, drug safety is still monitored. Sponsors of the NDA must periodically submit reports of adverse events. For newly approved drugs, these reports are filed quarterly for the first three years, then annually thereafter. For adverse events that are considered serious and unexpected (that is, fatal or life-threatening, permanently disabling, or requiring or prolonging hospitalization), the sponsor must provide a report to the FDA as soon as possible (a written report within 15 days of receipt of the information and a telephone or facsimile report within 7 calendar days). The FDA's MedWatch program (see http://www.fda.gov/Safety/MedWatch/default.htm) encourages healthcare providers and patients to directly report serious adverse reactions to drugs to the FDA. The program also provides alerts to practitioners regarding actions and recommendations by the FDA. Serious adverse events may require minor labeling changes or the addition of warning or precaution statements. If serious safety concerns arise, the FDA may withdraw approval of the NDA. Another alternative is the addition of a "Boxed Warning" in the product label. Boxed warnings are usually accompanied by a "Dear Health Professional" letter that is sent directly to licensed health providers to increase awareness of the potential problem. The boxed warnings may specify a newly identified risk or provide additional guidelines for use of the products in certain

patient groups. Often, an FDA Advisory Committee reviews the NDA in light of the new data prior to an official NDA withdrawal. In some instances, manufacturers have withdrawn drug products prior to FDA action.[18]

For certain medications that pose a serious and significant public health concern, the FDA requires the distribution of approved patient medication information. This Medication Guide is intended to ensure patients' safe and effective use of the drug products. The FDA Amendments Act of 2007 further requires a risk evaluation and mitigation strategy (REMS) from manufacturers to ensure that the benefits of a drug or biological product outweigh its risks. A draft guidance on the subject of REMS and Medication Guides was recently issued by the FDA and can be found on its website, along with a list of products subject to a risk evaluation and mitigation strategy.

Changes to an approved product

Any change made to an FDA-approved drug product, including component or composition, chemical synthesis, analytical methods, manufacturing site, manufacturing process, batch size, or labeling, must be submitted to the FDA. Some of the so-called scale-up and post-approval changes (SUPAC) require FDA approval prior to the implementation of the change. Depending on the type of change made and the impact the change may have on the quality of the drug product, notification to the FDA may be provided through annual reports or supplemental new drug applications (SNDA).

Clinical trial planning and design

Once preclinical testing has been completed, the company will determine whether to pursue further development of the drug, often based on the attractiveness and competitiveness of the pharmaceutical.[19] The pharmacological profile must be such that the product be equal to or better than existing competitors regarding therapeutic effect. The drug should address an unmet medical need or improve therapy in a population of individuals. The incidence of morbidity and mortality associated with the illness impacts medical need. The market potential must be sufficient to sustain profitability, and risk factors for drug development are assessed. Potential risk is impacted by the pharmacological profile, specifically the efficacy and toxicity of the drug. The potential expenses associated with activities required to continue development of the drug are considered, and success in the marketplace is estimated. Success is determined by the number of competitors, regardless whether the drug is the first in its class, and the potential for patients to change from other competing products. Once the pharmaceutical company determines the product has good potential for success, clinical trials are planned and conducted to move the product forward. The remaining sections of this chapter discuss the clinical trial design and planning process for pharmaceutical development and subsequent therapeutic research of marketed products.

Selecting trial objectives

Trial objectives vary depending upon the phase of the trial. Objectives for Phase I trials are limited to determining toxicity at a range of dosages. Phase I trials of treatments for terminal illnesses, such as cancer chemotherapy or human immunodeficiency virus (HIV), may also involve efficacy assessment. Objectives of Phase II and III trials are usually based upon clinical efficacy of the product in increasingly large samples of patients, respectively. Phase IV trials assess efficacy and side effects in specific patient populations.

A statement of trial objectives should include, at minimum, the approach of the trial (for example, to compare, assess, evaluate), the specific disease, the types of patients, drug therapy(ies) and dosages being studied, the purpose (for example, safety, efficacy, pharmacokinetic properties), and the clinical endpoints to be measured (for example, biologic measure, rate of cure, cost effectiveness).[20] Clinical trial objectives drive the entire project, from determination of sample size, to recruitment, to measurement of effects of the drug. They also determine feasibility of the trial, because trial duration and costs are directly impacted by the objective under consideration. Objectives involving ultimate outcomes, such as mortality or hospitalizations, can require durations of several years, as well as large sample sizes and multiple trial sites. Trial objectives limited to pharmacokinetic or clinical measurements may be conducted over a shorter time period, at a single site,

and with a small number of patients. Broader objectives have more generalizability and, thus, greater clinical implications.

Often, several trial objectives are of interest. When this is the case, the most crucial clinical question becomes the primary objective, and the others become secondary objectives. Selecting the primary objective is important, because sample size and data analyses techniques are dependent upon it. Although secondary objectives should be assessed in regards to sample size, it is understood that sample size may be inadequate to address all of them. Data collection procedures and statistical analyses are established from the trial objectives during planning.

Occasionally, results indicate no significant difference in the primary objective, yet the secondary objectives are significant. An example is the DIG trial,[21] where no significant differences in the primary objective of all-cause mortality were found between the digoxin versus placebo treatments, but there were significant differences in rates and days of hospitalization and quality of life. Thus, secondary objectives can be very important and should be well-described prior to the trial being conducted.

Trial designs

Various designs are used in clinical trials, and the most suitable may be related to the testing phase of the research trial. During Phase I trials, all patients receive the drug, thus an unblinded, open label trial is suitable. In Phase II through III trials, clinical efficacy trial objectives usually dictate that the drug be compared to placebo or an alternative therapy. Usually, patients receive one of the treatments during the entire course of the trial. This is referred to as a parallel design. Depending on the objectives of the trial, the treatments may vary by drug, combinations of drug therapy, or dosage levels. In some parallel trials, the same patients may receive various dosages of a drug therapy over time. A factorial design is a type of parallel design used to compare different types and combinations of drug therapy. It allows comparisons between single drug therapies and the combination of the two drugs. Factorial designs answer several clinical questions with one trial but are complex and must include sufficient sample sizes to detect differences between all treatment options. An example is the Veterans Affairs Cooperative Studies Program (CSP) trial of terazosin, an alpha blocker, and finasteride, an antiandrogen, for benign prostatic hypertrophy.[22] The research question included comparisons between each drug and each drug versus placebo, plus the combination of both drugs versus the other three therapies.

Another type of trial is the crossover design. Crossover designs allow patients to receive more than one drug treatment or dosage level during the course of the trial. The assumption with a crossover design is that the drug therapy does not have a carryover effect between the different treatment periods. Usually, there is a "washout" period between drug treatment periods in which patients receive a placebo or no medication. The length of time of the "washout" period is dependent on the duration of action and rate of elimination of the trial drug(s). A key issue addressed in crossover designs is whether the washout period is sufficient to eliminate potential carryover effects of the drug(s). If a drug may have long-term effects after discontinuation, the crossover design is inappropriate. In crossover studies, the type or dosage of therapy may be randomly assigned to allow detection of crossover effects (see Table 3.1). During the washout period, trial data and clinical measures are collected to assess the impact of the previous treatments. These measures are considered baseline data for subsequent treatments. Crossover designs are efficient in regards to numbers of patients required to collect a great deal of scientific data. Repeated measures statistical analyses are used to account for the potential impact of collecting data in the same patients over time and different treatments.

In post-marketing surveillance (Phase IV) trials, nonexperimental (observational) designs are used. These include epidemiologic designs, such as case–control or cohort studies, in which drug therapy is not assigned by the researcher.[23]

Controlling for bias

A critical component to minimize bias in a clinical trial is control of the intervention studied. Control occurs primarily at three levels: assignment of patients to the interventions, application of the intervention, and measurement of the trial outcomes.

Assignment of intervention (randomization)

The ability to control assignment is important, because cause and effect relationships between drug

Table 3.1 Patient treatment regimens in a crossover design with three treatments and washout periods

Patient	First Treatment	Washout Period	Second Treatment	Washout Period	Third Treatment
1	A	Placebo or no treatment	B	Placebo or no treatment	C
2	A	C	B		
3	B	C	A		
4	B	A	C		
5	C	B	A		
6	C	A	B		

therapy and clinical outcomes can then be established. Unless the assignment is controlled, confounding variables may affect the outcomes measured in the trial. Control of assignment of interventions is accomplished through randomization, whereby patients are assigned to treatment groups by chance. A randomization scheme generated by a computer program or from random numbers lists is often used to ensure assignment to treatment intervention is unbiased.

In most trials, patients have an equal chance of receiving each treatment. However, some trials are designed to have imbalance in treatment assignment. For example, if previous clinical research indicates one treatment is likely to be superior, more patients may be randomly assigned to that treatment (for example, 2 : 1 or 3 : 1). Specific statistical analysis techniques are used to adjust for the differences in sample size.

Stratified randomization is used to adjust for potential differences in response between specific patient groups or trial sites. The characteristic of concern (for example, type or severity of disease, gender, age, race, or site) is determined, and then patients are randomized within their stratification group. This assures that equal numbers of patients with these characteristics are assigned to each trial treatment. For example, after stratified randomization, equal proportions of patients in each treatment group would be male, over age 65, etc.

Block randomization is also used in clinical trials. The sample size for a specific number of patients is established, so that, as randomization occurs, at regular intervals, equal numbers of patients are assigned to each treatment group. This procedure avoids an imbalance in enrollment between the treatment groups as the trial progresses. Often, the sizes of the blocks of trial patients are randomly varied (for example, 8, 4, 16, 12) to help prevent site personnel from guessing patient treatment assignment.

Application of interventions

The protocol is used to control the application of the intervention during a clinical trial. Unless the interventions are provided similarly to all patients between and within each treatment group, variations in outcomes may be due to differences in how the intervention was administered. Protocols are designed to address most potential contingencies that occur during the trial, including requirements for dosage adjustments associated with varying patient conditions. Protocol adherence is monitored throughout the trial. Deviations from the protocol are documented and discussed by individuals administering the trial. Clinical site personnel may need to be retrained regarding the protocol or, if deviations are common, the protocol may need revision. In multicenter trials, repeated deviations by a particular site may result in disciplinary action, such as removal from the trial.

Measurement of trial outcomes

Control of the measurement of trial outcomes is also critical to decrease bias and is accomplished in several manners. If a special type of measurement tool or instrument is used to measure outcomes, training of all trial personnel in the use of the instrument is

performed prior to trial start-up. Training includes an assessment tool to determine whether personnel are using the instrument(s) uniformly. To eliminate the impact of different laboratory procedures, a centralized laboratory for analysis of specimens is often used. Another method is to have a centralized group review and analyze assessments conducted at the trial site(s). When the determination of a trial outcome (endpoint) involves medical judgment, a centralized endpoints committee is used. The endpoints committee reviews the data and determines whether the outcome assessment has been correctly identified and attributed to treatment. The endpoints committee comprises specialists in the medical subject of the research.

Selecting the trial population

Patients are selected for clinical trials using inclusion and exclusion criteria. For Phase I trials, healthy volunteers are generally enrolled, with the exception of drug trials for the treatment of life-threatening diseases. In contrast, patients with the disease are enrolled in Phase II and III trials, and the goal is to select patients to participate in the trial who will likely benefit from the treatment. Inclusion criteria are also used to identify patient groups specified by the trial objectives. Exclusion criteria are used to eliminate patients who might be harmed by treatment, who are unlikely to survive the entire trial period due to nonrelated health problems, or who should not receive the drug treatment due to allergy, concomitant illness, or a contraindication.

Sample size

Determination of sample size is a critical aspect of clinical trial design. Sample size is based on four factors: the expected difference in clinical outcomes between the treatments, the level of error in measurement of clinical outcomes, the alpha level, and the power desired for the trial. Table 3.2 depicts the interrelationships between these four concepts and sample size in clinical trials.

The size of the difference between treatments is predicted based on the difference considered "clinically-important" and results of previous research. The question to consider is: How great a difference in the outcome is needed for a clinician to consider changing from standard (or placebo) therapy to the new treatment? Medical literature and/or specialists in the field are consulted to answer this question. If the intervention is unlikely to achieve this difference in outcomes, then the trial is not feasible. If the difference selected is so small that it is unlikely to change clinical practice, the trial will be inefficient or superfluous.

The "clinically-important" difference is adjusted by the level of inherent error in measurement of outcome. For clinical outcomes that are parametric measures, which have a definite 0 and are mathematically uniform across the scale of measurements, this is expressed as standard deviation, or the inter-related terms, variance, or standard error. The "clinically-important" difference in outcomes is divided by the amount of inherent error in measurement of outcomes to determine effect size of the treatment expected.

The statistical alpha level is also incorporated into sample size analysis. Alpha is equivalent to Type I error which is defined as the chance of accepting the conclusion that treatments are different when the two treatments are equal. An alpha level of 0.05 is accepted for medical research. This is equivalent to 5 chances in 100 of making the wrong conclusion for difference between the treatments.

The beta level is known as the chance of a Type II error, the chance of concluding that no difference exists between the treatments when difference truly does exist. In medical research, beta levels of 0.1 or 0.2 are generally acceptable. This can be interpreted as 10 to 20 chances in 100 that no difference is found by the trial when difference truly does exist. Power of the trial is 1.00 – beta. The concept of power can be interpreted as the likelihood of finding a difference when difference truly does exist. Thus, power levels between 80% and 90% are considered sufficient in medical research.

Sample size estimation requires consideration of several scientific aspects of the trial. Since all four factors must be balanced in this calculation, several potential alternative sample size scenarios are developed before a decision regarding sample size is reached. Planning the appropriate sample size is critical to the success of the trial. An inadequate sample size may cause the trial to have insufficient power to detect a significant difference. An excessive sample size results in unnecessary costs and risks exposing patients unnecessarily to ineffective treatment.

Table 3.2 Interrelationships between factors used to determine sample size in clinical trials

Factor in Calculating Sample Size	Impact of increasing the factor on sample size requirements*	Rationale
Clinically-important difference between treatments	↓	A larger difference between treatments is needed so fewer subjects will be needed to determine if the difference exists.
Inherent error in measurement of outcome	↑	More error in measurement is less accurate so more subjects are needed to overcome the error.
Statistical alpha level	↓	The researchers are willing to accept a greater likelihood of accepting a difference by chance.
Desired power level	↑	The researchers are less willing to accept that no difference between treatments exists even when the results indicate it.

*Note: For each factor, decreasing the factor will have the opposite impact on sample size requirement.

Feasibility of conducting the trial

Feasibility is dependent on the trial purpose, the intended application of trial results, and access to trial sites and patients. The question of feasibility comes down to overall trial cost and timeline, which are intertwined with the primary objective and the sample size required to complete the trial. If the trial purpose is extensive and the results are intended to be generalizable across a broad population, the sample size will be large. Prevention of disease events may require long observation periods, significantly lengthening trial duration, and, thus, incur greater costs. If the trial population is transient, it may be difficult to perform sufficient patient follow-up over long time periods.

Another aspect of trial purpose that impacts feasibility is type of outcome. Outcomes of mortality often require lengthy observation periods, depending on the baseline mortality rate of the trial population. Furthermore, outcomes intended to be generalizable across a wide range of patients need broad inclusion criteria and few exclusion criteria to ensure that all relevant types of patients are represented in the trial. Lastly, the trial outcome measurements directly affect the type and quantity of data required, as well as additional testing requirements specific to the trial.

Access to trial patients impacts feasibility of conducting the clinical trial. Prior to trial initiation, the number of available patients in a health system is estimated, along with the percentage likely to meet inclusion criteria and agree to enroll. These values are used to determine the number of patients required for recruitment. The rate of estimated enrollment is frequently much greater than actual enrollment.[24] Increasing the number of trial sites can enhance access but with substantial cost. Many pharmaceutical companies outsource this portion of the drug development process to contract research organizations (CROs) that help identify and provide access to patients. Proper management of outsourcing projects can provide a cost-efficient method for new drug development, saving a pharmaceutical company time, space, and manpower.

Drug product design and blinding

Blinding involves the disguising of drug therapy to the patient and health professionals to minimize the introduction of bias into the trial. It is often an essential characteristic of a controlled trial. Blinding is categorized as single, double, or triple. Single blinding indicates that only the patient is unaware of which treatment group is assigned. Double blinding indicates that both the patient and the health professional evaluating the effect and collecting data are unaware of trial drug assignment. Triple blinding indicates additional blinding of the Data Safety and Monitoring Board and statisticians, who assess the comparative safety and efficacy of the treatments during the trial.

Blinding is achieved by developing dosage forms of active and placebo (inert ingredients only) or comparator product that are indistinguishable in size,

shape, color, odor, weight, and other characteristics. Blinding requires some type of manipulation of the dosage form, and common techniques and considerations for blinding drug products are presented in Table 3.3.[25] Ideally, the manufacturer produces a matching placebo (or active comparator) for each drug, using a similar formulation but without the active ingredient. However, it may not be economical or timely for the pharmaceutical company to do so. In these cases, the researcher may need to develop matching drug products. Irrespective of the technique used, blinding must not significantly alter the drug release characteristics, the physical stability of the dosage form, or the chemical stability of the active component.[26]

In vitro tests for dissolution and potency may be needed to ensure the blinding technique does not affect the performance of the dosage form. In addition, the labeling used must ensure that different drugs or dosages used in the trial are indistinguishable.

When factorial designs are used, blinding of each drug product is required. Although it is sometimes possible to make all study drugs match, it is more common to use a "double dummy" approach, where a separate matching placebo for each drug product is used in the trial. For example, a patient may take two placebo products, an active and placebo combination, or two active drug products. A disadvantage of the double dummy method is that, for drugs used in multiple daily doses, patients may be required to ingest a large number of dosage forms each day, which can affect patient adherence to the therapeutic regimen.

Trial drug packaging

Packaging clinical trial drugs involves creativity, as well as consideration of the scientific aspects of the study. Drugs are packaged to (1) meet trial design requirements, (2) maintain the blinding, (3) minimize the chances for dosing errors, (4) enhance patient adherence to the therapeutic regimen, and (5) maintain drug potency/stability. Package sizes (for example, count per bottle and number of bottles per patient kit) are designed to meet trial requirements of dosage adjustments, clinical visit periods, visit windows, and dosing frequency. For example, in the DIG trial,[21] patients were dosed from 0.125 mg to 0.5 mg (one to four tablets) per day, depending on clinical response. Patient clinic visits were scheduled for every 4 months ± 14 days. Patients taking one or two tablets daily were dispensed one bottle of 270 dosage units (0.125 mg digoxin or matching placebo tablets), whereas two bottles were dispensed to patients taking three or four tablets daily. Therefore, the package size of 270 tablets was sufficient to meet the requirements of all dosage levels used in the trial for the maximum 134 day visit window.

Clinical trial drug packaging helps maintain the blinding of the drug by ensuring that package style and labeling are exactly equivalent between the different drugs and their matching placebos (or comparators). Each package is labeled with unique bottle numbers or patient therapy numbers to ensure that the therapy matches the treatment assignment. A database is maintained, which provides the correspondence between the bottle or therapy number and treatment assignment. Bottle or therapy number assignments can be provided to clinical trial personnel through predetermined lists or through real-time methods, such as telephone assignment systems, web-based programs, or scanning devices.

Complicated dosage regimens must occasionally be accommodated. For example, a patient may receive induction (ramp-up) dosing, taper dosing, or individualized dosing with multiple dosage adjustments during a trial. For oral dosage forms, blister cards can accommodate these alternatives, while helping to minimize dosing errors. For example in a double dummy trial comparing clozapine versus haloperidol, blister card dosing allowed for combinations of active and placebo capsules of both drugs to be included in each daily dosing regimen.[28] Patients received doses based on symptoms of schizophrenia, ranging from 100 to 1200 mg per day for clozapine or 5 to 30 mg for haloperidol. Patients received four to nine matching capsules daily with combinations of active and placebo capsules of three strengths of clozapine (12.5 mg, 25 mg, or 100 mg) and one strength of haloperidol (5 mg). Patients randomized to clozapine or haloperidol received matching placebo capsules of the other drug. The use of combinations of active and placebo capsules allowed blinded dosing adjustments, as well as induction and taper dosing. Through a computerized assignment system, specific cards were assigned according to the clinical criteria established in the protocol. Once the card was assigned, dosage errors were minimized, because all patients took

Table 3.3 Techniques and considerations for blinding of drug products[27]

Original Dosage Form	Technique	Considerations
Tablet	Removal of markings	• Time consuming and manually intensive • Still must match size/shape/color of tablet • Process may alter release properties of a film coating
Over-encapsulation	• Time consuming and manually intensive • Patients may open capsule and discover original dosage form	
Grinding and re-tableting	• Properties of new dosage form may be different from original form, affecting patient response • Complexity in developing new formulation	
Grinding and encapsulating	• Properties of new dosage form may be different from original form, affecting patient response • Assuring consistency in blend of grinded dosage form while encapsulating • Manually intensive, unless automated encapsulating equipment is available	
Tablet overcoating	• Tablet coatings are developed to match original dosage form • Preserves original dosage form • Pharmaceutical testing (i.e. dissolution) can help verify similarity to original dosage • Cannot be used for embossed tablets	
Capsules	Removal of markings	• Time consuming and manually intensive • Still must match size/shape/color of capsule
Over-encapsulating	• Same as above tablets	
Grinding and re-encapsulating	• Capsule shells from original dosage form may be visible in manufactured product	
Removing ingredients from capsule shells and encapsulating	• Manually intensive • Time consuming • Capsules may be difficult to open and contamination by capsule shell pieces may occur	
Oral solutions	Matching solution without active ingredient	• Taste and odor may be unique to active ingredient • Discoloration of active ingredient over time may occur and cause unblinding
Injectables	Matching solution without active ingredient	• May be difficult to obtain in same packaging and labeling • Differences in odor or color
Blinding just prior to administration	• Unblinded pharmacy personnel prepare injectable dosage form • Additional opportunity for communication of actual treatment to trial personnel	
Topical, including skin patches	Matching product without active ingredient	• Difficult to match packaging, unless prepared by manufacturer • Odor, texture, or color may differ between products

the same number of capsules daily, regardless of dosage levels.

Blister card packages can also help improve adherence with orally-administered drugs, because dosage times can be specified on the cardboard overlays. In addition, the blister packs provide direct and timely feedback to patients and clinical trial personnel regarding adherence to the treatment regimen. Pharmaceutical potency and stability are further considerations for clinical trial drug packaging. Any drug product not stored in the original manufacturer's packages should be subjected to periodic, scheduled testing (potency, dissolution) to verify stability during the clinical trial.

Regulations governing the conduct of clinical trials

Prior to initiation of any trial among human subjects, approval must be obtained from the investigator's local institutional review board (IRB). Composed of experts and laymen with varying backgrounds, IRB committees critically review clinical protocols to ensure patient safety and institutional, regulatory, and professional acceptability. IRBs also assess the trial protocol regarding scientific validity and whether the study involves unwarranted risks to the patients. The IRB also determines if the protocol includes appropriate patient populations and whether inducements to participate in the trial are reasonable and noncoercive. Approval signals that the IRB has determined the trial is appropriate and does not involve undue risks to participants. IRB approval must be renewed annually for the trial to continue.

A critical aspect of clinical trial conduct is informed consent from participants. Participants must be informed of all aspects of the trial, including the rationale and previous research, potential risks and benefits, treatment alternatives, the likelihood of being randomized to a particular treatment, discomforts associated with the trial, their own ability to voluntarily disenroll at any time, and their rights for future treatment should they be affected adversely by the trial. Informed consent documents must be at a reading level understandable by patients. IRB committees review and approve these documents. In addition to written informed consent, the trial must be verbally discussed with the patient. Each page must be initialed and dated by the patient and clinical personnel, as well as signed on the final page of the document. A copy of this legal document is given to the patient, as well as maintained in patient records throughout the trial.

In April 2003, the Health Insurance Portability and Accountability Act of 1996 (HIPAA) was implemented. This act provides that patients be informed of their rights to maintain the privacy of their health information. Data collection for clinical trials is impacted by HIPAA, in that patients must be informed of their rights and provide written consent to researchers to access their medical records. Researchers must verify that they will not allow data collected during the trial to be distributed with patient-identifiable information. HIPAA requirements can be addressed within the informed consent process. More information is available at http://www.hhs.gov/ocr/privacy.

Good clinical practice monitoring

FDA regulations governing the conduct of clinical trials, referred to as Good Clinical Practices (GCP), are specified in 21 CFR Parts 50, 56, 312, and 314. In addition, the International Conference on Harmonization has established guidelines to assure patient safety during clinical trials at an international level, which can be found at http://www.ich.org. GCP training is necessary for all personnel involved in the conduct of a clinical trial.

In addition to addressing patient safety, GCP regulations help protect against fraud and falsification of trial data. There are significant incentives to healthcare professionals to ensure that patients are enrolled and complete all follow-up visits and that positive trial results are achieved. These incentives include direct financial gain, because some trial sponsors reimburse investigators or institutions based on *per capita* enrollment and/or follow-up visit. In addition, future funding may be discontinued if results are negative. Sometimes, clinical researchers even have financial investments in the company sponsoring the trial. There are also academic pressures to achieve positive results, as trials with positive results tend to more likely be published in prestigious journals. Failure to attempt to publish negative results has been considered a form of scientific misconduct.[29] Fraud and falsification of data have been identified in published literature.[30,31]

The GCP monitoring of clinical trials involves outside reviewers who monitor trial conduct and data collection. Reviewers are specially trained to match trial data with source documentation (that is, data that are not collected as part of the trial) to identify fraud and falsification of data. GCP monitoring is required for any trial used to gain FDA approval or change the labeling or advertising of a drug product. FDA inspections of study sites are also conducted after completion of the trial to verify the appropriate conduct of the trial and the veracity of the results. The FDA requires that all trial records be maintained and accessible at the trial sites for a minimum of two years after marketing or changing labeling of a drug product. If marketing or change in labeling is not pursued, records must be maintained for two years after completion of the study and FDA notification.

Monitoring and reporting adverse events during clinical trials

Safety data are important outcomes of clinical trials. Due to randomization, blinding, and placebo control, trials can provide unbiased reports of prevalence and incidence rates of adverse events. FDA regulations specify how adverse events should be reported. Serious adverse events (SAEs) are defined as those that result in death, are life threatening, cause hospitalization or prolong hospitalization, cause cancer or congenital abnormalities, or require extensive treatment to prevent hospitalization. Unexpected adverse events are defined as events not previously identified as associated with the drug by nature of the event, its severity, or its frequency. Unexpected SAEs must be reported to the FDA, by telephone or facsimile safety reports, within 7 calendar days of disclosure to the trial sponsor. SAEs must also be reported to site investigators, who are required to report them to their local IRB. SAEs are summarized in the IND annual report submitted to the FDA. Furthermore, SAEs resulting in termination from the trial must also be included in the IND annual report. All clinical and subjective information relevant to the event are reported in the SAEs. For ongoing SAEs, follow-up reports are also completed.

Other adverse events (AEs) are also collected regularly during clinical trials. Although these are less severe, they provide important information regarding the impact of drug therapy. Adverse events are usually coded to a common glossary, so that, although clinicians may use different descriptors for similar events, the events can be consolidated. The FDA has adopted the Medical Dictionary for Drug Regulatory Affairs (MedDRA) as the standard coding system for adverse event reports. Adverse events can be categorized by type of event, severity, relatedness to study treatment, intervention used to address the adverse event, and outcome of the adverse event. Comparisons of incidence rates (the number of events per person-years) between drug treatment groups are specified in clinical trial publications. Adverse event data from a minimal number of patients are required for NDAs. However, the limited number of patients exposed at the approval stage, usually about 3000–5000, is insufficient for determination of rare adverse events. Thus, post-marketing studies of adverse events are used to identify rare events.[32] The reporting of unusual adverse events to the FDA during clinical trials helps provide additional data on rare events.

For trials over one year in duration, monitoring of the results of the trial is conducted periodically. An impartial group, such as a Data Safety and Monitoring Board (DSMB), provides this oversight. Monitoring usually includes both clinical efficacy and adverse events. Interim reports are provided to the DSMB group in a blinded format, so that, although the treatment groups are compared, the DSMB cannot determine which group is better or worse in terms of efficacy or adverse events. The DSMB has the power to recommend discontinuance of the trial and will do so if there is clear evidence that it may be detrimental to patients assigned to one of the treatment groups if the trial continues. This may be due to strong evidence of efficacy or safety differences between the groups. Interim statistical analyses provided in DSMB reports are preplanned and included in the overall adjustment for statistical testing.[33]

Overview of statistical analysis of clinical trial data

It is not possible to provide comprehensive descriptions of statistical methodologies in this chapter; the reader should refer to statistical textbooks for further information.[34,35] However, certain general statistical issues are discussed in brief.

Good clinical research will always be conducted using an intention to treat analysis (ITA).[36] This

means that, even if the patient has stopped taking the medication, did not complete the assigned treatment, or has been switched to an active alternative therapy, the data from the patient are included in the original treatment group to which the patient was randomized. The impact of intention to treat analysis is to lessen the likelihood of finding a difference between the treatments. However, the intention to treat analysis is more analogous to what happens outside of the clinical trial situation. Patients typically do not fully comply with therapy or may change therapies. Thus, intention to treat analysis is a key statistical feature of clinical trials.

Adjustment for multiple comparisons is another statistical consideration of clinical trials. The adjustment involves lowering the statistical boundary at which the researcher will consider the results significantly different. When the same data are used for multiple statistical tests, such as in provision of multiple reports to the DSMB, there is an increased likelihood that a significant difference will be found by chance. If one considers alpha = 0.05 to be acceptable, this means the researcher is willing to accept one chance in 20 that a significant finding will be in error. By doing multiple tests, for example four tests on the same data, the alpha level changes to four chances in 20 or one chance in five. A conservative adjustment of alpha for multiple tests is Bonferroni correction, which involves dividing the alpha level by the number of tests. For example, performing four tests at an overall alpha = 0.05 would change to alpha = 0.0125, thus the researcher would not consider the result significant unless the statistical finding was $p \leq 0.0125$.

Another statistical consideration in clinical trials is subgroup analysis. Once the data are obtained, researchers sometimes reanalyze data from different perspectives; for example, dividing the data into several different patient groups. Preplanned comparisons, such as those in secondary objectives, are acceptable. However, results of comparisons conducted post-hoc should be interpreted cautiously, especially if based on trends in the data, as the findings may be misleading. Some potential causes of the deceptive findings are (1) the trial was not designed to assure there was adequate sample size for the subgroup analysis, (2) potentially confounding variables were not measured or controlled, and (3) insufficient theoretical underpinnings for the test. The number of subgroup analyses should be minimized and, if results of subgroup analyses are published, these limitations should be clearly stated as speculative.

Summary

New drug products must be shown as safe and effective before they are approved by the FDA for marketing in the United States. Other countries have regulatory authorities similar to the FDA that oversee new drug approvals. This chapter, focused on drug approval in the United States, outlined the various stages involved in new drug development, including the milestones of Investigational New Drug Application and New Drug Application submission. The costs associated with the development of new drug products are substantial, and the most significant expenditures occur during clinical testing. Thus, the design and conduct of clinical trials are critical to successful drug product development. Several considerations in clinical trial design have been highlighted. The reader is encouraged to refer to specific FDA guidance documents and other referenced materials for further information.

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4

Information resources in pharmacy and the pharmaceutical sciences

Introduction

This chapter describes many significant information resources used by the pharmacy professional student, the pharmaceutical sciences graduate student, the pharmacist, and the pharmaceutical scientist. It is not possible to be comprehensive, since there is a vast array of resources, which is growing exponentially. This chapter arranges the resources in three categories: the original research literature or primary literature, which comprises the largest volume of the literature; the secondary literature, which provides access to the primary literature; and the tertiary literature, which sums up the best practice based on the primary literature. Pharmacy practitioners and PharmD students use the literature to provide evidence-based medicine or the integration of the best research evidence into their practice or studies. Pharmaceutical scientists and their graduate students use the literature to support research in such fields as pharmacology, toxicology, medicinal chemistry, and pharmaceutics.

Locating appropriate types of information resources

The nature and depth of the question and the level of experience of the researcher will determine the appropriate type of literature used. Whereas an expert may go directly to a database, a less experienced pharmacy student who is asked to find primary literature to write a paper on a therapeutic or pharmaceutical topic may first need to get general background information from a tertiary resource, such as a textbook, handbook, or subject encyclopedia either online or in print. Once the student is familiar with the basics and the professional vocabulary, he or she will frequently perform a search in either the PubMed/Medline database or the International Pharmaceutical Abstracts database to located relevant review articles (secondary sources) and original research (primary sources). Fortunately, these databases often provide links to the full text of the journal article. A basic search statement for these databases should include synonyms for the search terms, including professional or scientific terms. The terms can be combined using the OR logical operator. The search can be refined by adding a term, using the AND operator. For example, if a student is looking for primary literature on possible future improvements in HPV vaccines, they could try searching for: (future OR advances OR second generation) AND (HPV vaccines OR papillomavirus vaccines). Nesting the parallel terms using parentheses will result in the most relevant articles. Additional limits, such as a

date range and language, can easily be applied to the search.

A subject specialist often pursues one or more topics over a longer period and can create a series of search alerts in a database or set up RSS feeds to receive timely, updated search results from a specialized database. More information on search updates can be found in the section on Databases.

Primary literature

The first formal reports of scientific or clinical findings are found in journals. Journals can be distinguished from trade magazines by the lack of advertisements. Some primary literature, however, can be found in several trade magazines under sections entitled "Peer-reviewed reports." The peer review process is a rigorous evaluation of manuscripts submitted to the journal. After concluding a study, authors write up their findings in a format consistent with the journal's "instructions for authors." The editor of the journal assigns two or more reviewers who are experts in the particular area of research. The reviewers are volunteers from the scientific community who elect to participate in the peer-review process. In addition to the reviewers' recommendations to the editor on whether to publish the manuscript, they provide feedback to the authors, such as how to make the study design more clear to the reader and any additional experiments to allow the conclusions to be stronger. The peer-review process can take several months before the reviewers, authors, and editor agree on the final text for publication. The process is designed so only those manuscripts with clear scientific merit pass peer-review and are published. Each journal has its own criteria for acceptance of manuscripts, which can include whether the manuscript reports results within the area of research covered by that journal and whether the contribution is important to the scientific community.

The discrimination of the peer-review process is not uniform among all journals. For someone new to a field, it is difficult to discern which journals provide the clearest reports that are reproducible and for which the interpretation of the results is thorough without being too speculative. It is prudent to consult an expert in the field to determine which journals are best. Additionally, a general ranking system has been devised by the Institute for Scientific Information (ISI), which is now part of Thomson Reuters, which measures the "impact" of a journal. The Impact Factor of a journal for a given year is the average number of times articles published in that journal in the preceding two years is cited by others. Although this provides a general guide, the Impact Factor has its critics.

Experts, as well as those new to a field, follow the primary literature in a few publications related to their area of interest. Scanning the titles of the research articles, reviewing the abstracts of key articles, and reading those closely related to a particular area of research is the traditional approach to keep up to date on the general trends, as well as progress in one's own specific area. This can be done by subscribing to print journals or simply accessing the websites of the journals of interest on which the titles and abstracts are generally available without charge. In addition, "open access" journals allow non-subscribers access to the full-length detailed articles. The Directory of Open Access Journals (http://www.doaj.org/) provides an up-to-date list. In some cases, journals allow open access to non-subscribers after a period of time, during which only subscribers can view full-length articles on-line.

Of the thousands of journals spanning the areas of clinical and pharmaceutical research, as well as related areas, pharmaceutical scientists often publish in:

Journal of Medicinal Chemistry (Eaton, PA; American Chemical Society)
Journal of Natural Products (Washington, DC; American Chemical Society and American Society of Pharmacognosy)
Journal of Pharmacology and Experimental Therapeutics (Baltimore, MD; Williams and Wilkins)
Pharmaceutical Research (New York, NY; Kluwer Academic Publishers)

Clinical pharmacists refer to major medical and pharmacy journals:

American Journal of Health-System Pharmacy (Bethesda, MD; American Society of Health-System Pharmacists)
JAMA – The Journal of the American Medical Association (Chicago, IL; American Medical Association)

Journal of the American Pharmacists Association (Washington, DC; American Pharmacists Association)
New England Journal of Medicine (Boston, MA; Massachusetts Medical Society)

Clinical pharmacists also refer to journals that focus on a particular disease state or patient population:

Circulation (Dallas, TX; American Heart Association)
American Journal of Veterinary Research (Chicago, IL; American Veterinary Medical Association)
Diabetes (Alexandria, VA; American Diabetes Association)
Pediatrics (Evanson, IL; American Academy of Pediatrics)

A guide to journals and trade magazines recommended for the collections of libraries associated with schools/colleges of pharmacy has been developed and is updated by the Libraries/Educational Resources Section of the American Association of Colleges of Pharmacy (http://www.aacp.org/governance/SECTIONS/libraryeducationalresources/Pages/LibraryEducationalResourcesSpecialProjects-andInformation.aspx). The 2013 list has 693 entries.

When searching for primary resources, patents and dissertations should also be considered. The purpose of a patent is to protect intellectual property, not disclose research findings. So, information claimed in patents should not be considered equal to that found in peer-reviewed research articles. Similarly, dissertations have not undergone the rigorous peer-review process; however, they can be quite useful to find details of studies that are too lengthy to include in a journal article.

Secondary literature-reviews and databases

Secondary literature is created by experts in the subject field. These resources are organized to either describe or evaluate the original primary literature and to provide useful access to this literature. Secondary literature consists of review articles, including systematic reviews and meta-analyses and bibliographic databases, such as PubMed.

Reviews/systematic reviews

As individual articles, the findings in the primary literature are often more useful to those working in that specialty than to those new to the field. A review article that integrates the information from individual articles from the primary literature may be more useful to someone outside the field or new to the field, as reviews provide the perspective gained from many authors over many years. Reviews provide a good starting place for a literature search into a new area. When beginning a literature search, one can often "refine" his or her search of a database to identify only review articles. Additionally, there are an increasing number of journals consisting of only review articles, such as *Trends in Pharmacological Sciences* (Amsterdam; Elsevier) and *Advanced Drug Delivery Reviews* (Amsterdam; Elsevier).

Systematic reviews are those with a more structured methodology to collect and evaluate the primary literature relevant to a particular research question. The most common type of systematic review in pharmacy literature is the meta-analysis. Using carefully selected sets of data from the primary literature and weighting their findings according to a protocol, the meta-analysis can use the much larger pool of data to produce quantitative findings. The use of statistical measures and the large number of data can often produce a clearer answer from many sometimes contradictory findings in the primary literature. More information on meta-analysis can be found in *Cochrane Handbook for Systematic Reviews of Interventions*.[1]

Databases

Bibliographic databases provide access to original research articles or the primary literature and cover a wide range of specialties, depth, and breadth of the literature. It is important for the searcher to consider the goal when selecting a database. If the searcher is unsure of where to begin or how to structure the search, he or she should consult the librarian or information specialist. In the absence of a resource person, there are subject guides and tutorials available online that can assist the searcher. A basic Google search will include non-peer reviewed and non-scholarly resources, so it is more effective to search professional scholarly databases. Occasionally,

a Google Scholar search is useful in searching a new interdisciplinary area.

For comprehensive research on clinical or therapeutic topics, the searcher may begin with PubMed, which is available to anyone with an internet connection. This database is produced by the National Center for Biotechnology Information at the US National Library of Medicine (http://www.pubmed.gov). If access to subscription databases is unavailable, this may be the only affordable option. PubMed has an excellent thesaurus of professional terms, or a controlled vocabulary named MeSH, which stands for Medical Subject Headings. Common search terms are "mapped" to the MeSH terms, which are also searched by PubMed. For example, if the term "tylenol" is entered in the search box, acetaminophen is also automatically searched. Another useful tool, which requires free registration, is My NCBI. A My NCBI account allows the researcher to run search alerts and set up preferences, such as preferred display formats and colored highlighting of the search terms. While signed into My NCBI, a researcher can save a search in many of the NCBI health databases, including PubMed, and schedule email updates or alerts to run on a monthly, weekly, or even a daily basis. Email will only be received if there are new search results. References can also be saved by topics in online Collections. An author may create a bibliography of his or her own work, which can be linked to the NIH Manuscript Submission System. The data from PubMed is also available through several commercial vendors, such as the Medline database. Although the data are the same, the search platforms are proprietary and can give the searcher varying results while using the same search strategy.

International Pharmaceutical Abstracts (IPA) is a database that is focused on pharmacy and pharmaceutical science and is produced by Thompson Scientific in cooperation with the American Society of Health-System Pharmacists (ASHP). The database indexes and abstracts more than 800 pharmacy and pharmaceutical science related journals and covers drug use and development, as well as pharmacy related topics, including pharmacy education and ethics. IPA is also useful for finding articles on herbs and natural products. In addition to peer reviewed articles, IPA includes meeting abstracts from the meetings of organizations, including the American Pharmacists Association, the American College of Clinical Pharmacy, the American Association of Colleges of Pharmacy, and ASHP.

The Cochrane Library provides reliable and reasonably up-to-date information on the effects of interventions in healthcare. These interventions may be either therapeutic or diagnostic. There are six separate databases in the Cochrane Library, which may be searched separately or together. The well known Cochrane Systematic Reviews database provides access to the full text of the reviews and the protocols for proposed reviews. There is a Feedback tool that allows users to provide comments and criticisms of Cochrane Reviews and Protocols. The Cochrane Collaboration publishes a list of accepted comments. These comments can be used to further improve and update both Cochrane Reviews and Protocols. Abstracts of non-Cochrane systematic reviews, with a commentary on their overall quality, are available in the Database of Abstracts of Reviews of Effects. The Cochrane Central Register of Controlled Trials merges the trials listed in Medline, Embase, and other published and unpublished sources. The bibliographic information on publications on the methods used in the conduct of controlled trials is available in the Cochrane Methodology Register. Economic evaluations of healthcare interventions are identified and appraised in the NHS Economic Evaluation Database. Free registration for saved search alerts and RSS feeds from the Cochrane Library is available to the residents of several countries. Cochrane provides a monthly Journal Club publication that introduces a recent Cochrane Review, with a podcast summarizing the review, discussion questions, and key figures and tables in the form of PowerPoint slides. You can also learn more about the Cochrane Library through various social media, including Facebook. The Cochrane Library also includes the *Cochrane Handbook for Systematic Reviews of Interventions*,[1] which provides a thorough methodology for evaluating the clinical research literature and strict guidelines for creating a Cochrane systematic review.

Other heavily used databases in pharmacy and pharmaceutical sciences include such specialized databases as BIOSIS Previews (Biological Abstracts); SciFinder Scholar (Chemical Abstracts and related chemical databases); Toxline and other TOXNET

databases, from the US National Library of Medicine; and Embase, a comprehensive, fee-based health science database from Elsevier, which indexes and abstracts many non-English language journals and focuses heavily on pharmaceutical issues. BIOSIS Previews, SciFinder Scholar, and Embase have specialized indexing terms to help the researcher dig deeply into the life science, chemical, and pharmaceutical literature. In addition to indexing journal articles, they also include report, review, patent, and meeting abstracts. The Toxnet databases are a combination of bibliographic and full text databases, which encompass both secondary and tertiary toxicological literature. There is more on these full text databases in the section on Toxicology in the Tertiary literature section.

Important comprehensive citation databases, which allow the researcher to find which articles cited a seminal article, include SciVerse Scopus and Web of Science. Citation searching allows the searcher to see the evolution of an idea and emerging fields of research. SciVerse Scopus from Elsevier includes the data from the Embase database and is quite comprehensive in the sciences and social sciences. SciVerse Scopus also provides links to scientific websites and patents from five patent offices in its search results. Web of Science from Thomson Reuters began several decades ago with the print indexes named Science Citation Index, Social Science Citation Index, and Arts and Humanities Citation Index from the Institute for Scientific Information and has evolved into an extensive, multifunctional set of databases. In both databases, the researcher can save searches and set up search alerts or RSS feeds.

Tertiary literature

Tertiary literature provides an introduction to the research literature regarding the practice of pharmacy and the pharmaceutical sciences. It introduces key research findings and accepted concepts. It is usually written by clinical or research specialists within the subject area. These resources are particularly useful to the pharmacy professional and pharmaceutical science graduate students. They comprise textbooks, government monographs, encyclopedias, and other familiar reference works. As we move from print to electronic formats, these resources can provide additional value by allowing students, clinicians, and researchers to make notes, link to related resources, assess learning through online self tests, and share these with inter-professional teams and their peers, colleagues, or instructors. The ability to add more frequent updates to the material online, including videos, will aid the evolution of this literature.

Advantages to tertiary literature include ease of access and well vetted standards of best practice. A major disadvantage still remaining is that the resources take years to compile and, therefore, can contain dated material.

Textbooks

As electronic access is making it possible to use the best chapters or sections from multiple resources, the use of textbooks is evolving. Textbooks are often provided as part of electronic packages from vendors, such as AccessPharmacy from McGraw Hill. Electronic book readers also provide greater access and convenience. New editions of classic textbooks are valuable for students. They are also useful to professors or subject specialists, who can read a new edition to see the recent changes in their area. Dipiro's *Pharmacotherapy: A Pathophysiologic Approach*,[2,3] and *Goodman and Gilman's The Pharmacological Basis of Therapeutics*[4] are all available both in print, as well as electronically through AccessPharmacy. The online resources include additional online updates. The classic title *Foye's Principles of Medicinal Chemistry*[5] is available through a variety of ebook vendors, as well as in print.

Nomenclature

To locate comprehensive information concerning a drug, the researcher should know the nonproprietary name. Most databases use this name in its controlled vocabulary and may map the brand name to the nonproprietary or generic name. For research into the early development of drugs the chemical names, CAS registry numbers or investigational names are also useful. The two most commonly used resources for naming conventions are the *USP Dictionary of USAN and International Drug Names*[6] and the World Health Organization's *International Nonproprietary Names* (INN).[7] The researcher should be aware that the INN name is sometimes different from the US Adopted Name.

The *American Drug Index*[8] is published annually and includes over-the-counter drugs, combination products, and drugs currently available in the United States. There is a convenient list of manufacturers and distributors included, along with other useful information at the end of the drug monographs.

The *Merck Index: An Encyclopedia of Chemicals, Drugs, and Biologicals*[9] provides chemical, nonproprietary, and generic names, as well as graphic chemical structures, CAS Registry Numbers, and chemical formulas. There is a comprehensive cross index to the monographs. The monographs also include useful references to articles, patents, and other tertiary sources on preparation and to comprehensive descriptions of the drug, such as the monograph of the drug in the *Profiles of Drug Substances, Excipients and Related Methodology*.[10] There are also many supplementary tables and organic name reactions. The online version includes structure searching as well.

Index Nominum: International Drug Directory[11] is a valuable resource for researchers searching for foreign drug substances. Information on over 5300 drugs includes the therapeutic category and manufacturer or country. There is also information on approximately 10,000 manufactures around the world.

Japanese Accepted Names for Pharmaceuticals[12] is a free online database maintained by the Japanese National Institute of Health Sciences (http://jpdb.nihs.go.jp/jan/index.aspx). It is searchable by the CAS Registry Number, the chemical name, or the Japanese Accepted Name.

Pharmacopeias and resources for drug and excipient standards

A pharmacopeia is a list of drugs and drug products that describes the purity, strength, method of preparation, and other information. Pharmacopeias are issued or authorized by governments or international agencies. The *United States Pharmacopeia/National Formulary*[13] (USP/NF) is compiled by a nongovernmental organization, the United States Pharmacopeial (USP) Convention (http://usp.org), and recognized by the Federal Food, Drug, and Cosmetic (FDC) Act as the official pharmacopeia of the United States. It contains a list of those drugs, drug products, dietary supplements, excipients, and other relevant compositions for which standards have been agreed to by the USP Convention. The Convention is a representative group of volunteers from the various stakeholders – healthcare practitioners, industrial scientists, and educators. The USP/NF is revised yearly and supplemented by updates. The *Pharmacists Pharmacopeia*[14] contains the information from the USP/NF most relevant to practicing pharmacists, along with additional helpful resources, and is updated less often.

The *Japanese Pharmacopeia* is published by the Japanese government through its Pharmaceuticals and Medical Devices Agency (PMDA). It is available in both Japanese and English versions. More information on the *Japanese Pharmacopeia* can be found at the PMDA website (http://www.pmda.go.jp/english/pharmacopoeia/about.html).[15] The European Directorate for Quality of Medicines and Healthcare (EDQM) publishes the *European Pharmacopeia*.[16] (More information is available at http://www.edqm.eu/). The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) is working with the regulatory authorities of the United States, Japan, and Europe to find and encourage commonalities among these three major pharmacopeias.

Other countries have well-recognized pharmacopeias, such as the *British Pharmacopeia*[17] (BP), published by British Pharmacopoeia Commission Secretariat of the Medicines and Healthcare products Regulatory Agency. *Martindale: The Complete Drug Reference*[22] is the new name for Martindale's Extra Pharmacopeia, which lists more than 6000 drugs found internationally.

Standards for excipients can be found in these pharmacopeias. In addition, the *Handbook of Pharmaceutical Excipients*,[18] although not an official pharmacopeia, is a widely used resource for standards and functionality of excipients. Additionally, since many excipients are also food additives, they can be found in the *Food Chemicals Codex*,[19] published by the United States Pharmacopeial Convention. Finally, the "GRAS list" is a listing of additives that are generally recognized as safe (http://www.fda.gov/Food/FoodIngredientsPackaging/GenerallyRecognizedasSafeGRAS/GRASSubstancesSCOGSDatabase/default.htm). The list can be found in searchable form in the Select Committee on GRAS Substances (SCOGS) database. Each of more than 370 entries provides

the opinion of the Select Committee and the year in which the opinion was rendered.

Drug information on prescription products

The most popular resources for finding basic background information on drugs include the following titles: The American Society of Health-System Pharmacists publishes the *AHFS Drug Information: American Hospital Formulary Service*,[20] a well recognized reference on prescription drugs. It is organized by therapeutic category, with a general overview of the category, including drug interactions, before the individual listings of the drugs. The succeeding individual drug monographs include the uses, dosage and administration, cautions, pharmacokinetics, chemistry, and stability. Preparations and comparative pricing are included in the online version of this resource. Mobile versions of this resource are also available.

Most pharmacies have traditionally had a looseleaf copy of *Drug Facts and Comparisons*[21] on their shelves. Updated monthly, it is a reliable current resource. The drug monographs are arranged by therapeutic category and class hierarchy. The online version, Facts and Comparisons eAnswers, includes a variety of tools, including clinical calculators, drug identifiers, and the ability to view comparative data tables and side-by-side monograph summaries of two or more drugs. There is also a mobile version of the databases.

DRUGDEX is part of the *MICROMEDEX* online suite of databases from Thomson Reuters and is often available at hospital pharmacies and health centers. *DRUGDEX Evaluations* monographs are remarkably thorough and well referenced. Dosing information, pharmacokinetics, cautions, and clinical applications are well covered. Although *DRUGDEX* focuses on prescription drugs, it also includes information on some investigational and nonprescription drugs. There is also a mobile version.

Martindale: Tthe Complete Drug Reference[22] is a comprehensive listing of worldwide drugs, including herbal medicines. It is also available electronically, through a variety of vendors, and is included in the *MICROMEDEX Healthcare Series*.

Other international drug compendia include *CPS: Compendium of Pharmaceutical Specialties*,[23] from the Canadian Pharmaceutical Association; *Diccionario de Especialidades Farmaceuticas*,[24] providing drug and pharmaceutical information from Mexico; *Rote Liste*,[25] with complete coverage of drugs and medicines available in Germany; and *Vidal: le dictionnaire*,[26] a compendium of French drug and consumer healthcare products.

The *Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations*[27] is often simply referred to as the Orange Book. It is available for free at the US Food and Drug Administration website (http://www.fda.gov/cder/ob). This government resource is searchable by active ingredient, proprietary name, or by patent number. Therapeutic equivalence, drug approval date, and marketing status (prescription, nonprescription, or discontinued) are listed on a summary page for each drug formulation, as well as patent and exclusivity information.

Trissel's *Handbook on Injectable Drugs*[28] summarizes information on parenteral drug stability and compatibility for clinicians. In the most recent edition, there are 372 monographs arranged alphabetically by nonproprietary name. There is also an Appendix with parenteral nutrition formulas.

The *Drug Topics Red Book*[29] covers both prescription and nonprescription products. Each drug entry includes product and supplier names, the National Drug Code number, route of administration, strength and quantity, and Average Wholesale Price and Direct Price. This book is used primarily by pharmacists and pharmacy students for drug price information. Additionally, there are many lists, including manufacturers' addresses and phone numbers, state boards of pharmacy, and a product identification guide with color photos.

Drug information on compounded preparations

Like manufactured drug products, compounded preparations must be safe and efficacious for the entire period of their use. Existing drugs are prepared or compounded in new dosage forms, sometimes for new routes of administration designed to meet the needs of individual patients. In addition to safety and efficacy, often information on stability, solubility, and permeability is required to prepare a new formulation or evaluate an existing formulation. The *United States Pharmacopeia*[14] and the *Pharmacists' Pharmacopeia*[30] contain official monographs of compounded preparations that have been evaluated by experts in

the field to meet the quality and purity standards for the period prior to the "beyond use date." Additional formulations can be found in standard texts, such as *The Art Science and Technology of Pharmaceutical Compounding*.[31] Formulations specific for certain patient populations are found in references such as *Plumbs' Veterinary Drug Handbook*[32] and *Pediatric Drug Formulations*.[33] Although many texts provide formulation and preparation information, one must generally search the primary literature to find the limited data on efficacy of these specialized dosage forms. International Pharmaceutical Abstracts (IPA) is the preferred database for finding such information. IPA is also a useful database to find stability information for those drugs and drug preparations not listed in *Trissel's Stability of Compounded Formulations*.[34] Journals that often contain new formulations along with stability data are *International Journal of Pharmaceutical Compounding* (Edmond, OK; IJPC) and *American Journal of Health-System Pharmacy* (Bethesda, MD; American Association of Health-System Pharmacists).

Drug information on nonprescription products

Although there is some information on nonprescription drug products in the prescription drug resources listed previously in this chapter, the most valuable resource for this information is the *Handbook of Nonprescription Drugs: An Interactive Approach to Self-Care*,[35] which is available both in print and in PharmacyLibrary, the new electronic package from the American Pharmacists Association. The handbook is arranged into sections beginning with the practitioner's role in self-care, followed by sections on diseases, with chapters arranged in each section by body systems; a section on home medical equipment; and a section on complementary and alternative medicine. To help pharmacy students develop problem-solving skills, case studies are provided in each section. Chapter updates are available for the online version.

The *Physicians' Desk Reference for Nonprescription Drugs, Dietary Supplements and Herbs*[36] is a useful supplement to the *Handbook of Nonprescription Drugs: An Interactive Approach to Self-Care*.[35] It is available in print and electronically.

Herbal medicines and natural products

Herbal medicines and natural products are very popular with consumers, who often perceive the terms "natural" or "herbal" as connoting safety. Hence, there is active research in this area, and students and pharmacists need to be well informed. Luckily, there are a variety of well known textbooks and tertiary databases on this subject. *Trease and Evans' Pharmacognosy*[37] is a classic, basic textbook, now in its 16th edition. It focuses on the use of plants in medicine, covering plant taxonomy, commercial production, biological activity, and phytochemical examination and investigation of herbal products. *Tyler's Honest Herbal: A Sensible Guide to the Use of Herbs and Related Remedies*[38] provides well-referenced monographs on herbs and their efficacy and safety. It is a good starting point for researchers and useful for consumers, although consumers may view the standards for rating efficacy as too conservative. *Leung's Encyclopedia of Common Natural Ingredients Used in Food, Drugs, and Cosmetics*[39] is a more extensive resource covering the source, chemical composition, pharmacology and biological activity, uses, and commercial preparation of each natural ingredient. It is extensively referenced, with appendices providing glossaries of abbreviations and botanical terms and morphological descriptions of plant organs.

Online resources provide search options and special features. Two well known natural product databases are Natural Standard and Natural Medicines Comprehensive Database. Natural Standard provides evidence-based information about alternative and complementary therapies and has a variety of databases. Each therapy is graded according to the evidence for its effectiveness in treating a particular medical condition. Natural Standard databases include Foods, Herbs, and Supplements; Comparative Effectiveness; and Genomics and Proteomics. Natural Medicines Comprehensive Database from Therapeutics Research Center covers natural medicines sold in North America and has evidence-based comprehensive monographs on these medicines, as well as a natural product effectiveness checker. Checkers for interactions and depletions, patient education handouts, and Continuing Education Programs are also available with both databases. Both natural product databases have mobile and print versions and provide RSS feeds.

Drug interactions, side effects and adverse reactions

Patients and pharmacy practitioners are very concerned about interactions, side effects, and adverse reactions. These also concern pharmaceutical scientists developing new products.

Meyler's Side Effects of Drugs: An Encyclopedia of Adverse Reactions and Interactions[40] has a long history. According to the Preface of the 15th edition of *Meyler's Side Effects of Drugs: An Encyclopedia of Adverse Reactions and Interactions*, Leopold Meyler, a Dutch physician, experienced adverse drug effects in the 1940s, while undergoing treatment for tuberculosis. He searched for information on this topic and, finding only a nineteenth century tome, he went to work to fill this significant gap. The first edition of this work was published in Dutch in 1951, and an English edition was published in 1952. Editions of *Meyler's Side Effects of Drugs: An Encyclopedia of Adverse Reactions and Interactions* are updated by *Side Effects of Drugs Annual*[41] and cover prescription drugs, anesthetics, antiseptics, drugs of abuse, herbal medicines, and devices and methods in alternative medicine. *Meyler's Side Effects of Drugs: An Encyclopedia of Adverse Reactions and Interactions* is available both in print and electronic formats.

Drug Interactions Analysis and Management[42] is written by two well-known authorities in this area, Philip D. Hansten, PharmD and John R. Horn, PharmD. The focus is on the management of drug interactions and gives the reader options to avoid patient harm and decrease risk. Suggestions regarding monitoring and alternative drugs are recommended when appropriate. Specific information on each interaction also includes risk factors, the mechanism of action, a clinical evaluation of cited reports, closely related drugs that may interact in a similar manner, and references. Each interaction is also assigned a Significance Number, which is based on the intervention needed to minimize risk.

An important specialty resource is *Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk*.[43] This resource provides fetal risk and breast feeding risk summaries, which include animal reproduction data, placental transfer, reports of human pregnancy exposure, and a list of references for more than 1200 drugs. A related database is the Drugs and Lactation Database (LactMed), one of the TOXNET set of databases. It focuses on the levels of the drug in breast milk and infant blood and the possible adverse effects on the nursing infant.

Another special topic is covered by *Food-medication Interactions*,[44] available either as a spiral bound book or a mobile version. More than 1000 drug monographs are arranged alphabetically and cover drug class or action; side effects; renal, hepatic, cardiac, and pregnancy information; contraindications; monitoring information; and special dietary precautions and nutritional effects. There are many tables, including a useful laboratory value table. Canadian brand names are exclusive to the mobile version.

Medication safety is a major concern. *Drug-induced Diseases: Prevention, Detection, and Management*[45] provides information for students and healthcare practitioners to address and improve the standard of care regarding drug-induced diseases. This comprehensive textbook introduces the magnitude of the problem and follows up with sections arranged by anatomical region, such as drug-induced gastrointestinal diseases.

Poisoning and toxicology

Two well know textbooks on toxicology are *Casarett and Doull's Toxicology: The Basic Science of Poisons*[46] and *Goldfrank's Toxicologic Emergencies*.[47] *Casarett and Doull's Toxicology* covers the various aspects of the subject, including toxicokinetics, carcinogenicity, mutagenicity, developmental toxicology, target organ toxicity, toxic agents, environmental toxicology, food toxicology, analytic toxicology, clinical toxicology, and occupational toxicology. *Goldfrank's Toxicologic Emergencies* presents in-depth information on antidotes, general principles, and techniques to evaluate and manage toxic exposures, biochemical toxicology, organ system principles, and classes of compounds. Case studies and study questions are given, and the answers are provided at the end of the book.

TOXNET is a set of databases made available by the US National Library of Medicine (http://toxnet.nlm.nih.gov/). They provide indexing and abstracting and full text information concerning toxicology, hazardous chemicals, environmental health, and toxic releases. Databases may be searched individually or as a set. The Hazardous Substances

Databank (HSDB) contains more than 5000 chemical records and is enhanced with additional material on nanomaterials, regulatory requirements, and emergency handling procedures. Other TOXNET databases include the Chemical Carcinogenesis Research Information System (CCRIS), Integrated Risk Information System (IRIS), GENE-TOX, and the previously described LactMed database. The National Cancer Institute provides data on mutagenicity and tumor promotion and inhibition in CCRIS. IRIS contains data in support of human health risk assessment and is compiled by the US Environmental Protection Agency (EPA). GENE-TOX, created by the US EPA, contains genetic toxicology (mutagenicity) test data on more than 3000 chemicals and recommends proper testing protocols and evaluation procedures.

Formulation and manufacturing

Many of the standard textbooks on formulation and manufacturing are now quite dated. There is a need for additional educational material in this area. The National Institute of Pharmaceutical Technology and Education (http://nipte.org/), which is dedicated to fundamental research and education in pharmaceutical product development and manufacturing, has developed a draft curriculum in this area; development of educational resources is a planned activity of the group. In the meantime, the *Encyclopedia of Pharmaceutical Technology*[48] has monographs on many of the aspects related to formulation and the various pharmaceutical manufacturing processes. For detailed information on drug substances necessary for pre-formulation research, Britain's *Profiles of Drug Substances, Excipients, and Related Methodology*[10] provides comprehensive monographs. Additionally, PharmaHub (http://pharmahub.org/) has an increasing array of useful databases and process modeling software for formulation and manufacturing.

Product identification

Emergency and other medical personnel need to be able to quickly identify capsules or tablets. Many resources include sections on identifying drug or related products. These include the *Physician's Desk Reference*, the *Red Book*, and several online and mobile resources, including Facts and Comparisons eAnswers and Lexi-Comp. The two most well-known titles are *Ident-a-drug Reference*,[49] which identifies the drug by the color, shape, size, and imprint code, and the *IDENTIDEX System*, a part of *MICROMEDEX*.

Consumer drug information

It is important to know where to find reliable and accurate consumer drug information, especially since consumers frequently use the internet to find information. There are many such resources on the internet. MedlinePlus from the US National Library of Medicine (http://www.medlineplus.gov) includes a vast array of features for the consumer, including information on drugs and supplements and a medical dictionary with pronunciation. Drugs.com includes an Interactions Checker. WebMD includes a useful Pill Identifier tool.

An example of expanded access to drug information on the internet is the Drug Information Portal (http://druginfo.nlm.nih.gov), which provides a search interface to information on more than 20,000 drugs from US government agencies, including the National Library of Medicine. There is information for researchers, clinicians, students, and consumers.

Two popular print resources include the *Pill Book*[50] and the *Complete Guide to Prescription and Nonprescription Drugs*.[51] The *Pill Book* includes information on affordable generic alternatives, side effects, adverse effects, drug–drug and drug–food interactions, addictiveness, safe handling of injectables, and when to call the physician. Aside from the usual drug information, the *Complete Guide to Prescription and Nonprescription Drugs* includes the length of time before a drug starts working and warnings regarding premature discontinuation of a drug. At the beginning of the book, there is a list of commonly used drugs to treat specific diseases or conditions.

Personalized medicine

As pharmacists become more focused on the individual patient, pharmacogenetics is becoming more important than ever before. Two valuable resources in this area are Ginsberg and Willard's *Essentials of Genomic and Personalized Medicine*[52] and Catania's *An A–Z Guide to Pharmacogenomics*.[53] *Essentials of Genomic and Personalized Medicine* provides an overview of the field, with translational approaches

to bring the information into the clinical world. *An A–Z Guide to Pharmacogenomics* introduces the terminology and techniques related to this growing field to students and professionals who have a basic understanding of molecular biology.

Professional associations

Associations for almost every specialty of pharmacy in the various regions of the United States and around the world can be found at the Virtual Pharmacy Library (http://www.pharmacy.org/) by clicking on the Associations tab. The list of more than 100 pharmacy-related associations is complete, with links to each association's website.

Emerging trends

The majority of electronic books are still simply copies of the original print versions. Although they can be accessed from anywhere at any time, they are still rather static. According to the *2011 Horizon Report*,[54] the product of collaboration between the EDUCAUSE Learning Initiative (ELI) and the New Media Consortium, this is rapidly changing, and the newer electronic books with added features will become more in demand than the print. Social features will connect the reader to other researchers, enabling collaboration. Self-directed, interactive experiences and activities are beginning to be provided. Videos and other audiovisual resources will integrate into these electronic resources. Links to supporting materials can enrich the reading experience. Cloud tags will make locating useful chapters or sections vastly simpler.

Mobile resources have been used by pharmacy professional students, pharmacists, and faculty for several years. According to the *2011 Horizon Report*, "Internetcapable mobile devices will outnumber computers within the next year." With the spread of smart phones and other devices, students and scientists will demand more resources and applications compatible with the platforms they have chosen. One example is PubMed on Tap, which allows the user to search PubMed and manage references from the iPod Touch, iPhone, or iPad.

Data planning and management is becoming a major thrust in the sciences. Websites, such as PharmaHUB at http://pharmahub.org, were created to facilitate the collaborative creation and sharing of pharmaceutical engineering and science information and modeling tools. The PharmaHUB website states that their goal is to "support innovations in product and process development and manufacturing methodology for pharmaceutical products."[55] This is an area in which the amount of data can be massive, and these data have been isolated in individual research groups or institutes until now. Sharing the data will allow faster progress in the research area.

For further information

The American Association of Colleges of Pharmacy Libraries/Educational Resources Section's Basic Resources for Pharmacy Education (http://www.aacp.org/governance/SECTIONS/libraryeducationalresources/Pages/LibraryEducationalResourcesSpecialProjectsandInformation.aspx) provides a benchmark to use in selecting many of the resources listed herein and is a good place to explore for more references in a specific pharmacy related field. An excellent book on pharmaceutical resources is Bonnie Snow's *Drug Information: A Guide to Current Resources*.[56]

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5

Pharmaceutical Chemistry

Inorganic pharmaceutical chemistry

Inorganic chemicals have been used in pharmacy and medicine for many reasons, ranging from therapeutic agents to nutritional supplements to pharmaceutical necessities. In this section a review of some chemical principles and properties of elements is followed by a discussion of the wide variety of useful inorganic chemicals.

Basis of chemical reactions

Although many subatomic particles have been identified, only the protons and neutrons of the nucleus of an atom and the extranuclear electrons will be considered here.

Each atom of an element is described uniquely by two pure numbers: its atomic number and its atomic weight. The atomic number gives the number of protons present in the nucleus and therefore its positive charge. Because the ground-state atom must be neutral, this in turn defines the number of extranuclear electrons. The difference between the atomic number and the atomic weight of a given *isotope* of an element defines the number of neutrons in the nucleus. Atomic weights in the tables are not whole numbers because they represent the weighted average of the atomic weights of all isotopes present.

- The electrons are arranged in major quantum groups (energy levels or orbitals) occupying the space about the nucleus. Each electron is assigned four quantum numbers:
- The principal quantum number, n, describes the relative position of an energy level with respect to the other energy levels present.
- The subquantum number, l, describes the different electron distributions possible for a given value of n.
- The magnetic quantum number, m_L, is best described as the magnetic contribution to the angular momentum due to the movement of the electrons in space.
- The magnetic spin quantum number, m_S, is the magnetic component contributed by the spin of the electron.

The permitted values for n are 1, 2, 3, …, and for l are 0, 1, 2, … $(n - 1)$, for m_L are −l, … 0, … +l, and for $m_S \pm 1/2$. Returning to the subquantum number l, when l is 0 the electrons occupying the suborbital are known as s electrons; when l is 1, they're known as p electrons; when l is 2, they're known as d electrons; and when l is 3, they're known as f electrons. Thus, if two electrons occupy suborbital 0 of major quantum group 3, they are represented as $3s^2$.

In assigning electrons to the atom the Aufbau principle is used. It is an application of quantum theory, Hund's rules, and the Pauli exclusion principle. Simply stated, a given entering electron must occupy the lowest unoccupied energy level of the atom. In other words, each electron must have a unique set of quantum numbers.

As a result of the above process, all atoms, except hydrogen and the inert gases, have one or more completely occupied lower major quantum groups and have the suborbitals of their highest major quantum group only partially filled. The electrons of this outer, partially filled energy level give each element its distinct chemical properties. These are the *valence electrons*.

Chemical reactions entail the removal of valence electrons, adding electrons to a partly filled valence shell, or sharing a pair of valence electrons between two atoms. Most atoms attempt to achieve a rare-gas outer shell (ns^2 or ns^2np^6) by these processes. The energy required for the removal of the electron of least energy is known as the *first ionization potential*. It is unique for each element. The metals have low ionization potentials and therefore readily form cations. Nonmetals have high ionization potentials.

The attraction of a nucleus for electrons is termed its *electronegativity*. Metals have low electronegativities (they are electropositive), whereas nonmetals (especially the halogens) have high electronegativities. This allows the latter to attract additional electrons to form anions.

When atoms with widely differing electronegativities react (e.g., sodium at 0.93, with chlorine at 3.98), an electron transfer takes place. The one valence electron of sodium ($3s^1$) enters the incompletely filled ($3s^2 3p^5$) valence shell of the chlorine atom. Sodium now has an inert-gas (Ne) electron structure with a +1 charge. The chlorine achieves the argon structure with a −1 charge. There is no formal electron-pair bond between the two entities. A crystal of sodium chloride consists of equal numbers of sodium and chloride ions held in place by the interaction of the spherically symmetrical positive cation field and the spherically symmetrical negative anion field. These ionic (electrostatic) compounds are characterized by high boiling and melting points, and most are water soluble.

If two reacting atoms have similar electronegativities, such as two hydrogen atoms, a sharing of electrons takes place. One electron is donated to the bond from an incompletely filled suborbital of each atom. A covalent bond is formed by the overlap of the two atomic orbitals involved. With the formation of the bond, a molecule results. The bonding electrons are no longer restricted to their atomic orbitals; they now are free to move in an orbit between the two atoms in what is known as a molecular orbital.

When the electronegativities of the two atoms involved in the formation of a covalent bond are not identical, the atom with the higher electronegativity tends to attract the electrons of the molecule more strongly than its partner. This leads to polarization of the molecule, resulting in a *dipole*. The extent of polarization is directly proportional to the difference in electronegativities. Such bonds are said to have partial ionic character.

In practice, only the most electropositive atoms reacting with the most electronegative atoms result in purely electrostatic compounds, and only atoms with equal electronegativities form purely covalent bonds. Those bonds formed from elements between these extremes have partial covalent or partial electrostatic character.

Atoms with orbitals occupied by an unshared pair of electrons can share this electron pair with an atom lacking two or more electrons in its valence shell. The bond formed is said to be a *coordinate covalent bond*. Once this bond has been formed, it cannot be distinguished from an ordinary covalent bond; the difference lies only in the manner of formation. The formation of the ammonium ion from an ammonia molecule, which has an unshared electron pair, and a hydrogen ion, which has an empty s orbital, illustrates this type of reaction.

Covalent compounds have low melting and boiling points, and usually are insoluble in water. Solubility in water can be induced by introducing an

acid or base group into the molecule. Reaction with base or acid will then give a soluble salt.

Other types of bonding also exist. Those of interest are weakly bonded; the compounds formed decompose more readily than the electrostatic and covalent types. Hydrogen bonding (bridging) is an example of this type of bonding, and is common among many molecules. Dipole–dipole bonding also is possible, resulting in very weak associations.

Complexes are compounds or ions formed when an atom or cation's *central unit* acts as a center about which anions or molecules (ligands) arrange themselves. The central unit is said to have a coordination number equal to the number of ligands forming the complex. The maximum number of ligands that can arrange themselves about the central unit is known as its *maximum coordination number* and is a function of the size of the central unit. Usual maximum coordination numbers are 2, 4, 6, or 8. The number of ligands that can coordinate with the central unit also is a function of ligand size. Thus, even though the maximum coordination number of aluminum is 6, only four of the relatively large chloride ions can be accommodated as ligands, for example, $[AlF_6]^{3-}$ vs. $[AlCl_4]^{1-}$. The bonding involved in the formation of complexes can be coordinate covalent or electrostatic. Bonds depending on permanent dipoles are also common, such as with hydrates.

Acids, bases, and buffers

Acids and bases

Acid–base theories range from the limited, classic Arrhenius theory to the comprehensive theory of Lewis. In between are the Franklin solvent system of acids and bases and the Brønsted proton donor theory.

Because physiological functions involve aqueous media, and because pharmaceuticals are frequently dispensed in aqueous solution, the Brønsted theory is convenient for use in pharmacy. A molecule or ion that can provide a proton (proton donor) is an *acid*; one that can accept a proton (proton acceptor) is a *base*. On accepting a proton, a base becomes an acid; on losing its proton, the acid becomes a base. An acid and its base are related by the presence or absence of a proton, and are known as a *conjugate pair*. The transfer of a proton from the acid of one conjugate pair to the base of another conjugate pair is *neutralization*.

Table 5.1 Conjugate acid–base pairs

Acid	Base	Acid	Base
H_2O	OH^-	H_2SO_4	HSO_4^-
H_3O^+	H_2O	HSO_4^-	SO_4^{2-}
NH_4^+	NH_3	H_3PO_4	$H_2PO_4^-$
RNH_3^+	RNH_2	$H_2PO_4^-$	HPO_4^{2-}
HCl	Cl^-	$[A](H_2O)_6]^{3+}$	$[A](H_2O)_5(OH)]^{2+}$
H_2CO_3	HCO_3^-	$[A](H_2O)_5(OH)]^{2+}$	$[A](H_2O)_4(OH)_2]^+$
HCO_3^-	CO_3^-	$H_3BO_3 \cdot H_2O$	$[B(OH)_4]^-$

Some conjugate pairs of pharmaceutical interest are given in Table 5.1. It is evident that acids and bases can be cations, neutral molecules, or anions. Some structures can be members of two different conjugate pairs, as an acid in one and as a base in the other.

A strong acid is an acid that loses its proton easily; a *weak acid* holds its proton tenaciously. The conjugate base of a strong acid is a *weak base*, whereas that of a weak acid is a *strong base*. In neutralization, the proton goes to the strongest of the bases present. The percent ionization and the ionization constant are measures of the strength of a given acid.

Acids and bases are used in pharmacy for analytical procedures, as buffer systems, and to dissolve insoluble medicinals. To accomplish the latter the insoluble compound must have a functional group capable of acting as a strong base or as an acid. Lidocaine Hydrochloride Injection USP and Niacin Injection USP are examples. The former is prepared by reacting lidocaine with hydrochloric acid; the diethylamino group is a stronger base than either the water molecule or the chloride ion. Lidocaine goes into solution as a cation. Niacin Injection USP is prepared by reacting niacin with either sodium carbonate or sodium hydroxide; the carboxyl group loses its proton to the carbonate or hydroxyl ion, and the niacin goes into solution as an anion.

In neutralization, as above, the pharmacist must be cognizant of two requirements that are not important in ordinary chemical neutralizations. The counterion being introduced – chloride ion and

sodium ion, respectively, in the above examples – must be compatible physiologically with the body fluids. Also, because strong acids or bases are being used, there can be no excess acid or base because of the corrosive nature of these reagents.

Acids and bases are also necessary for the preparation of effervescent mixtures, a medicinal dosage form sometimes used to render a medicinal more palatable for oral administration. Sodium bicarbonate is used as the carbon dioxide source. Solid acids such as citric acid, tartaric acid, or sodium dihydrogen phosphate are used, frequently in combination. Reaction rate is very important in these formulations. Sodium bicarbonate must have the correct particle size; if too fine, the reaction is too violent, and if too coarse, the reaction is too slow. To lower the activity of the acid, a normal salt of the acid is included in the mixture as a diluent.

Some acids and bases listed in the compendia at present are Calcium Hydroxide, Potassium Bicarbonate, Potassium Hydroxide, Sodium Bicarbonate, Sodium Carbonate, Sodium Hydroxide, Strong Ammonia Solution, Acetic Acid, Hydrochloric Acid and Diluted Hydrochloric Acid, Nitric Acid, Sulfuric Acid, Phosphoric Acid and Diluted Phosphoric Acid.

Stability and storage problems of these compounds must be considered. All strong bases are subject to reaction with carbon dioxide if proper closures are not maintained. Volatile compounds, such as ammonia and hydrogen chloride, must be sealed tightly at all times, as must hygroscopic compounds such as sodium hydroxide.

Buffers

Buffers are used to maintain the pH of a medicinal at an optimal value. A *buffer* is a solution of a weak acid and its conjugate base, the base being provided by one of its soluble salts.

Physiological control of pH

Brønsted acids and bases have been used for many years to maintain and adjust the pH of body fluids. By far the greatest interest has been in development of gastric antacids. However, an adequate number of suitable reagents are available for systemic pH adjustments.

Gastric antacids

The present official magnesium antacids include Magnesium Hydroxide, Milk of Magnesia, Magnesia Tablets, Alumina and Magnesia Oral Suspension (and Tablets), Magnesium Carbonate, Magnesium Carbonate and Sodium Bicarbonate for Oral Suspension, Magnesium Oxide, Magnesium Phosphate, and Magnesium Trisilicate (and Tablets). The official aluminum antacids include Aluminum Hydroxide Gel, Dried Aluminum Hydroxide Gel (and Capsules and Tablets), Aluminum Phosphate Gel, Dihydroxyaluminum Aminoacetate (and Magma, and Capsules and Tablets), Dihydroxyaluminum Sodium Carbonate (and Tablets), Alumina, Magnesia, and Calcium Carbonate Oral Suspension (and Tablets), Alumina and Magnesium Trisilicate Oral Suspension (and Tablets), and the Alumina and Magnesia preparations already listed. The calcium antacids include Precipitated Calcium Carbonate (and Tablets), Calcium Carbonate and Magnesia Tablets, and Calcium and Magnesium Carbonates Tablets. Magaldrate, an aluminum magnesium hydroxide sulfate, is official, as is its Oral Suspension and Tablets. Miscellaneous official antacids include Milk of Bismuth, Sodium Bicarbonate, and Potassium Bicarbonate.

There are other gastric antacid dosage form monographs, some including simethicone (an antiflatulent), and they are Magnesium Oxide Capsules (and Tablets); Basic Aluminum Carbonate Gel; Dried Basic Aluminum Carbonate Gel Capsules (and Tablets); Alumina and Magnesium Carbonate Oral Suspension (and Tablets); Alumina, Magnesium Carbonate, and Magnesium Oxide Tablets; Alumina, Magnesia, and Simethicone Oral Suspension (and Tablets); Calcium Carbonate Oral Suspension; and Magaldrate and Simethicone Oral Suspension (and Tablets). A monograph for Magnesium Hydroxide Paste, which contains about 31g of magnesium hydroxide per 100g, describes a suspension that is an intermediate in the manufacture of Milk of Magnesia and other suspensions of magnesium hydroxide.

Systemic alkalizers and acidifiers

Sodium Bicarbonate USP and Potassium Bicarbonate USP are used as systemic alkalizers. Because the bicarbonates are unstable to heat, chemical problems

arise in the sterilization of bicarbonate solutions.

$$2HCO_3^- \leftrightarrow CO_3^{2-} + CO_2 + H_2O$$

To depress the forward reaction, the solution can be saturated with carbon dioxide. To prevent the loss of the gas, which would result in the permanent formation of the strong carbonate base, the ampules used must be sealed tightly before sterilization, and must be made of glass sufficiently strong to withstand the gas pressure developed during sterilization. On cooling, the reverse reaction becomes dominant.

Ammonium Chloride USP, Monobasic Sodium Phosphate USP, and Calcium Chloride USP are employed as systemic acidifiers.

Electrolytes and essential trace elements

It is instructive to review the physical and chemical properties that make possible the respective roles of electrolytes and essential trace elements in pharmacy. Examination of orbital electron structures, ionic radii, oxidation states, etc., as given in Tables 5.2 through 5.12, can yield valuable clues to their behavior.

The transition elements have incompletely filled 18-electron outer shells, and each can exist in several different oxidation states. In most cases the shift between two electron states is relatively easy; for example,

$$Fe^{2+} \leftrightarrow Fe^{3+} + e^-$$

As a result, the transition elements can act as electron sinks and are active in those systems involved in oxidation or reduction reactions.

On the other hand, an element such as zinc achieves a completely filled outer 18-electron shell on becoming zinc ion. In the 2+ oxidation state this shell becomes stable. Unlike the tightly held spherical 8-electron shell, the 18-electron shell is *mushy*, and is deformed or polarized easily by external fields. In turn, it can cause polarization of other moieties. This ion is not found in redox systems but rather in systems such as carbonic anhydrase, which aid in the splitting or forming of molecules.

Table 5.2 Elements of group I-A

Element	Hydrogen	Lithium	Sodium	Potassium	Rubidium	Cesium	Francium
Symbol	H	Li	Na	K	Rb	Cs	Fr
Atomic number	1	3	11	19	37	55	87
Atomic weight	1.008	6.94_1	22.99	39.10	85.47	132.91	(223)
Orbital electrons	$1s^1$	$[He]2s^1$	$[Ne]3s^1$	$[Ar]4s^1$	$[Kr]5s^1$	$[Xe]6s^1$	$[Rn]7s^1$
Oxidation states	1+, 1−	1+	1+	1+	1+	1+	1+
Atomic radius (Å)	0.37	1.50	1.86	2.31	2.44	2.62	–
Ionic radius (Å)	1.36 (1−)[a]	0.60 (1+)	0.95 (1+)	1.33 (1+)	1.48 (1+)	1.69 (1+)	1.76 (1+)
Ionic (hydrated) radius (Å)	–	3.40	2.76	3.32	2.28	2.28	–
Ionization potential (eV)	13.527	5.39	5.14	4.34	4.18	3.89	–
Electronegativity[b]	2.1	0.98	0.93	0.82	0.82	0.79	0.7
% of earth's crust	0.127	6.5×10^{-3}	2.8	2.6	3.1×10^{-2}	7×10^{-4}	–

[a] Hydride ion; figure in parentheses is the oxidation state.
[b] Pauling scale.

Table 5.3 The elements of groups I-B and II-B

Element	Copper	Silver	Gold	Zinc	Cadmium	Mercury
Symbol	Cu	Ag	Au	Zn	Cd	Hg
Atomic number	29	47	79	30	48	80
Atomic weight	63.54	107.87	196.97	65.38	112.4	200.59
Orbital electrons	$[Ar]3d^{10}4s^1$	$[Kr]4d^{10}5s^1$	$[Xe]4f^{14}5d^{10}6s^1$	$[Ar]3d^{10}4s^2$	$[Kr]4d^{10}5s^2$	$[Xe]4f^{14}5d^{10}6s^2$
Oxidation states	1+, 2+	1+, 2+	1+, (2+), 3+	2+	2+	1+, 2+
Atomic radius (Å)	1.40	1.70	1.70	1.40	1.60	1.50
Ionic (crystal) radii (Å)	0.96 (1+) 0.72 (2+)	1.26 (1+) 0.89 (2+)	1.37 (1+) 0.99 (3+)	– 0.88 (2+)	– 1.09 (2+)	1.27 (1+) 1.16 (2+)
Ionization potential (eV)	7.724	7.574	9.223	6.92	8.99	10.42
Electronegativity	1.90	1.93	2.54	1.65	1.69	2.00
% of earth's crust	10^{-4}	10^{-8}	10^{-9}	1.3×10^{-2}	1.5×10^{-5}	$\sim 10^{-6}$

Table 5.4 The elements of group II-A

Element	Beryllium	Magnesium	Calcium	Strontium	Barium	Radium
Symbol	Be	Mg	Ca	Sr	Ba	Ra
Atomic number	4	12	20	38	56	88
Atomic weight	9.012	24.31	40.08	87.62	137.3	226.03
Orbital electrons	$[He]2s^2$	$[Ne]3s^2$	$[Ar]4s^2$	$[Kr]5s^2$	$[Xe]6s^2$	$[Rn]7s^2$
Oxidation states	2+	2+	2+	2+	2+	2+
Atomic radius (Å)	0.90	1.70	1.74	1.92	1.98	–
Ionic (crystal) radius (Å) (coordination number 6)	0.31 (2+)[a]	0.65 (2+)	0.99 (2+)	1.13 (2+)	1.35 (2+)	1.43 (2+)
Ionization potential (eV)	9.3	7.6	6.1	5.7	5.2	5.252
(II)[b]	18.2	15.0	11.9	11.0	9.95	10.099
Electronegativity	1.57	1.31	1.00	0.95	0.89	0.9
% of earth's crust	6×10^{-4}	2.1	3.6	0.03	0.025	1.3×10^{-10}

[a] Coordination number 4.
[b] Second ionization potential.

Table 5.5 The elements of group III-A

Element	Boron	Aluminum	Gallium	Indium	Thallium
Symbol	B	Al	Ga	In	Tl
Atomic number	5	13	31	49	81
Atomic weight	10.81	26.98	69.72	114.8	204.37
Orbital electrons	$[He]2s^2 2p^1$	$[Ne]3s^2 3p^1$	$[Ar]3d^{10} 4s^2 4p^1$	$[Kr]4d^{10} 5s^2 5p^1$	$[Xe]4f^{14} 5d^{10} 6s^2 6p^1$
Oxidation states	3+	(1+), 3+	1+, 2+, 3+	1+, 3+	1+, 3+
Atomic radius (Å)	0.82	1.25	1.26	1.44	2.0
Ionic (crystal) radius (Å)	–	–	1.90 (1+)	1.90 (1+)	1.64 (1+)
(coordination number 6)	0.20 (3+)[a]	0.675 (3+)	0.76 (3+)	0.94 (3+)	1.03 (3+)
Ionization potential (eV)	8.30	5.95	6.0	5.8	6.1
(II)[b]	25.15	18.82	20.4	18.8	20.3
(III)[c]	37.92	28.44	30.6	27.9	29.7
Electronegativity	2.04	1.61	1.81	1.78	1.62
% of earth's crust	3×10^{-4}	8.13	1.5×10^{-3}	10^{-5}	$\sim 10^{-4}$

[a] Coordination number 4.
[b] Second ionization potential.
[c] Third ionization potential.

Unlike the incompletely filled shells of the transition elements or the 18-electron shell of the zinc ion, 8-electron-shell ions ordinarily are stable and are not deformed easily by external fields. Those 8-electron outer-shell ions with a high charge (e.g., calcium) have intense charge densities in the volume surrounding the ion. This results in strong interactions with the fields of other moieties to form strong permanent associations. However, an 8-electron shell effectively screens the single charge of ions such as sodium. They are therefore chemically inert with very weak interactions with other ions. This explains their simple roles in the body fluids as osmotic regulators, etc.

There are a fair number of monographs for parenteral infusions intended to supply electrolytes, water, and carbohydrates as nutrients. In addition to monographs in the USP for Ringer's and Dextrose Injection and Lactated Ringer's and Dextrose Injection (with Half-Strength and Modified variations), a series of monographs are found with the designation Multiple Electrolytes in each title; these monographs offer choices of cations from Na^+, K^+, Ca^{2+}, Mg^{2+}, and NH_4^+; of anions from chloride, acetate, citrate, lactate, gluconate, phosphate, and sulfate; plus a choice of carbohydrate nutrient from invert sugar and dextrose. These monographs indicate an awareness of the importance of inorganic cations (including magnesium) and anions, and provide a variety of choices to allow treatment of patients on an individualized basis.

In addition to providing official standards for various infusions used as parenteral rehydration solutions or electrolyte replenishers, USP has a generic monograph for Oral Rehydration Salts, a dry mixture of sodium chloride, sodium bicarbonate (or

Table 5.6 Transition elements

		Group III-B			Group IV-B	
Element	**Scandium**	**Yttrium**	**Lanthanum**	**Titanium**	**Zirconium**	**Hafnium**
Symbol	Sc	Y	La	Ti	Zr	Hf
Atomic number	21	39	57	22	40	72
Atomic weight	44.96	88.91	138.9	47.90	91.22	178.5
Orbital electrons	$[Ar]3d^1 4s^2$	$[Kr]4d^1 5s^2$	$[Xe]5d^1 6s^2$	$[Ar]3d^2 4s^2$	$[Kr]4d^2 5s^2$	$[Xe]4f^{14} 5d^2 6s^2$
Oxidation states	3+	3+	3+	2+, 3+, 4+	2+, 4+	(2+), 4+
Atomic radius (Å)	1.51	1.8	1.87	1.36	1.45	1.44
Ionic radii (Å)	0.81 (3+)	0.93 (3+)	1.15 (3+)	1.00 (2+)	–	–
(coordination number 6)				0.75 (4+)	0.86 (4+)	0.85 (4+)
Ionization potential (eV)	6.7	6.5	5.6	6.82	6.84	~5.5
Electronegativity	1.54	1.53	1.3	–	–	–
% of earth's crust	0.44	0.022	4.5×10^{-4}	0.629	0.028	–

sodium citrate), potassium chloride, and dextrose to be dissolved and used to treat chronic diarrhea.

In recent years there has been an increased awareness of the importance of minerals in the diet and of the value of mineral supplements. Generally, gluconates, like other organic salts, are less irritating to the gastrointestinal tract; thus, the following metal gluconates are found in the USP: Zinc, Sodium, Copper, Magnesium, and Manganese. The USP includes a monograph for Selenious Acid Injection, which can provide a source of selenium as a mineral supplement.

In a new USP section entitled Nutritional Supplements are monographs for Mineral Capsules and Mineral Tablets. The minerals present in these dosage forms are potassium, calcium, magnesium, phosphorous, zinc, iron, manganese, copper, molybdenum, fluorine, chromium, iodine, and selenium.

When it is necessary to administer trace elements parenterally, the monograph entitled Trace Elements USP describes a sterile solution that may be used to administer zinc, copper, chromium, manganese, selenium, iodine, and molybdenum.

Topical agents

Oxidizing germicides

Hydrogen Peroxide, Sodium Hypochlorite, Iodine, and/or their various solutions are cited in the USP. Hypochlorous acid, the active moiety in sodium hypochlorite solution, owes its germicidal activity to both oxidizing and chlorinating activity.

Precipitating germicides

Silver Nitrate, Silver Nitrate Ophthalmic Solution, and Toughened Silver Nitrate are listed in the USP, as is Ammoniated Mercury. Zinc Acetate, Zinc Chloride, Zinc Sulfate, and Zinc Undecylenate are also official. Only two boron compounds are cited in the NF: Boric Acid and Sodium Borate. The antimony compounds listed are Antimony Potassium Tartrate USP and Antimony Sodium Tartrate USP.

Astringents

Aluminum ion in solution is an excellent local astringent over wide concentration ranges. It is also

Table 5.7 The elements of group IV-A

Element	Carbon	Silicon	Germanium	Tin	Lead
Symbol	C	Si	Ge	Sn	Pb
Atomic number	6	14	32	50	82
Atomic weight	12.01	28.08	72.59	118.69	207.2
Orbital electrons	$[He]2s^2 2p^2$	$[Ne]3s^2 3p^2$	$[Ar]3d^{10} 4s^2 4p^2$	$[Kr]4d^{10} 5s^2 5p^2$	$[Xe]4f^{14} 5d^{10} 6s^2 6p^2$
Oxidation states	4− to 4+	4− to 4+	2+, 4+	2+, 4+	2+, 4+
Atomic radius (Å)	0.77	1.17	1.22	1.41	1.54
Ionic (crystal) radii	2.6 (4−)	2.71 (4−)	0.87 (2+)	0.93 (2+)	1.20 (2+)
(coordination number 6)	0.3 (4+)[a]	0.54 (4+)	0.67 (4+)	0.83 (4+)	0.91 (4+)
Ionization potential (eV)	11.264	8.149	8.09	7.30	7.38
Electronegativity	2.55	1.90	2.01	1.58	1.87
% of earth's crust	2.7×10^{-2}	27.7	7×10^{4}	6×10^{-4}	1×10^{-3}

[a] Coordination number 4.

Table 5.8 The elements of group V-A

Element	Nitrogen	Phosphorus	Arsenic	Antimony	Bismuth
Symbol	N	P	As	Sb	Bi
Atomic number	7	15	33	51	83
Atomic weight	14.01	30.97	74.92	121.75	208.98
Orbital electrons	$[He]2s^2 2p^3$	$[Ne]3s^2 3p^3$	$[Ar]3d^{10} 4s^2 4p^3$	$[Kr]4d^{10} 5s^2 5p^3$	$[Xe]4f^{14} 5d^{10} 6s^2 6p^3$
Oxidation states	3−, 1+, 3+, 5+	3−, 3+, 5+	3−, 3+, 5+	3−, 3+, 5+	3−, 3+, 5+
Atomic radius (Å)	0.70	1.06	1.21	1.41	1.5
Ionic (crystal) radii (Å)	1.32 (3+)	0.58 (3+)	0.72 (3+)	0.90 (3+)	1.17 (3+)
(coordination number 6)	0.27 (5+)	0.52 (5+)	0.60 (5+)	0.74 (5+)	0.90 (5+)
Ionization potential (eV)	14.48	11.10	10.5	8.5	8.0
Electronegativity	3.04	2.19	2.18	2.05	2.02
% of earth's crust	4.6×10^{-8}	0.12	5×10^{-4}	10^{-4}	2×10^{-5}

Table 5.9 Transition elements

		Group V-B			Group VI-B	
Element	**Vanadium**	**Niobium**	**Tantalum**	**Chromium**	**Molybdenum**	**Tungsten**
Symbol	V	Nb	Ta	Cr	Mo	W
Atomic number	23	41	73	24	42	74
Atomic weight	50.94	92.91	180.95	52.00	95.94	183.85
Orbital electrons	$[Ar]3d^3 4s^2$	$[Kr]4d^4 5s^1$	$[Xe]4f^{14} 5d^3 6s^2$	$[Ar]3d^5 4s^1$	$[Kr]4d^5 5s^1$	$[Xe]4f^{14} 5d^4 6s^2$
Oxidation states	2+, 3+, 4+, 5+	2+, 3+, 4+, 5+	2+, 3+, 4+, 5+	2+, 3+, 4+, 6+	2+ . . . 6+	2+ . . . 6+
Atomic radius (Å)	1.22	1.34	1.34	1.18	1.30	1.30
Ionic (crystal) radii (Å)	0.40 (5+)	0.70 (5+)	0.73 (5+)	0.76 (3+)	0.79 (4+)	0.80 (4+)
(coordination number 6)				0.58 (6+)	0.73 (6+)	0.74 (6+)
Ionization potential (eV)	6.71	6.79	~6	6.77	7.38	7.98
Electronegativity	–	–	1.33	1.66	2.2	2.36
% of earth's crust	0.021	–	–	2×10^{-2}	$\sim 5 \times 10^{-4}$	$\sim 1.5 \times 10^{-4}$

Table 5.10 The elements of group VI-A

Element	**Oxygen**	**Sulfur**	**Selenium**	**Tellurium**	**Polonium**
Symbol	O	S	Se	Te	Po
Atomic number	8	16	34	52	84
Atomic weight	16.00	32.06	78.9_6	127.6	(209)
Orbital electrons	$[He]2s^2 2p^4$	$[Ne]3s^2 3p^4$	$[Ar]3d^{10} 4s^2 4p^4$	$[Kr]4d^{10} 5s^2 5p^4$	$[Xe]4f^{14} 5d^{10} 6s^2 6p^4$
Oxidation states	2–, 1–	2–, 2+, 6+	2–, 4+, 6+	2–, 4+, 6+	4+, 6+
Atomic radius (Å)	0.66	1.04	1.16	1.37	1.53
Ionic (crystal) radii (Å) (simple anion)	1.26 (2–)	1.70 (2–)	1.84 (2–)	2.07 (2–)	1.08 (4+)
(coordination number 6)	–	0.43 (6+)	0.56 (6+)	0.57 (6+)	0.81 (6+)
Ionization potential (eV)	13.61	10.36	9.75	9.0	–
Electronegativity	3.44	2.58	2.55	2.1	2.0
% of earth's crust	46.6	0.052	10^{-7}	10^{-7}	10^{-14}

Table 5.11 The elements of group VII-A

Element	Fluorine	Chlorine	Bromine	Iodine	Astatine
Symbol	F	Cl	Br	I	At
Atomic number	9	17	35	53	85
Atomic weight	19	35.45	79.90	126.90	(210)
Orbital electrons	$[He]2s^2 2p^5$	$[Ne]3s^2 3p^5$	$[Ar]3d^{10} 4s^2 4p^5$	$[Kr]4d^{10} 5s^2 5p^5$	$[Xe]4f^{14} 5d^{10} 6s^2 6p^5$
Oxidation states	1−	1−, 1+, 3+, 5+, 7+	1−, 1+, (3+), 5+	1−, 1+, (3+), 5+, 7+	–
Atomic radius (Å)	0.64	0.99	1.14	1.33	–
Ionic (crystal) radii (Å) (halide anion)	1.19	1.67	1.82	2.06	–
(coordination number 6)	0.022 (7+)	0.41 (7+)	0.53 (7+)	0.67 (7+)	0.76 (7+)
Ionization potential (eV)	17.42	13.01	11.84	10.44	–
Electronegativity	3.98	3.16	2.96	2.66	2.2
% of earth's crust	8×10^{-2}	3×10^{-2}	1.6×10^{-4}	3×10^{-5}	–

mildly antiseptic. Aluminum Chloride USP was once used in this application, but the high acidity of its solutions caused problems. The acidity results from ionization of the hexa-aquo ion,

$$[Al(H_2O)_6]^{3+} + H_2O \leftrightarrow [Al(OH)(H_2O)_5]^{2+} + H_3O^+$$

and is approximately that of acetic acid. Today, the mixture of two compounds (aluminum hydroxychloride, aluminum chlorhydrate, aluminum chlorhydrol) obtained by partial neutralization of aluminum chloride is used.

$$[Al(H_2O)_6]^{3+} + OH^- \rightarrow [Al(OH)(H_2O)_5]^{2+} + H_2O$$

$$[Al(OH)(H_2O)_5]^{2+} + OH^- \rightarrow [Al(OH)_2(H_2O)_4]^+ + H_2O$$

The reaction is stopped before complete conversion to the dihydroxy hydrate. The resulting solution (or dried product) retains the excellent astringent (and deodorant) properties of the aluminum ion, but the pH of the solution's approximate neutrality (5 to 6).

Aluminum Subacetate Topical Solution USP is essentially a solution of the above ions prepared from aluminum sulfate using carbonate ion ($CaCO_3$) as the base. Aluminum Sulfate, Ammonium Alum, and Potassium Alum are found in the USP and are also used as astringents. Alum can be either the potassium or ammonium form. It is shaped into a pencil form to be used as a styptic.

Iron(III) and aluminum ions are very similar. Iron(III) is astringent, and preparations of ferric salts for such use formerly were recognized. Although it is efficient in this capacity, its staining property is a major disadvantage. Lime water, a saturated solution of fresh calcium hydroxide, is used as a local astringent. Bismuth subnitrate and the other bismuth subsalts are used as astringents and protectives.

Protective agents

To possess good adhering properties, protective agents must be in very finely powdered form. They must also be relatively inert, insoluble compounds. A wide range of compounds are suitable as protective agents. They are usually used externally, but some

Table 5.12 Transition elements

		Group VII-B		Group VIII – First Triad		
Element	**Manganese**	**Technetium**	**Rhenium**	**Iron**	**Cobalt**	**Nickel**
Symbol	Mn	Tc	Re	Fe	Co	Ni
Atomic number	25	43	75	26	27	28
Atomic weight	54.94	(98)	186.2	55.85	58.93	58.71
Orbital electrons	$[Ar]3d^5 4s^2$	$[Kr]4d^5 5s^2$	$[Xe]4f^{14} 5d^5 6s^2$	$[Ar]3d^6 4s^2$	$[Ar]3d^7 4s^2$	$[Ar]3d^8 4s^2$
Oxidation states	2+, 3+, 4+, 6+, 7+	2+, 3+, 4+, 6+, 7+	3+, 4+, 5+, 6+, 7+	2+, 3+	2+, 3+	2+, 3+
Atomic radius (Å)	1.17	1.27	1.25	1.17	1.16	1.15
Ionic (crystal) radii (Å)	0.81 (2+)	–	0.81 (3+)	0.75 (2+)	0.79 (2+)	0.83 (2+)
(coordination number 6)	0.40 (6+)	0.56 (7+)	0.69 (5+)	0.69 (3+)	0.69 (3+)	0.70 (3+)
Ionization potential (eV)	7.43	7.23	7.87	7.83	~8.5	7.6
Electronegativity	1.55	1.9	1.9	1.85	1.88	1.91
% of earth's crust	0.085	Zero (?)	10^{-7}	5	2.3×10^{-3}	8×10^{-3}

applications involve the gastrointestinal tract. Some are slightly soluble (e.g., ZnO) and give some astringent action; others (e.g., kaolin) have adsorbent action.

Zinc Oxide, Calamine (and Calamine Lotion and Phenolated Calamine Lotion), and Zinc Stearate (all USP) are used for their protective and slightly astringent properties. Calamine is the calcined native zinc oxide ore. The iron oxide impurity gives calamine a flesh color that is cosmetically more appealing. Zinc stearate, a mixture of fatty acid zinc soaps, has an unctuous feel. White Lotion USP is used for its astringent and protective powers.

Magnesium trisilicate, basic aluminum carbonate, and chalk are used as protective compounds, as are the various insoluble bismuth subsalts. Talc is used because of its smooth, unctuous feel. Kaolin and bentonite are used as they also have some absorptive properties; titanium dioxide is used as a solar screen.

Inorganic pigments

The most important innocuous pigments are the iron oxides. They give colors throughout the visible spectrum. Three variables are involved: particle size, oxidation state, and degree of hydration.

Acid	Conjugate base
H_2SO_4	HSO_4^-
HNO_3	NO_3^-
HF	F^-
H_3PO_4	$H_2PO_4^-$
H_2S	HS^-
HS^-	S^{2-}
NH_4^+	NH_3

Miscellaneous inorganic applications

Artificial atmospheres

Five gases are official: Nitrogen, Oxygen, Helium, Carbon Dioxide, and Nitrogen(I) Oxide (nitrous oxide or laughing gas). Nitrogen is used as a diluent for oxygen and may be used as a protective atmosphere for easily oxidized medicinals.

Helium, because of its low density compared to nitrogen, is used to prepare a gaseous mixture composed of 20% oxygen and helium. This mixture is used to alleviate respiration difficulties. Because of the low solubility of helium in blood, the same mixture is used as an atmosphere for those performing under high atmospheric pressures (deep-sea divers, caisson workers). When ordinary air is used, rapid decompression causes bubbles of gaseous nitrogen to form in the blood; the resulting painful, and sometimes fatal, condition is known as the bends.

Oxygen is used when respiratory problems exist. Ordinarily, it is diluted with nitrogen or helium; 100% oxygen should not be used continuously. In hyperbaric oxygen therapy, oxygen is breathed inside a tank at up to 3atm (atmospheres) of pressure. Although the amount of oxygen carried by the hemoglobin is little affected, the higher oxygen pressure increases the amount of dissolved oxygen in the plasma (Henry's law).

It is possible to produce oxygen that is medicinally useful on site, as in a hospital or nursing home, by the use of oxygen concentrators. There are two types of membranes that are used in the concentrators: permeable plastic membranes and molecular sieves. The monograph for Oxygen 93 percent USP sets standards for the oxygen produced by the molecular-sieve process.

Nitrogen(I) oxide usually requires 20 to 25% oxygen during administration. It is used for surgical procedures of short duration. Xenon has a general anesthetic action but is too rare for use. Magnesium ion has anesthetic action; however, the anesthetic dose and the toxic dose of magnesium are too close for it to be used as a general anesthetic. Magnesium Sulfate Injection USP is used as an anticonvulsant and central nervous system depressant.

Carbon dioxide absorbers

When, as in general anesthesia, a patient rebreathes air, dangerous levels of carbon dioxide build up. To prevent this, *carbon dioxide absorbers* are used. Soda Lime NF is prepared by fusing calcium hydroxide with sodium hydroxide, potassium hydroxide (or both) with sufficient diatomaceous earth to yield a hard, non-friable product. For Barium Hydroxide Lime USP, barium hydroxide is substituted for the alkali hydroxide. The particles formed must be large enough to allow free passage of air, but small enough to give a large surface area for absorption. The particles must be hard to prevent dust formation with handling. Entrainment of absorber dust in the breathed air could cause serious alkali burns in the respiratory tract. A colored indicator is included in the preparation to indicate when the carbon dioxide capacity is depleted.

Respiratory stimulants

Carbon dioxide is used as a respiratory stimulant, usually with 5 to 7% oxygen. Because it is the normal respiratory stimulant it is of no value where the respiratory center is already depressed. Carbon dioxide also is used as an inert gas in the headspace over medicinals in sealed containers.

Ammonium Carbonate NF is used as a respiratory stimulant. The name is a misnomer as it is a mixture of ammonium bicarbonate and ammonium carbamate. At room temperature it decomposes to ammonia and carbon dioxide, two respiratory stimulants.

$$NH_4HCO_3 + NH_2CO_2NH_4 \rightarrow 3NH_3 + 2CO_2 + H_2O$$

The substance must be stored in tightly sealed containers. Aromatic Ammonia Spirit USP is prepared from ammonium carbonate, strong ammonia solution, various aromatic oils, alcohol, and water. Light-resistant containers must be used.

Expectorants

Water vapor, an excellent expectorant, is currently considered the best. Ammonium chloride and carbonate, and ammonium and potassium iodides are used commonly as expectorants. Hydroiodic acid syrup was official at one time. If the iodides are used in solution, they must be protected by an antioxidant such as sodium thiosulfate.

Laxatives, enemas, and irrigation solutions

Cathartics are divided into classes according to mode of action. With the exception of sulfur, the inorganic cathartics are saline (osmotic, bulk) laxatives. For laxative action, one or both of the ions of the salt must not be absorbed, or be absorbed with difficulty. This creates an osmotic imbalance in the intestinal tract that the body attempts to correct by secreting water into the intestine. The large volume of fluid in the intestine acts as a mechanical stimulus for peristalsis.

The commonly used salts of monohydrogen phosphate, monohydrogen tartrate, tartrate, and citrate ions are absorbed slowly, but in laxative doses their osmotic action is rapid and effective. They are swept out of the intestinal tract before appreciable absorption can take place. Sulfate ion is relatively non-absorbable and is used either as the magnesium or sodium salt (Epsom salt and Glauber's salt, respectively).

Insoluble laxatives, such as Milk of Magnesia, must be dissolved in the stomach before they can exert a laxative effect. The soluble magnesium sulfate and citrate of magnesia are used widely as laxatives. However, soluble magnesium salts frequently are not recommended as laxatives because of the danger of absorbing free magnesium ion. Dibasic Sodium Phosphate, Sodium Phosphates Oral Solution, Sodium Citrate and Citric Acid Oral Solution, Potassium Sodium Tartrate, Milk of Magnesia, and Sodium Sulfate are cited officially.

PEG 3350 and Electrolytes for Oral Solution USP (Polyethylene glycol 3350, $NaHCO_3$, NaCl, Na_2SO_4, and KCl) is a dry mixture that is to be dissolved at the time of use and then consumed within a prescribed time so as to function as a cathartic and accomplish oral colonic lavage in preparation for a barium enema or a colonoscopic examination.

Sulfur, when ingested, has an irritant laxative effect. The element is thought to be reduced to hydrogen sulfide by reducing agents present in the intestinal fluid. Hydrogen sulfide is a mild intestinal irritant.

Sodium Phosphates Enema USP is a mixture of dibasic and monobasic sodium phosphates or dibasic sodium phosphate and phosphoric acid in water to give a solution of pH 5 to 5.8.

Some solutions are used for irrigating various parts of the body. For example, Citric Acid, Magnesium Oxide, and Sodium Carbonate Irrigation USP is defined as a sterile solution that, after the chemical reactions between citric acid and the other two compounds are completed and the resulting solution is sterilized, is suitable for use as a urinary-bladder irrigant; its acidic pH is conducive to dissolving any bladder calculi in patients such as those using an indwelling catheter.

Radiopaques and imaging agents

Radiopaque compounds are capable of interfering with the passage of X-rays. This interference is directly proportional to atomic number. The soft tissues of the body are composed of atoms of very low atomic number (1, 6, 7, 8, 15, and 16) that do not interfere sufficiently to be discerned. To make visible the soft tissues, the lumen of organs, and body channels, atoms of high atomic number must be used.

Because of the toxicity of these elements, the choices are limited. Only two, barium and iodine (atomic numbers 56 and 53, respectively) have proved useful. Barium Sulfate USP and Barium Sulfate for Suspension USP are used for studies of the intestinal tract. Iodine is incorporated into organic molecules designed to concentrate in the organ or cavity to be studied, such as Iopanoic Acid USP designed for visualization of the gall bladder. Each molecule of the acid has three iodine atoms.

The introduction and development of magnetic resonance imaging as a means of acquiring images of parts of the body by noninvasive methods has made medical diagnoses simpler and more scientific. The use of gadolinium (element 64) in various complexes such as a cationic diethylenetriamine pentaacetic acid complex with a meglumine anion has dramatically facilitated the visualization of intracranial lesions by paramagnetic enhancement.

Structural repairs

Occasionally, temporary or permanent replacement of body support structures is necessary. The materials used should be chemically inert and insoluble in the body fluids, they must be non-toxic, and they must have the strength to withstand any physical stress to which they are subjected. Tantalum has been used as a bone replacement for temporary braces of long bones, and to close openings in the skull. Silver has found similar applications. It reacts slightly with body fluids, but as insoluble silver chloride is

the principal product, this is not a serious threat. Mercury amalgams of gold and silver are used for dental fillings, but this venerable use of mercury is being questioned because of possible chronic toxicity. Zinc-eugenol cement is also used for dental fillings.

Plaster of Paris is used for temporary support structures, especially for broken bones. The formula, $CaSO_4 \cdot {}^1/_2H_2O$, suggests a hemihydrate, but there is experimental evidence indicating the existence of local gypsum ($CaSO_4 \cdot 2H_2O$) nuclei in anhydrous calcium sulfate.

Plaster of Paris is also used for taking dental impressions; because it expands slightly on setting, it fills all spaces completely to give a true surface replica.

Organic pharmaceutical chemistry

Introduction

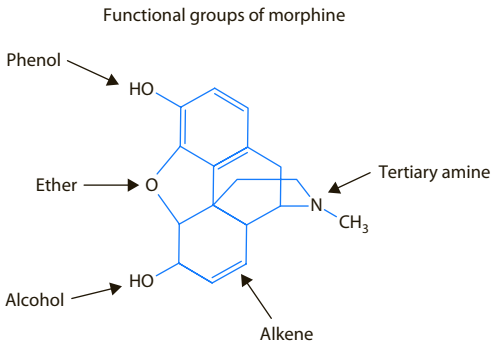
The purpose here is to provide a brief introductory overview of organic chemistry concepts that are very relevant to the very small subclass of organic compounds called pharmaceutical agents. It is assumed that the reader has basic knowledge of organic chemistry at the typical one-year college level in the United States and has access to basic and advanced books for follow-up as need be. Detailed treatments of many of the important concepts introduced are provided elsewhere.

Organic chemicals used as drugs can be classified into three main categories based on chemical, pharmacological, and therapeutic properties. For example, consider the drug metoprolol. It can be classified as an aryloxypropanolamine (chemical), beta-2 (β_2) adrenergic receptor antagonist (pharmacological), and antihypertensive agent (therapeutic), depending on context.

Here, we will briefly examine functional groups, acid–base concepts, stereochemistry, intermolecular forces of attraction, and quantitative structure–activity relationship studies as they relate to organic pharmaceutical agents such as metoprolol. Expatiations on pharmacological and therapeutic effects are carried out in other chapters. The chemical classification of metoprolol as an aryloxypropanolamine indicates the various functional groups present on the molecule, i.e., aryl, oxygen (ether), and propanol (alcohol) amine.

Functional groups

Functional groups are specific combinations of atoms linked through covalent bonds. A functional group or set of functional groups may also be referred to as a chemical moiety. Functional groups are responsible for characteristic physicochemical properties of a molecule, including synthetic reactivity and biological activity. Several common functional groups, including phenol, ether, alcohol, alkene, and amine, are illustrated below with the opioid analgesic morphine.



Metabolism and enzymatic reactions usually result in transformation or addition of functional group(s). For example, esterase enzymes convert ester functional groups of substrates into corresponding alcohols and carboxylic acids. The enzymatic reactions involved in the biosynthesis of the neurohormone epinephrine from amino acid tyrosine provide an example of a series of enzymes working in tandem, with each one carrying out a functional group transformation, as depicted in Fig. 5.1. Metabolism is classified into two categories, known as phase I and phase II. Phase I metabolism results in creation of polar functional group, which then acts as substrate in phase II conjugation reaction. Phase I reactions are commonly carried out by cytochrome P450 oxidase enzymes via a monooxygenase reaction:

$$RH + O_2 + 2H^+ \rightarrow ROH + H_2O$$

Phase II conjugations are catalyzed by a variety of transferase enzymes, including glutathione *S*-transferase, sulfotransferase and glucuronosyltransferase. It can be illustrated with:

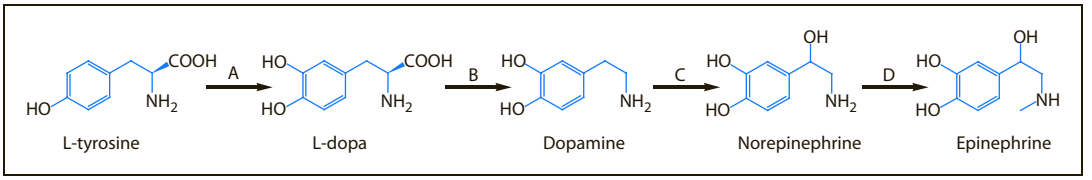
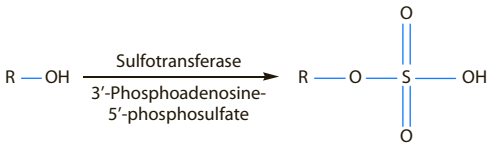


Figure 5.1 Biosynthesis of epinephrine. (A) Tyrosine hydroxylase, (B) aromatic L-amino acid decarboxylase, (C) dopamine beta-hydroxylase, (D) phenethanolamine-*N*-methyltransferase.



In many cases, enzyme names reflect the functional group transformation that they help catalyze. A decarboxylase enzyme removes carboxyl group from substrate. Likewise, an esterase cleaves ester bond to give corresponding carboxylic acid and alcohol.

A central concept in drug design is the pharmacophore. A pharmacophore is a three-dimentional arrangement of functional groups that is responsible for a particular biological activity. The pharmacophore contains the complementary spatial and electrostatic arrangement of functional groups for binding to a biological target, such as a receptor. This concept again illustrates the importance of functional groups.

Acids and bases

According to Arrhenius, an acid is a substance that produces hydrogen ions (H^+) in aqueous solution, whereas a base produces hydroxyl ions (OH^-) in the same solution. There is no complementary relationship between an acid and a base besides the formation of water when hydrogen ions neutralize hydroxyl ions. In the Arrhenius definition of acids and bases, the opposite nature of their characters is emphasized. There is no account for their behavior in non-aqueous media.

In 1923, Brønstead and Lowry developed a definition of acids and bases which expands the Arrhenius definition. According to their theory, an acid is any substance capable of donating a hydrogen ion (proton), and a base is a substance capable of accepting a proton. Their relation is expressed by

$$HA \rightleftharpoons H^+ + A^-$$

where HA is the acid and A^- is the base.

A conjugate acid–base pair refers to a pair of substances related by loss or gain of a proton. Examples are shown below.

In addition to neutral molecules, cations and anions can also function as acids or bases. An acid will not release a proton unless a base that is capable of accepting it is present. In this way, acid–base behavior involves interaction between two sets of conjugate acid–base pairs, as depicted below.

$$A_1 + B_2 \rightleftharpoons B_1 + A_2$$

where A_1 is $acid_1$, B_1 is $base_1$, A_2 is $acid_2$, and B_2 is $base_2$. The above relationship is termed a protolytic reaction or protolysis. A_1 and B_1 constitute one acid–base pair, and A_2 and B_2 the other. A proton is given up by A_1 and is transferred to B_2; A_1 becomes B_1, and B_2, upon accepting the proton, becomes A_2. An example occurs when the acid hydrogen sulfide is dissolved in water:

$$\underset{acid_1}{H_2S} + \underset{base_2}{H_2O} \rightleftharpoons \underset{acid_2}{H_3O^+} + \underset{base_1}{HS^-}$$

H_3O^+, hydronium ion is an ionic species that is always formed when an acid is dissolved in water. It is generally written as H^+ (hydrogen ion).

When a base such as sodium hydroxide (NaOH) is dissolved in water, the protolytic reaction that occurs is as follows:

$$\underset{base_1}{OH^-} + \underset{acid_2}{H_2O} \rightleftharpoons \underset{acid_1}{H_2O} + \underset{base_2}{OH^-}$$

Protolysis is not limited to dissimilar conjugate acid–base pairs. H_2O can behave both as an acid and a base. Because of this, H_2O is referred to as an amphoteric or amphiprotic substance. When sodium acetate is dissolved in water, the following acid-base reaction occurs:

$$\underset{\text{base}_1}{CH_3COO^-} + \underset{\text{acid}_2}{H_2O} \rightleftharpoons \underset{\text{acid}_1}{CH_3COOH} + \underset{\text{base}_2}{OH^-}$$

In an aqueous solution of ammonium chloride, the reaction is:

$$\underset{\text{acid}_1}{NH_4^+} + \underset{\text{base}_2}{H_2O} \rightleftharpoons \underset{\text{base}_1}{NH_3} + \underset{\text{acid}_2}{H_3O^+}$$

Although the proton concept of acids and bases is widely applicable, it does not indicate the reason for proton transfer nor does it explain how substances such as sulfur trioxide, boron trichloride, or carbon dioxide (none of which is capable of donating a proton) can behave as acids. In 1923, Lewis provided the definition of acids and bases which avoids the deficiencies of the proton theory. The theory defines an acid as an electron pair acceptor and a base as an electron pair donor.

Ionization of acids and bases

Ionization is a process in which an atom or molecule is converted into an ion by the addition or removal of charged particles. Acids and bases are generally classified as strong or weak depending on whether they ionize extensively or slightly in an aqueous solution. For example, if 1 N aqueous solutions of hydrochloric acid and acetic acid are compared, it is found that the former is a better conductor of electricity, reacts more readily with metals, and catalyzes certain reactions more efficiently. However, both solutions neutralize identical amounts of base. A similar comparison is found with 1 N solutions of sodium hydroxide and ammonia; the former is more reactive than the latter though both solutions will neutralize the same quantity of acid. For two acids, the difference in hydrogen ion concentration is attributed to the differences in their properties. Hydrochloric acid is ionized to a greater extent; thus, it contains a higher concentration of hydrogen ions than acetic acid at equivalent concentrations. Similarly, the difference in strength between sodium hydroxide and ammonia solutions is attributed to a higher hydroxide ion concentration in the former.

The incomplete or partial ionization of acids may be considered a reversible reaction:

$$HA \rightleftharpoons H^+ + A^-$$

where HA is the acid and A^- is its conjugate base. An equilibrium expression based on the law of mass action may be applied to the reaction

$$K_a = [H^+][A^-]/[HA] \tag{5.1}$$

where K_a is the ionization or dissociation constant and the brackets signify concentrations. For weakly ionized acids in a specified solvent and at a constant temperature, K_a is constant irrespective of the concentrations. For increasingly stronger acids, higher K_a values occur.

Although the strength of an acid is commonly measured in terms of the ionization or dissociation constant (equation), the process of ionization is not that simple. A proton does not simply detach itself from one molecule unless it is accepted simultaneously by another molecule. When an acid is dissolved in water, the water acts as a base, accepting proton from the acid. The lone pair of electrons to form the covalent bond with proton comes from water. This reaction can be written as

$$\underset{\text{acid}_1}{HA} + \underset{\text{base}_2}{H_2O} \rightleftharpoons \underset{\text{base}_2}{A^-} + \underset{\text{acid}_2}{H_3O^+}$$

Applying the law of mass action to the reaction gives

$$K_a = \frac{[H_3O^+][A^-]}{[HA][H_2O]} \tag{5.2}$$

Because change in the concentration of H_2O is negligible, a constant taking this into consideration can be written as

$$K_a = \frac{[H_3O^+][A^-]}{[HA]} \tag{5.3}$$

Equations (5.1) and (5.3) are equivalent because $[H_3O^+]$ is numerically equal to $[H^+]$.

Acids capable of donating more than one proton are termed polyprotic. The ionization of polyprotic acids is stepwise and can be illustrated by

considering the equilibria involved in the ionization of sulfuric acid.

$$H_2SO_4 + H_2O \rightleftharpoons HSO_4^- + H_3O^+$$

$$HSO_4^- + H_2O \rightleftharpoons SO_4^{2-} + H_3O^+$$

Application of the law of mass action to the series of reaction gives

$$K_1 = \frac{[HSO_4^-][H_3O^-]}{[H_2SO_4]} \quad (5.4)$$

$$K_2 = \frac{[SO_4^{2-}][H_3O^+]}{[HSO_4^-]} \quad (5.5)$$

To obtain the overall ionization constant K, the two expressions for their ionization constants are multiplied together

$$K = K_1K_2 \quad (5.6)$$

According to Le Chatelier's principle, each subsequent ionization is suppressed by the hydronium ion formed in the preceding stage. Successive dissociation constants decrease in value, and subsequent species are more negatively charged. This can be seen in Table 5.13, in which K_1 for phosphoric acid is 100,000 times greater than K_2, which is in turn approximately 100,000 times greater than K_3. Although successive dissociation constants are always smaller, the difference is not always as large as observed for phosphoric acid. For example, succinic acid has K_1 of 6.4×10^{-5} and K_2 of 2.3×10^{-6}.

The ionization of a weak base (B) can be illustrated by examining the ionization of the conjugate acid. We can then define K_a in a similar manner as done previously for weak acids.

$$HB^+ \rightleftharpoons H^+ + B$$

$$HB^+ + H_2O \rightleftharpoons B + H_3O^+$$

where HB^+ is the conjugate acid and B is the base.

$$K_a = \frac{[B][H_3O^+]}{[HB^+][H_2O]} \quad (5.7)$$

Table 5.13 Dissociation constants of several weak acids and bases

Substance	Formula	*K*
Acetic acid	CH_3COOH	1.8×10^{-5}
Acrylic acid	CH_4O_2	5.5×10^{-5}
Ascorbic acid	$H_2C_6H_6O_6HC_6H_6O_6^-$	K_1: 6.8×10^{-5} K_2: 2.8×10^{-12}
Bromoacetic acid	$HC_2H_2BrO_2$	1.3×10^{-3}
Benzoic acid	$HC_7H_5O_2$	6.3×10^{-5}
Boric acid	H_3BO_3	5.9×10^{-10}
Chromic acid	$H_2CrO_4HCrO_4^-$	K_1: 1.5×10^{-1} K_2: 3.2×10^{-7}
Chloroacetic acid	$HC_2H_2ClO_2$	1.4×10^{-3}
Chlorous acid	$HClO_2$	1.1×10^{-2}
Cyanic acid	HOCN	3.5×10^{-4}
Dichloroacetic acid	$HC_2HCl_2O_2$	5.5×10^{-2}
Trichloroacetic acid	$HC_2Cl_3O_2$	3.0×10^{-1}
Diethylammonium ion	$(C_2H_5)_2NH_2^+$	1.4×10^{-11}
Dimethyl-ammonium ion	$(CH_3)_2NH_2^+$	1.7×10^{-11}
Ethylenedi-ammonium ion	$NH_2CH_2CH_2NH_3^+$	1.9×10^{-11}
Fluoroacetic acid	$HC_2H_2FO_2$	2.6×10^{-3}
Formic acid	$HCHO_2$	1.8×10^{-4}
Hydrogen peroxide	H_2O_2	2.2×10^{-12}
Hydrosulfuric acid	H_2S	1.0×10^{-7}
Hydroselenic acid	H_2SeHSe^-	K_1: 1.3×10^{-4} K_2: 1.0×10^{-11}

With $[H_2O]$ being constant, this expression can be rewritten as

$$K_a = \frac{[B][H_3O^+]}{[HB^+]} \quad (5.8)$$

An example is ammonia (NH_3). We can define K_a by examining ionization of the conjugate acid, ammonium ion. This reaction can be written as

$$NH_4^+ + H_2O \rightleftharpoons NH_3 + H_3O^+$$

The equilibrium expression for this reaction is

$$K_a = \frac{[NH_3][H_3O^+]}{[NH_4^+][H_2O]} \quad (5.7a)$$

With $[H_2O]$ being constant, this expression can be rewritten as

$$K_a = \frac{[NH_3][H_3O^+]}{[NH_4^+]} \quad (5.8a)$$

A trend to remember, based on the equilibrium equation, is that as K_a of the conjugate acid of a base increases, [B] and $[H_3O^+]$ increase and $[HB^+]$ decreases. Alternatively, as base strength increases, K_a decreases and pK_a increases.

Ionization of water

Water is a poor conductor of electricity although it can ionize through autoprotolysis:

$$2H_2O \rightleftharpoons H_3O^+ + OH^-$$

Application of the law of mass action to the reaction above gives

$$K = \frac{[H_3O^+][OH^-]}{[H_2O]^2} \quad (5.9)$$

where K is the equilibrium constant for the reaction. Because the concentration of H_2O (molecular water) is very much greater than either the hydronium ion or the hydroxylion concentration and undergoes negligible change, it is considered to be constant and can be multiplied by K to give a new constant, K_w, known as the ion product of water, and equation (5.9) becomes

$$K_w = [H_3O^+][OH^-] \quad (5.10)$$

The numerical value of K_w varies with temperature; at 25°C, it is approximately equal to 1×10^{-14} mol^2L^{-2}.

Autoprotolysis of pure water yields one hydronium ion for each hydroxyl ion produced; therefore, $[H_3O^+]$ equals $[OH^-]$. At 25°C each has a value of 1×10^{-7} mol/L ($1 \times 10^{-7} \times 1 \times 10^{-7} = K_w = 1 \times 10^{-14}$). A solution in which $[H_3O^+]$ is equal to $[OH^-]$ is termed a neutral solution.

When an acid is added to water, hydronium-ion concentration increases, and the equilibrium between hydronium and hydroxyl ions is momentarily disturbed. To restore equilibrium, some hydroxyl ions originally present in the water combine with some of the added hydronium ions to form un-ionized water molecules until the product of the concentrations of the two ions is reduced to 10^{-14}. When equilibrium is restored, the concentrations of the two ions are no longer equal. For example, if the hydronium-ion concentration is 1×0.01 N, when equilibrium is established, the concentration of the hydroxyl ion will be 1×10^{-12} (the product of the two concentrations being equal to 10^{-14}). Because $[H_3O^+]$ is much greater than $[OH^-]$, the solution is acidic. Similarly, the addition of an alkali to pure water momentarily disturbs the equilibrium between hydronium and hydroxyl ions. To restore equilibrium, some of the hydronium ions originally present in the water combine with part of the added hydroxyl ions to form un-ionized water molecules. The process continues until the product of the hydronium and hydroxyl ion concentrations again equals 1×10^{-14}. Because $[OH^-]$ is much greater than $[H_3O^+]$, the solution is basic or alkaline.

Relationship of K_a and K_b

There is a particularly interesting and useful relationship between the strength of an acid and its conjugate base or a base and its conjugate acid. For illustration purposes, consider the strength of the weak base NH_3 and its conjugate acid NH_4^+ in water. The behavior of NH_3 in water is expressed by

$$NH_3 + H_2O \rightleftharpoons NH_4^+ + OH^-$$

$$K_b = \frac{[NH_4^+][OH^-]}{[NH_3]} \quad (5.11)$$

The behavior of NH_4^+ as an acid is represented by

$$NH_4^+ + H_2O \rightleftharpoons NH_3 + H_3O^+$$

$$K_a = \frac{[NH_3][H_3O^+]}{[NH_4^+]} \tag{5.12}$$

Multiplying the two equations gives

$$K_aK_b = \frac{[NH_3][H_3O^+][NH_4^+][OH^-]}{[NH_3][NH_4^+]} \tag{5.13}$$

It is clear that

$$K_w = K_aK_b \tag{5.14}$$

where K_w is the ion product of water as defined in equation (5.10).

The utilization of this relationship, which is standard for any conjugate acid–base pair, is evident from the following deductions: (1) the strength of an acid may be expressed in terms of the K_a or K_b of its conjugate base, or vice versa; (2) the K_a of an acid may be calculated if the K_b of its conjugate base is known, or vice versa; and (3) the stronger the acid, the weaker its conjugate base or vice versa.

Bases capable of accepting more than one proton are termed polyprotic and can be illustrated by

$$SO_4^{2-} + H_2O \rightleftharpoons HSO_4^- + OH^-$$
$$HSO_4^- + H_2O \rightleftharpoons H_2SO_4 + OH^-$$

Application of the law of mass action to the series of reactions combined with the concepts outlined in equations (5.4) and (5.5) gives the relationship between the various K_a and K_b values for sulfuric acid:

$$K_w = K_{a1} \times K_{b2} \times K_{a2} \times K_{b1} \tag{5.15}$$

K_{a1} and K_{a2} refer to the equilibrium constants given by equations (5.4) and (5.5), and K_{b1} and K_{b2} refer to the reaction of SO_4^{2-} and HSO_4^- with water, respectively.

Electronegativity and dissociation constants

Electronegativity is the ability of an atom or functional group to attract electron density. Electronegativity of an atom is affected by its atomic number and the distance of its valence electrons from the nucleus. A bond between two atoms with different electronegativity results in unequal distribution of electrons and, therefore, dipole.

Table 5.13 gives the dissociation constants of several weak acids and bases in water at 25°C. It shows great variation in strengths of acids and bases. The effects of various substituents on the strength of acids and bases depend on the electronegativity of the substituent. For example, the substitution of a proton on acetic acid with a chlorine atom increases the degree of ionization of the acid. Substitution with two chlorine atoms further increases the degree of ionization. Substitution with three chlorine atoms yields a still stronger acid. Acetic acid ionizes primarily because the oxygen atom adjacent to the hydrogen atom of the carboxyl group has a stronger affinity for electrons than the hydrogen atom. Therefore, when acetic acid is dissolved in water, polar water molecules have a stronger affinity for the hydrogen of acetic acid than the hydrogen atoms of other water molecules. Acetic acid ionizes as a consequence of this difference in affinities. When chlorine is introduced into an acetic acid molecule, forming $ClCH_2COOH$, the electrons in the molecule are attracted to the chlorine because of its relatively high electronegativity; the bond between the hydrogen and the oxygen in the carboxyl group is thereby weakened through inductive effects, and the degree of ionization increases. Alternatively, substituting chlorine into the molecule of ammonia reduces the strength of the base because of its decreased affinity for hydrogen ions. Dissociation constants for strong acids and bases cannot be determined in water because they do not obey the law of mass action.

Ionic strength and dissociation constants

Ionic strength of a solution is a measure of concentrations of ions in that solution. When an ionic compound is dissolved in an aqueous solution, it dissociates into ions. Most solutions of pharmaceutical interest are in a concentration range wherein the ionic strength of the solution can have a marked effect on

ionic equilibria and observed dissociation constants. One method of correcting dissociation constants for solutions with ionic strength up to about 0.3 is to calculate the apparent dissociation constant or pK_a' as

$$pK_a' = \frac{pK_a + 0.51(2Z-1)\sqrt{\mu}}{1+\sqrt{\mu}} \qquad (5.16)$$

in which pK_a' is the calculated thermodynamic dissociation constant, Z is the charge on the acid, and μ is the ionic strength.

Example: Calculate the pK_2' for succinic acid at an ionic strength of 0.5, given pK_2 is 4.78. The charge on the acid species is −1.

Solution:

$$pK_2' = \frac{4.78 + 0.51(-2-1)\sqrt{0.5}}{1+\sqrt{0.5}} = 4.14$$

Experimental determinations of dissociation constants

The dissociation constant of a weak acid or base can be obtained using a variety of methods including conductivity measurements, absorption spectrometry, and partition coefficients. The most widely used method is the potentiometric pH measurement. The simplest method involving potentiometric pH measurement is based on the measurement of hydronium ion concentration of a solution containing equimolar concentrations of acid and its conjugate base. When equimolar concentrations of HA and A^- are present, K_a is related to the pH of the solution (the pK_a of the acid is equal to the pH of the solution). Although this method is simple and rapid, the dissociation constant obtained is not of sufficient accuracy for some purposes.

To obtain the dissociation constant of a weak acid with high degree of accuracy and precision, a dilute solution of the acid (about 10^{-3} to 10^{-4} M) is titrated with a strong base, and the pH of the solution is taken at many points. The resulting data can be handled in a variety of ways, perhaps the best of which is the method proposed by Benet and Goyan. The proton balance equation for a weak acid, HA, titrated with a strong base such as KOH, would be

$$[K^+] + [H_3O^+] = [OH^-] + [A^-] \qquad (5.17)$$

in which $[K^+]$ is the concentration of base added. equation (5.17) is then rearranged to give

$$Z = [A^-] = [K^+] + [H_3O^+] - [OH^-] \qquad (5.18)$$

When a weak monoprotic acid is added to water, it can exist in the un-ionized form, HA, and in the ionized form, A^-. After equilibrium is established, the sum of the concentrations of both species must be equal to C_a, the stoichiometric concentration of acid added, or

$$C_a = [HA] + [A^-] = [HA] + Z \qquad (5.19)$$

[HA] can be replaced using equation (5.3) to give

$$C_a = \frac{[H_3O^+]Z}{K_a} + Z \qquad (5.20)$$

which can be rearranged to

$$Z - C_a - \frac{Z[H_3O^+]}{[K_a]} \qquad (5.21)$$

According to equation (5.20), if Z, which is obtained experimentally using equation (5.18), is plotted against $Z[H_3O^+]$, a straight line results with slope equal to $-1/K_a$, and an intercept equal to C_a. In addition to obtaining an accurate estimate for the dissociation constant, the stoichiometric concentration of the substance being titrated is also obtained. This is of importance when the substance being titrated cannot be purified, or has an unknown degree of solvation. Similar equations can be applied for obtaining the dissociation of a weak base.

The dissociation constants for diprotic acids can be obtained by defining P as the average number of protons dissociated per mole of acid or

$$P = Z/C_a \qquad (5.22)$$

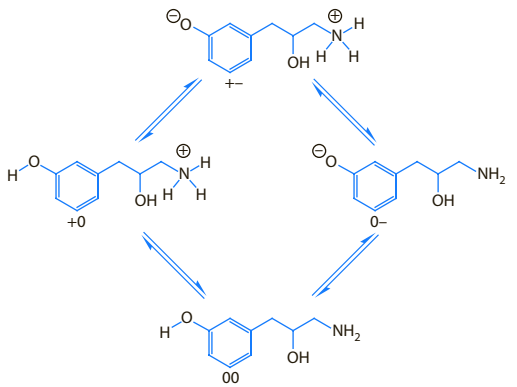
and

$$\frac{[H_3O^+]^2 P}{(2-P)} = K_1K_2 + \frac{K_1[H_3O^+](1-P)}{(2-P)} \qquad (5.23)$$

A plot of equation (5.23) should yield a straight line with slope equal to K_1 and intercept K_1K_2. Dividing the intercept by the slope yields K_2.

Micro dissociation constants

The dissociation constants for polyprotic acids as determined by potentiometric titrations are generally known as macro or titration constants. As carboxylic acids are stronger acids than protonated amino groups, there is no difficulty in assigning K_1 and K_2 to carboxyl and amino groups, respectively, of a substance such as glycine hydrochloride. In other chemicals or drugs such as phenolamine, in which the two acidic groups are the phenolic and protonated amino groups, determining dissociation constants is more difficult. This is because, in general, both groups have dissociation constants of similar magnitude. Therefore, there will be two ways of losing the first proton and two ways of losing the second, resulting in four possible species in solution. This can be illustrated using the convention of assigning a plus (+) to a positively charged group, a zero (0) to an uncharged group, and a minus (−) to a negatively charged group. For example, consider a phenolpropanolamine. The +0 represents the fully protonated phenolpropanolamine, +− the zwitterions, 00 the uncharged molecule, and 0−, the anion. The total ionization scheme can therefore be written as



The micro constants are related to the macro constants as

$$K_1 = k_1 + k_2$$
$$K_2 = k_3 + k_4 \qquad (5.24)$$
$$K_1K_2 = k_1k_3 = k_2k_4 \qquad (5.25)$$

It can be seen that unless k_1 or k_2 is very much smaller than the other, the observed macro constant is a composite of the two and cannot be assigned to one or the other acidic group in a nonambiguous way. Methods for determining k_1 are given by Riegelman (1962), Niebergall (1972), and their coworkers. Once k_1, K_1 and K_2 have been determined, all of the other micro constants can be obtained from equations (5.24) and (5.25).

Hydronium ion concentrations may vary enormously. For a strong acid, that value is approximately 1, whereas for solution of a strong base, it is approximately 1×10^{-14}. Due to the inconvenience in dealing with small numbers, Sorenson, in 1909, proposed that the hydronium ion concentration be expressed in terms of logarithm (log) of its reciprocal. He assigned the symbol pH to this value. Mathematically, it is written as

$$\mathrm{pH} = \log \frac{1}{[H_3O^+]} \qquad (5.26)$$

Since the log of 1 is zero, the equation can be rewritten as

$$\mathrm{pH} = -\log[H_3O^+] \qquad (5.27)$$

from which it is evident that pH also may be defined as the negative log of the hydronium ion concentration. This type of notation is used to indicate the negative logarithm of the term that is preceded by p, which gives rise to the following:

$$\mathrm{pOH} = -\log[OH^-] \qquad (5.28)$$
$$\mathrm{p}K = -\log K \qquad (5.29)$$

Taking the logarithms of equations (5.10) and (5.14) gives

$$\mathrm{p}K_a + \mathrm{p}K_b = \mathrm{p}K_w \qquad (5.30)$$
$$\mathrm{pH} + \mathrm{pOH} = \mathrm{p}K_w \qquad (5.31)$$

The relationship of pH to hydronium-ion and hydroxyl-ion concentrations may be seen in Table 5.14.

Examples:

1. Calculate the pH corresponding to a hydronium ion concentration of 1×10^{-6} M.

Table 5.14 Hydronium ion and hydroxyl ion concentrations

	pH	Normality in terms of hydronium ion	Normality in terms of hydroxyl ion
↑ Acidity increases	0	1	10^{-14}
1	10^{-1}	10^{-13}	
2	10^{-2}	10^{-12}	
3	10^{-3}	10^{-11}	
4	10^{-4}	10^{-10}	
5	10^{-5}	10^{-9}	
6	10^{-6}	10^{-8}	
Neutral	7	10^{-7}	10^{-7}
	8	10^{-8}	10^{-6}
	9	10^{-9}	10^{-5}
	10	10^{-10}	10^{-4}
	11	10^{-11}	10^{-3}
	12	10^{-12}	10^{-2}
Alkalinity increases ↓	13	10^{-13}	10^{-1}
	14	10^{-14}	1

Solution:

$$\begin{aligned} \text{pH} &= \log \frac{1}{1 \times 10^{-6}} \\ &= \log 1{,}000{,}000 \text{ or } \log(1 \times 10^{6}) \\ \log(1 \times 10^{6}) &= 6 \\ \text{pH} &= 6 \end{aligned}$$

2. Calculate the pH corresponding to a hydronium ion concentration of 4.9×10^{-6} M.

Solution:

$$\begin{aligned} \text{pH} &= -\log\ (4.9 \times 10^{-6}) \\ \log 4.9 &= 0.69 \\ \log 10^{-6} &= -6.00 \\ &= -5.30 = \log\ (4.9 \times 10^{-6}) \\ \text{pH} &= -(-5.30) = 5.30 \end{aligned}$$

The following example illustrates the conversion of pH to exponential notation.

3. Calculate the hydronium ion concentration corresponding to pH of 2.3.

Solution:

$$\text{pH} = \log \frac{1}{[H_3O^+]}$$

$$2.3 = \log \frac{1}{[H_3O^+]}$$

or

$$2.3 = -\log [H_3O^+]$$

$$-2.3 = \log [H_3O^+]$$

$$[H_3O^+] = 1/(200) = 5.0 \times 10^{-3}$$

Species concentration

When a weak acid, H_nA, is added to water, n + 1 species, including the un-ionized acid, can exist. After equilibrium is established, the sum of the concentrations of all species must be equal to C_a, the stoichiometric concentration of acid. Therefore, for a triprotic acid, H_3A:

$$C_a = [H_3A] + [H_2A^-] + [HA^{2-}] + [A^{3-}] \quad (5.32)$$

In addition, the concentrations of all acidic and basic species in the solution vary with pH and can be represented solely in terms of equilibrium constants and the hydronium-ion concentration. This relationship is expressed as

$$[H_nA] = [H_3O^+]^n C_a/D \quad (5.33)$$

$$[H_{n-j}A^{-j}] = [H_3O^+]^{n-j} K_1, \ldots, K_j C_a/D \quad (5.34)$$

in which n represents the total number of dissociable hydrogen on the parent acid, j is the number of protons dissociated, C_a is the stoichiometric concentration of acid, and K represents the acid dissociation constant. The term D is from $[H_3O^+]$ and K, starting with $[H_3O^+]$ raised to the nth power. The last term is the product of all the dissociation constants. The intermediate terms can be generated from the last term by substituting $[H_3O^+]$ for K_n to obtain the next-to-last term, then substituting $[H_3O^+]$ for K_{n-1} to obtain the next term, and onward until the first term is reached. The following examples show the denominator, D, to be used for various types of acids.

$$H_3A: D = [H_3O^+]^3 + K_1[H_3O^+]^2 + K_1K_2[H_3O^+] + K_1K_2 \quad (5.35)$$

$$HA: D = [H_3O^+] + K_a \quad (5.36)$$

The numerator in all instances is C_a multiplied by the term from the denominator that has $[H_3O^+]$ raised to the power of $n-j$. Therefore, for diprotic acids such as chromic, maleic, fumaric, and tartaric acids,

$$[H_2A] = \frac{[H_3O^+]^2 C_a}{[H_3O^+]^2 + K_1[H_3O^+] + K_1K_2} \quad (5.37)$$

$$[HA^-] = \frac{K_1[H_3O^+] C_a}{[H_3O^+]^2 + K_1[H_3O^+] + K_1K_2} \quad (5.38)$$

$$[A^{2-}] = \frac{K_1K_2 C_a}{[H_3O^+]^2 + K_1[H_3O^+] + K_1K_2} \quad (5.39)$$

Example: Calculate the concentration of each tartaric acid species in a 2.5×10^{-3} M solution of tartaric acid at pH 5.6. Assume that $K_1 = 9.6 \times 10^{-4}$ and $K_2 = 1.3 \times 10^{-1}$.

Equations (36–38) have the same denominator, D, which can be calculated as

$$\begin{aligned} D &= [H_3O^+]^2 + K_1[H_3O^+] + K_1K_2 \\ &= 1 \times 10^{-12} + 9.6 \times 10^{-4} \times 1.0 \times 10^{-6} \\ &\quad + 9.6 \times 10^{-4} \times 1.3 \times 10^{-1} \\ &= 1 \times 10^{-12} + 9.6 \times 10^{-10} + 1.248 \times 10^{-4} \\ &= 1.248 \times 10^{-4} \end{aligned}$$

Therefore,

$$\begin{aligned} [H_2A] &= \frac{[H_3O^+]^2 C_a}{D} \\ &= \frac{1 \times 10^{-12} \times 2.5 \times 10^{-3}}{1.248 \times 10^{-4}} \\ &= 2.00 \times 10^{-11}\ \text{M} \\ [HA^-] &= \frac{K_1[H_3O^+] C_a}{D} \\ &= \frac{9.6 \times 10^{-4} \times 1.0 \times 10^{-6} \times 2.5 \times 10^{-3}}{1.248 \times 10^{-4}} \\ &= 1.923 \times 10^{-8}\ \text{M} \\ [A^{2-}] &= \frac{K_1K_2 C_a}{D} \\ &= \frac{9.6 \times 10^{-4} \times 1.3 \times 10^{-1}}{1.248 \times 10^{-4}} \\ &= 1\ \text{M} \end{aligned}$$

Proton-balance equation

In the Bronsted–Lowry theory, the total number of protons released by acidic species must equal the total number of protons consumed by basic species. This observation results in a very useful relationship known as the proton-balanced equation or PBE. PBE forms the basis of a unified approach to pH calculations, for it is an exact accounting of all proton transfers occurring in a solution. When HBr is added to water, it dissociates yielding Br^- for each proton released. Thus, Br^- is a species formed by the release of a proton. In all aqueous solutions,

$$2H_2O \rightleftharpoons H_3O^+ + OH^-$$

where H_3O^+ is formed by proton consumption and OH^- is formed by proton release. Therefore, the PBE for the above reaction is

$$[H_3O^+] = [OH^-] + [Br^-] \qquad (5.40)$$

Guidelines for generating PBE are as follows:

1. Start with the species added to water.
2. Place all species that can form when protons are released on the right side of the equation.
3. Place all species that can form when protons are consumed on the left hand side of the equation.
4. Multiply the concentration of each species by the number of protons gained or lost to form that species.
5. Add $[H_3O^+]$ to the left side of the equation and $[OH^-]$ to the right side of the equation.

Example: When H_3PO_4 is added to water, the species $H_2PO_4^-$ forms with the release of one proton; HPO_4^{2-} forms with the release of two protons; PO_4^{3-} forms with the release of three protons, which gives the following PBE:

$$[H_3O^+] = [OH^-] + [H_2PO_4^-] + 2[HPO_4^{2-}] + 3[PO_4^{3-}] \qquad (5.41)$$

Example: When sodium bisulfate ($NaHSO_4$) is added to water, it dissociates into one Na^+ and one HSO_4^-. The sodium is neglected in the PBE because it does not form the release or consumption of protons. The species HSO_4^-, however, may react with water to give H_2SO_4 with the consumption of one proton, and SO_4^{2-} with the release of one proton to give the following PBE:

$$[H_3O^+] + [HSO_4^-] = [OH^-] + [SO_4^{2-}] \qquad (5.42)$$

Drug stability

A broad field of study is the investigation of the effects of hydrogen ion concentration on the reactivity of pharmaceutical systems. Evidence for enhanced stability of systems when they are maintained within a narrow pH range, as well as of progressively decreasing stability as the pH departs from the optimum range, is abundant. Proton gain or loss by a substrate molecule that reduces or increases the reactivity of the molecule could result in stability or instability of a system. When a substance that is desired to remain unchanged is converted to one or more unwanted substances, instability is said to occur. Instability may happen in aqueous solutions through the catalytic effects of acids and bases. With acids, this happens by transferring a proton to the molecule, and with bases, it occurs by accepting a proton. There are countless specific examples of the effect of hydrogen ion concentration on the stability of medicinals. The illustrations exhibited below show the importance of pH adjustment of solutions, especially ones that require sterilization.

During a 60-minute exposure at a temperature of 37.7°C, if the pK_a of a molecule is less than 5.5, neutral and alkaline solutions can be highly unstable. Minimum hydrolytic decomposition of solutions of cocaine occurs in the pH range 2 to 5. In one study a solution of cocaine hydrochloride, initially at pH 5.7, remained stable for two months (although the pH dropped to 4.2 during this time) while another solution buffered to about pH 6 underwent approximately 30% hydrolysis. Likewise, solutions of procaine hydrochloride containing some hydrochloric acid showed no appreciable decomposition when dissolved in water alone, with 5% of it hydrolyzed, whereas when buffered to pH 6.5, from 19 to 35% underwent decomposition by hydrolysis. Solutions of thiamine hydrochloride may be sterilized by autoclaving without appreciable decomposition if the pH is below 5; above this, thiamine hydrochloride is unstable.

Drug activity

Drugs may exist in ionized and un-ionized forms as a result of being weak acids or bases, and may be active in one form but not the other. Such drugs typically have optimum pH range for maximum activity. For example, mandelic, benzoic, and salicylic acids have antibacterial activity in the un-ionized form but have practically no antibacterial activity in the ionized form. As a result, these substances require acidic environments in order to thrive as antibacterial agents. For example, sodium benzoate is effective as a preservative in 4% concentration at pH 7, and in 0.06 to 0.1% concentration at pH 2.3 to 2.4. Other antibacterial agents mostly or entirely act in cationic form. Acridines and quaternary ammonium compounds are a part of this category.

Drug absorption

Two important factors that determine the rate of absorption of drugs from the gastrointestinal tract and subsequently their passage through cellular membranes are the degree of ionization as well as lipid solubility. Drugs that are weak organic acids or bases can exist in significant amounts in the un-ionized form which is absorbed by passive diffusion through lipophilic cell membranes. Conversely, ionized drugs are absorbed poorly or not at all. Rates of absorption of a variety of drugs are related to their ionization constants and, in many cases, may be predicted quantitatively on the basis of this relationship. The degree of the acidic or basic character of a drug, as well as the pH of the physiological medium in which a drug is dissolved or dispersed, become important limitations of drug absorption. The pH is important because it determines the extent to which the drug will exist in ionic or nonionic form. The difference between pH and pK_a is indicative of how much of the drug is in the ionized or un-ionized form, as illustrated in Table 5.15.

For example, for a drug containing a carboxylic acid group with pK_a of about 4, using the table above, one could determine that the drug is mainly in the ionized form at physiologic pH (about pH = 7.4). The carboxylic acid group will lose its proton to form the ionized form, carboxylate. However, in the stomach where the contents are more acidic (pH of about 1 to 2), the drug would remain in its protonated (un-ionized) form.

Table 5.15 Table showing ionization of a compound at different pH values

pH – pK_a	[Base]/[Acid]	Percent un-ionized	Percent ionized
4	10,000/1	0.01	99.99
3	1000/1	0.1	99.9
2	100/1	1	99
1	10/1	9	91
0	1/1	50	50
−1	1/10	91	9
−2	1/100	99	1
−3	1/1000	99.9	0.1
−4	1/10,000	99.99	0.01

Salts

A significant percentage of drugs contain acidic or basic groups which can undergo acid–base reactions generating salts. Salts are compounds composed of oppositely charged (cationic and anionic) species bound by strong ionic interactions. About half of the drugs used today are marketed as salts. Salts are preferred over the free base species, as they tend to have greater stability, dissolution, solubility, and ease of base handling. The selection of the appropriate counterion is an essential study in the pharmaceutical pipeline because different salts of a drug can have markedly distinct biopharmaceutical properties, including dissolution, stability, bioavailability, and compressibility. Salt choice also has relevance to patent and regulatory processes. Typically, a single salt of a drug is approved for marketing and any novel salt of an approved substance can be classified as a new chemical entity. Sometimes mixtures of different salt forms of a drug are marketed. This is the case with Adderall, which contains four distinct salts of racemic and dextro-amphetamine. The specific salt combination was chosen for pharmacokinetic properties and better therapeutic profile. If a more efficient salt of an approved drug is discovered, it may be patented,

further extending the protected drug lifetime. An example of this is Diclofenac®, which was marketed initially as the sodium salt (Voltaren®). Prior to patent expiration, new salts with superior topical applicability were discovered, patented, and marketed.

When acidic drugs (like ibuprofen) are ionized as anions, they form salts with cations like Na^+, K^+, and Ca^{2+}. These salts are commonly prepared by treating the un-ionized acid species with an equivalent amount of the counterion containing base, such as KOH, in solution. Basic drugs like morphine become protonated and are prepared by treating un-ionized form (freebase) with an equivalent quantity of acid, such as HCl gas.

$$R-COOH + NaOH \rightarrow R-COO^-Na^+ + H_2O$$

$$R_3N + HCl \rightarrow R_3NH^+Cl^-$$

The general rule for optimal salt formation is that the pK_a of the counterion should be two pK_a units or more above the pK_a of the drug for acidic drugs, or below for basic drugs. This pK_a difference is required for proton transfer to be energetically favorable.

A pharmaceutical salt is composed of an electrically neutral ratio of complementary charged drug and counterion. Factors influencing selection of counterion include the acidity or basicity of the ionizable group, intended usage, counterion safety (FDA GRAS [generally regarded as safe]), route of administration, and formulation properties. Choosing the right salt is typically a trial-and-error process and can be a burden on time and resources. The more recent advent and adoption of high throughput methods for salt and polymorph selection has greatly enhanced the selection process. Common counterions for acidic drugs include Na^+, K^+, Ca^{2+}, and NH_4^+. Counter ions commonly used with basic drugs include inorganic anions like Cl^-, Br^-, SO_4^{2-}, PO_4^{3-}, NO_3^- and organic anions including acetate, formate, oxalate, fumarate, maleate, tartrate, citrate, and aspartate.

Several organic acids like fumaric, maleic, and citric possess two or more acidic protons. As such, these compounds may form multiple salt types, based on the stoichiometric ratio of salt to drug. When two ratios are possible, the salts are referred to as the hemi- and stoichiometric forms. In the hemi-form, two molecules of drug interact with one of acid (or vice versa), whereas in the stoichiometric form an equal 1:1 mixture of drug to acid is formed. The salt types can have distinct physical and biopharmaceutical properties. Typically, formation of the desired salt can be accomplished by controlling addition and crystallization conditions.

One of the major reasons for salt formation is to obtain crystalline solid form of the drug. A crystal is a solid form of a compound (or mixture) held in an ordered lattice by non-covalent intermolecular interactions. Most salts and some free (un-ionized) forms of drugs can exist as crystalline materials. Pharmaceutically relevant crystallography includes crystallization techniques, salt formation, polymorphism, and cocrystallization. A detailed discussion of crystallography techniques is outside the scope of this section. The more common methods used for crystallization include solution crystallization, solid and solvent state grinding, melt, sublimation, and thermal treatment. More recent innovative techniques include capillary crystallization, laser-induced crystallization, sonocrystallization, and heterogeneous crystallization. By far the most common method used for crystal formation is solution crystallization, whereby crystals are grown from a supersaturated solution of drug in a solvent or solvent mixture. Crystal formation can be influenced by solvent choice, rate and method of generating supersaturation, presence of additives, and temperature.

Amorphates are non-crystalline solids that lack the long-range structural order of crystals but possess short-range molecular order. Amorphates are also called disordered systems or glassy solids. Although much less common than crystalline drugs, pharmaceutical interest in amorphates exists. As a result of the less ordered structure, the solubility of many amorphous solids represents a lower energy barrier than corresponding crystals. An example is novobiocin, whose amorphous form exhibits favorable dissolution properties, compared to its crystal state. Although use of amorphates may be a promising way to enhance drug pharmacokinetics, limitations could include reduced physical and thermodynamic stabilities and higher chemical reactivity.

Polymorphism

In addition to salt types, there is a related phenomenon relevant to pharmaceutical chemistry

and crystallography, known as polymorphism. Polymorphs are different crystalline forms of a compound. Depending on crystallization conditions, different polymorphs of a salt may form. Some drugs have many polymorphic forms. For example, 5-methyl-2-[(2-nitrophenyl)amino]-3-thiophenecarbonitrile has ten known polymorphic forms. As with salt types, polymorphs may have different physicochemical properties. Several categories of polymorphism exist, including packing polymorphism, conformational polymorphism, and pseudopolymorphism. Structures involved in packing polymorphism tend to be rigid, and these molecules orient themselves differently in the crystalline lattice (unit cell) of different polymorphs without conformational change. In conformational polymorphism, structures are more flexible and adopt different molecular conformations in different polymorphs. Lastly, pseudopolymorphism includes the phenomena of solvates and hydrates. In these cases, water or solvent molecules are incorporated into the crystalline lattice. Different stoichiometric ratios and packing structures give rise to the distinct pseudopolymorph forms.

Unlike salt formation, polymorphism can be highly variable and complex. A comprehensive understanding of the phenomenon is lacking. Reproducibility of particular polymorphs can be problematic, and polymorphs may even interconvert during formulation. For these reasons, the most stable polymorph is typically preferred.

Cocrystals

The phenomenon of cocrystals is relatively recent in drug development. A cocrystal is generally regarded as a homogenous crystalline material composed of a neutral drug and neutral coformer, held together in a defined stoichiometry through non-covalent interactions. Cocrystals, therefore, differ from salt crystals, given the absence of proton transfer and ionization, yet retain a long-range ordered structure. Cocrystals are not necessarily binary. Ternary and quaternary cocrystals are known, allowing greater possibilities and complexity in pharmaceutical crystallography.

Hydrogen bonding seems to be the most important intermolecular interaction in cocrystallization, although other weak intermolecular interactions can also occur. Coformers are selected based on ability to form intermolecular interactions with the drug. By understanding the varieties of interactions involved in cocrystals, scientists can begin to choose and/or engineer coformers, yielding cocrystals with the desired physicochemical properties. This makes selection of the appropriate conformer an important feature. The physicochemical properties of a drug can be modified in unique ways by selecting appropriate conformers. For example, cocrystals have been used to deal with difficulties in solubility, dissolution rate, absorption, and physical stability. Examples include celecoxib and nicotinamide, caffeine and theophylline, and carbamazepine and saccharin. Cocrystal technology greatly expands the possible solutions to physicochemical limitations and gives scientists an additional strategy to optimize biopharmaceutical properties.

Structural determinants of drug action

Lipophilicity is a very important factor influencing the pharmacokinetic parameters of drug absorption and distribution. To reach a site of action, most drugs must transverse several lipophilic membranes. An orally absorbed drug must cross the lipid membrane of small intestine epithelial cells. Although absorption can occur by several mechanisms, passive diffusion is the most important mechanism for most drugs, and lipophilicity is an essential component of this process. Following intestinal absorption, a drug enters the plasma from where it distributes. An optimal drug must be both hydrophilic and lipophilic. This limitation explains in part why the majority of drugs are weak acids or bases. Depending on the site of action, additional lipophilic barriers may need to be transversed. For example, central nervous system active drugs must cross the highly restrictive lipophilic blood–brain barrier (BBB), and drugs with intracellular targets must cross additional cell membranes.

Partition coefficient (*P*)

An important measure of the lipophilicity of a drug is the partition coefficient (*P*). *P* is typically determined experimentally by partitioning a compound between aqueous and lipid (typically octanol) phases. Octanol was chosen because of its similarities to

biological membrane lipids, i.e., polar head (OH) and hydrocarbon tail. After mixing, the concentrations of drug in the different phases are determined. P is the ratio of the concentration of drug in lipid to that in the aqueous phase:

$$P = \frac{[\text{Drug}]_{\text{lipid}}}{[\text{Drug}]_{\text{aqueous}}}$$

P is thus a measure of lipophilicity. The log of P ($\log P$) is commonly used. When $P < 1$, $\log P$ is negative and the greater the compound solubility in the aqueous phase. When $P > 1$, $\log P$ is positive, and the compound favors the lipid phase. Log P is typically a good predictor for *in vivo* lipophilicity. Collander observed that the rate of movement of many organic compounds across a cellular membrane correlates with $\log P$. Furthermore, Hansch and coworkers were able to correlate relative drug potency with $\log P$. Collander and Hansch's observations reveal that in certain cases the biological activity of a drug can be enhanced by designing derivatives with increased $\log P$. However, the enhancement is not infinite, and an optimal $\log P$ value exists; further increases of $\log P$ decrease biological response. The reason for this decrease is that a drug that is too lipophilic becomes sequestered in any lipid phase it encounters and is unable to cross membranes and re-enter the aqueous phase. Such molecule has inadequate pharmacokinetic properties, including poor solubility, absorption and distribution.

Many drugs are acids or bases that, depending on pK_a and pH, exist to a significant degree as the ionized form in physiological environments. Log D is used to describe the log of the distribution coefficient of an ionizable drug between 1-octanol and an aqueous buffer. Log D is the $\log P$ of a compound at a particular pH. For example, Log $D_{5.5}$ is the $\log P$ of an ionizable compound at pH 5.5. In general, a drug with a basic amine moiety exhibits greater ionization at pH values below its pK_a, resulting in a greater degree of drug in the aqueous phase. At higher pH (above the pK_a) the un-ionized species predominate, with the typical result of a greater affinity for the lipid phase and increase in $\log D$. The opposite trend is observed with acidic drugs as they are un-ionized at pH values below their pK_a and ionized at higher values.

Addition of functional groups to a structure can affect $\log P$ in somewhat predictable ways. A substitituent constant (π) exists for the contribution of individual atoms and functional groups to P. Many different π values are available.[1] Contributions are additive and depend on the molecular environment of the substituent. Induction, resonance, and steric factors all affect π. It is also affected by conformation. Intramolecular interactions, like H-bonds, can decrease π by decreasing apolar surface area. All these possibilities should be considered when calculating $\log P$ from π.

Although $\log P$ and $\log D$ values may be calculated simply by partition experiments, additional methods, such as reverse phase high-performance liquid chromatography (HPLC), can be used.[2] These HPLC methods have the advantage of being both quick and accurate, and possess high reproducibility. During drug discovery it may be necessary to predict $\log P$ prior to synthesis. While $\log P$ may be estimated manually by summing the component π values, a more convenient way is the use of one of numerous commercially available software programs. These user-friendly programs allow for simple and rapid estimation of $\log P$ or $\log D$, which are now determined as simply as drawing a chemical structure. While undeniably valuable, calculated values may deviate significantly (two or more units) from experimental values. A major rationale for this deviation is the constitutive nature of π values, especially in complex or exotic structures. In such cases, the experimental values from close structural relatives of the compound should be compared with calculated values from various software programs to determine the best program for the particular series.

Thermodynamic activity

While studying the narcotic effects of various chemicals on tadpoles, Ferguson theorized that at equilibrium, simple thermodynamic principles could be applied to drug activities and that relative saturation concentration (termed thermodynamic activity) of a drug in the external or extracellular phase correlates with narcotic activity. The correlation, known as Ferguson's principle, has value in classifying the mode of action and predicting biological response. It has also been used to classify drugs into structurally specific and structurally nonspecific drugs. Thermodynamic activities of structurally specific drugs are low, typically below 0.001. Structurally nonspecific drugs have

activities in the range of 0.01 to 1.0, indicating they are only active at relatively high concentrations.

In the case of structurally nonspecific drugs, biological activity correlates well with physical properties of the molecule, such as log *P*, solubility, vapor pressure, and surface area, rather than specific structural features. The biological activity of structurally nonspecific drugs typically results from accumulation of the drug in a particular lipophilic region of the cell, such as the plasma membrane. A few therapeutic categories of drugs are believed to act, at least partially, through nonspecific mechanisms. These include bacterial disinfectants and certain general anesthetics. This mechanism can be used to explain why structurally diverse molecules such as nitrous oxide, diethyl ether, halothane, and thiopental all have similar anesthetic effects.

Structurally specific drugs and receptors

Paul Ehrlich conceptualized and proposed the notion of a receptor. With structurally specific drugs, activity is dependent on the ability to interact with a specific physiological target, most often a protein such as an enzyme or receptor. In these instances, biological activity depends on a drug's chemical structure and thus its pharmacodynamic interactions. Many receptors are membrane-bound proteins that selectively bind small molecules called ligands. Binding takes place at a specific site also called the active or binding site. Several categories of ligands are recognized, including agonists, super agonists, partial agonists, inverse agonists and antagonists. In the case of an agonist, the ligand–receptor interaction is believed to lead to a conformational change, causing receptor activation. The active receptor initiates a physiological response, the specifics of which depend on the receptor type and environment. Numerous receptor categories exist and include ligand gated ion channels, G-protein coupled receptors, hormone receptors, and tyrosine kinase receptors.

Binding

The biological activity of a structurally specific drug is related to its affinity for a target receptor. Affinity is typically represented by the dissociation constant (K_d). K_d is the concentration of drug occupying half the available binding sites at equilibrium.

$$K_d = \frac{[\text{Drug}]\,[\text{Receptor}]\text{free}}{[\text{Drug–receptor complex}]}$$

The lower the K_d value, the higher the affinity, for less drug is required to occupy the receptor at equilibrium. K_d or the related K_i (equilibrium dissociation constant obtained by competitive ligand displacement) can be calculated using several *in vitro* techniques, including competitive binding studies followed by Scatchard or Schild analysis. K_d is influenced by entropic and enthalpic factors. Attractive forces lead to formation of enthalpically favored intermolecular interactions between ligand and receptor. Binding also results in restriction in conformational freedom of the involved parties and this loss of rotational and translational freedom is entropically unfavored. However, entropically favorable gains can occur from displacement of ordered water molecules constituting the hydration shells of the drug and receptor or other ordered water molecules at the binding site. Assuming that the sum of entropic and enthalpic conditions is favorable, binding will decrease the free energy of the system, facilitating interaction.

Bonds formed in the drug–receptor complex tend to be weak, reversible, non-covalent interactions and include ionic (electrostatic), ion–dipole, dipole–dipole, hydrogen bonding, charge transfer, hydrophobic, and van der Waals. Irreversible covalent bonding occurs only with a few select therapeutic agents, such as chemotherapeutics, antimicrobials, antivirals, and enzyme inhibitors.

Several models of binding have been proposed over the years to account for the observed pharmacodynamic activities of drugs. Some are outdated but proved useful historically in conceptualizing the binding phenomena. Models of receptor binding are constantly being adjusted to fit our evolving understanding of binding pharmacology. The earliest model of binding is the lock and key hypothesis where the receptor and drug were viewed as rigid structures in which the drug fits neatly into the active site like a key into a lock. This theory could not fully account for the dynamic conformational changes undergone by both drug and receptor. More recent theories include the zipper and induced fit models. In the zipper model the receptor site is viewed as

rigid. The drug is flexible and molds itself to the rigid receptor binding site through a stepwise series of conformational changes that derive the necessary energy from binding itself. The more widely accepted induced fit model views both the drug and receptor as flexible. As drug approaches the binding site, conformational changes take place in both drug and receptor to facilitate binding. The resulting conformational change in the receptor is believed to initiate the biological response. The induced fit model is able to explain different binding observations, including the notion of efficacy as it occurs with ligand-directed trafficking. While these models have been useful in conceptualizing receptor binding phenomenon, our understanding of binding is evolving and is still incomplete.

Quantitative Structure–Activity Relationship (QSAR) studies

As the name implies, QSAR is an attempt to identify and quantify the physicochemical properties of a drug and relate these to biological activities. When a relationship is observed, an equation can be generated. This relationship allows medicinal chemists to determine significance of a specific property to drug action. More importantly, it allows prediction of activity of novel derivatives. In this way, QSAR allows chemists to focus synthetic efforts on compounds more likely to be active, conserving time and resources. In theory, any structural, physical, or chemical property of a drug can be modeled by QSAR. Typically, it is most desired to focus on one or two of these properties at a given time. However, this may not be practical because many properties are interrelated and sometimes multiple properties are considered simultaneously. Essential requirements of QSAR are that the compounds being studied be structurally related, and act via the same receptor and mechanism.

Numerous physical, structural, and chemical properties can be studied by QSAR. The most common include hydrophobic, electronic, and steric properties. This observation is partially due to the ease of quantifying these properties, especially for individual substituents. Examples of QSAR methods include Hansch Linear Free-Energy and Free-Wilson models.

Hansch linear free-energy model

The Hansch equation allows biological activity to be related to multiple physicochemical properties. As the equation is typically linear, it is sometimes referred to as the Hansch linear free-energy equation. Since the equation accounts for the effects of multiple parameters, the results tend to be complicated, but can also be of greater relevance than models of only one parameter. Hydrophobicity (π, measured by log P), electronic features modeled by the Hammett substituent constant (σ for aromatics and σ_1 for aliphatics), and steric considerations estimated by Taft's steric factor (E_s) are the most commonly used physicochemical properties in the Hansch equation. A limitation of the Hansch equation is that a large number of derivatives must be measured experimentally prior to deriving the equation.

Free-Wilson method

The Free-Wilson approach considers the "overall effect" of a substituent on biological activity. In this way, specific physicochemical values are not required, and only biological activity is measured. To get an equation, the activity of the parent structure is measured and compared against various derivatives. The equation derived allows activity of substituents to be predicted. As with the Hansch equation, a major disadvantage in the Free-Wilson approach is that a number of derivatives must be obtained and tested. Both also require significant computational power.

Topliss scheme

Topliss scheme is a synthetic flow diagram and is a non-computer method of analog design. The scheme was designed to enhance the probability of discovering the most active compound in a series of structural derivatives as early as possible. The biological activity of a parent or lead compound is first measured. Then the first derivative specified by the scheme is synthesized and activity measured. Based on the activity of this compound to the lead (more, equal, or less), a synthetic path that amplifies or attenuates tested properties is followed. In this way each step in the scheme depends on the activity of the previous compound. The scheme is particularly useful when difficult or expensive synthetic procedures are necessary to obtain derivatives.

Bioisosterism

The concept of bioisosterism is central to organic pharmaceutical chemistry. Bioisostere exchange is a common strategy in drug discovery. Isosteres are atoms or functional groups with similar valence structures. Since isosteres are not identical, the physicochemical properties that they will impart on a molecule are not identical. Change in physicochemical properties can alter pharmacokinetic and pharmacodynamic properties of a drug and provide insight on the pharmacophore. Bioisosteres are atoms or functional groups which impart similar biological properties to a molecule (Fig. 5.2). In this way, bioisosteres can be exchanged, optimizing physical or chemical properties without significant structural change. The main use of bioisosteres is to improve pharmacokinetic parameters, such as absorption, metabolic stability, or half-life, or to reduce toxicity. An example of bioisosterism is observed with procainamide, the longer-acting amide derivative of procaine (an ester), resulting from substitution of an ester oxygen with nitrogen. By doing this substitution, the resulting compound is no longer susceptible to esterases and is thus longer acting. Common bioisosteres for benzene ring are thiophene and pyridine. Bioisoteres can be univalent, bivalent, tervalent (trivalent), or quadrivalent (tetravalent), based on the number of bonds (1, 2, 3, or 4, respectively) they can form.

Natural products

Natural products are chemical compounds found in nature. Terrestrial plants, marine organisms and microorganisms are some of the major sources of natural products. They are typically end products of secondary metabolism, have biological or pharmacological activity and are used for a variety of purposes. This section will focus on those natural products that have pharmaceutical importance (Table 5.16). Records show that in practically every country, certain foods and plants were the basis of early medicine.[3] More than 5000 years ago, the Sumerians described well-established medicinal uses for such plants as laurel, caraway, and thyme.[4] The first Chinese "herbal" book dates back to ~2700 BC and lists 365 medicinal plants and their uses, including ma-huang, the source of ephedrine.[4] A substantial record of the use of herbs as medicine comes from the first Code of Hammurabi (~1770 BC), which is a series of tablets carved under the direction of the King of Babylon and mentions medicinal plants such as

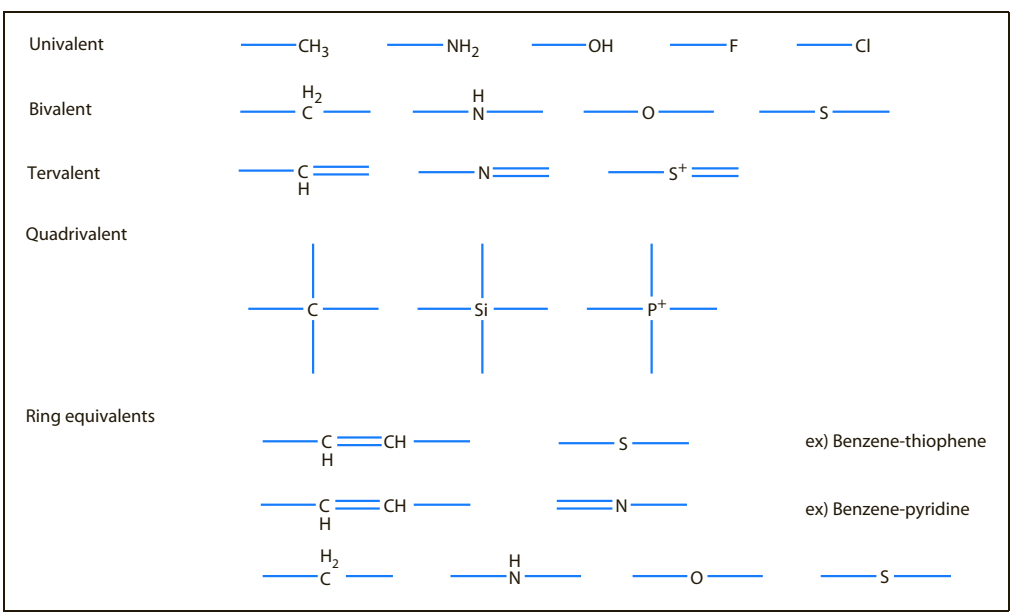


Figure 5.2 Bioisoteric atoms and groups.

Table 5.16 Examples of natural products having pharmaceutical importance

Natural product	Occurrence	Pharmacological use
Caffeine	Tea (the leaves of *Thea sinensis*-Ternstroemiaceae), cocoa beans (the seeds of *Theobroma cacao*-Sterculiaceae), and coffee beans (the seeds of *Coffea* spp. - Rubiaceae)	Stimulates mental activity
Morphine	Opium poppy, *Papaver somniferum* (Papaveraceae)	Analgesia
Pilocarpine	*Pilocarpus* spp. (Rutaceae)	Parasympathomimetic
Ephedrine	*Ephedra* spp. (Ephedraceae)	Peripheral vasoconstrictor
Theophylline	Tea (the leaves of *Thea sinensis*-Ternstroemiaceae), cocoa beans (the seeds of *Theobroma cacao*-Sterculiaceae), and coffee beans (the seeds of *Coffea* spp. -Rubiaceae)	Bronchodilator
Codeine	Opium poppy, *Papaver somniferum* (Papaveraceae)	Cough suppressant
Senna anthraquinones	*Cassia senna* and *Cassia angustifolia* (Leguminosae)	Laxative
Ergometrine	Ergot, a morbid growth formed when the fungus *Claviceps purpurea* develops on various plants of the Gramineae + Cyperacea families.	Uterine stimulation
Capsaicin	*Capsicum* spp. (Solanaceae)	Counter-irritant
Emetine	*Cephaelis ipecacuanha* (Rubiaceae)	Amoebic dysentery

henbane, licorice, and mint.[5] The ancient Egyptians treated their sick by giving them what they thought to be suitable foods. For example, they prescribed liver, a rich source of vitamin A, for night blindness and used moldy breads on wounds.[6] Among the ancient Greeks, Hippocrates (~460–377 BC), who is considered the father of medicine in Western cultures, based most of his protocols for disease prevention and treatment on his patients' diet. Hippocrates coined the famous aphorism, "Food be thy friend and enemy."[7] However, the most significant Greek contribution is often considered to be the five-volume work entitled *De Materia Medica* written by Dioscorides (AD 40–90). This work described the preparation of approximately 1000 simple drugs primarily from medicinal plants and is considered the prototype for future pharmacopeias.[5]

As advances in science continued to improve man's understanding of physiology and the pharmacological effects of food and herbals, these products remained an essential component in the management of disease around the world. By the early 1900s, it was well understood that many diseases were caused or aggravated by poor nutrition. In addition, vitamins were discovered during studies on deficiency diseases such as pellagra (nicotinic acid, a B-vitamin, deficiency) and rickets (vitamin D deficiency). By mid-1900s, vitamins were being isolated and synthesized and subsequently used as additives in other foods or to prepare vitamin supplements. In addition, most people in industrialized countries had achieved an adequate and nutritious food intake. Therefore, deficiency diseases all but disappeared, and as a result, there was little continued emphasis on the importance of foods and diet in health. At the same time, most industrialized nations also saw a rapid rise in drug development. Initially, many of these modern drugs had their origins in herbal products. Most were just isolated, purified products from plant extracts that had been used for centuries, such as morphine from

the opium plant and digitalis leaf glycosides. Medicinal chemists then began to modify these extracted compounds to produce new synthetic medications. Examples of these synthetic drugs include the opiate derivatives such as meperidine, the local anesthetics (novocaine, lidocaine) developed from cocaine and the various ephedrine derivatives originally discovered in *Ephedra* species.[7]

This transition from the use of subtle foods and herbals to rapidly acting and specific synthetic vitamins and drugs in disease management, which took place primarily in the United States, occurred for several reasons. First, these agents were more effective at curing and managing many diseases. Second, there was much disdain for "old-fashioned or folkloric medicine," especially after the hucksterism and quackery that took place at the beginning of the twentieth century. Many fortunes were made during this era (known as the patent-medicine era) by those proclaiming that certain foods or herbs could "cure all ills." This ultimately led to the formation of the FDA and later to laws that regulate dietary supplements and pharmaceuticals based upon sound scientific evidence. Third, there was a belief that human trial and error over the past centuries had discovered most of the plants having medicinal value and little was left to be discovered. Lastly, many pharmaceutical companies felt that it was too costly to screen plants for useful drugs given the low success rate, especially once advances in science had made it easier and cheaper to design synthetic drugs, which are more patentable.[5]

However, by the end of the past century, we saw another major revolution in healthcare. Millions of people have begun eating more healthily and using dietary supplements and herbal products to prevent disease and promote good health. The Dietary Supplement, Health and Education Act (DSHEA), which became law in 1994, and assured the American consumer access to dietary supplements, defines dietary supplement as "a product (other than tobacco) that is intended to supplement the diet; contains one or more dietary ingredients (including vitamins, minerals, herbs or other botanicals, and amino acids) or their constituents; is intended to be taken by mouth as a pill, capsule, tablet, or liquid; and is labeled on the front panel as being a dietary supplement."[8] Dietary supplements contribute substantially to total nutrient intake, as they can contain nutrients in amounts equal to or higher than the Institute of Medicine's Recommended Dietary Reference Intake; therefore monitoring their use over time has become an important component of the National Nutrition Monitoring System.[9] Data from National Health and Nutrition Examination Survey (NHANES) has revealed that use of dietary supplement is common, and increasing among the adult US population aged 20 and over, with over 53% reporting use of at least one dietary supplement in 2003 to 2006.[10] The US sales of dietary supplements estimated to be more than $20 billion, with multivitamin were multiminerals being the most commonly used products.

There are a number of reasons for the resurgence in popularity of these products: (1) it is now well recognized that diet and exercise alone can manage many disorders such as mature onset diabetes (Type II), cardiovascular disease, and those of inborn errors of metabolism (e.g., gout, galactosemia, phenylketouria);[7] (2) many diseases have been conquered and only old age, degenerative disorders, which traditional medicine has had limited success with, remain;[9] (3) people are realizing that, although highly successful, traditional medicine, with its scientific basis, is emotionally hollow, esthetically meaningless, and spiritually empty; (4) many individuals have lost faith in science, which is being blamed for many ills such as pollution due to pesticides, carcinogens, and other environmental toxins; and (5) rising medical costs and managed healthcare have caused the public to lose trust in their healthcare providers, drug manufacturers, and the government.[11] As a result, people are taking a more active role in managing/preventing disease and searching for alternative ways to attain full health.

While this trend toward self-awareness and increased participation in one's health is surely a good thing, there are also several concerns. There is much lacking, unsupported, and erroneous information about herbals and other dietary supplements, and individuals have a tendency to be less than discerning or are not adequately educated to appropriately evaluate information regarding these therapies. Since the reemergence of herbals and dietary supplements is primarily consumer driven and lacks much scientific evidence, many health professionals have regarded it as mere faddism.[7] Unfortunately, this has caused many healthcare professionals to completely dismiss

these products even though many of their patients use them for legitimate and useful reasons. This has resulted in a communication breakdown between patients and their healthcare providers. One study reported that 75% of individuals using dietary supplements neglect to share this information with their physicians.[12] This is most concerning in light of the building evidence of serious herbal–drug interactions such as with St. John's Wort. Table 5.17 lists the possible interactions of some popular herbs.

There are also major safety concerns with these products themselves. For example, early in 1998, a USP expert advisory panel determined that consumer use of comfrey could be harmful due to a lack of scientific evidence to support its safety and dispel the information on its hepatic toxicity.[13] An additional concern with the use of supplements or supplemented foods is that they tend to undermine the idea of healthy eating, which focuses on the whole diet and not just single ingredients. Healthy foods commonly contain several compounds with therapeutic activity or contain compounds that modify the effect of their active constituents on the body. Therefore, eating an orange is typically more beneficial than taking a vitamin C tablet. In addition, supplements may provide nutrients and active components in a potentially unbalanced and concentrated form, different than that used in research studies.[14] However, many of the natural compounds within foods are at too low a concentration to exert a significant effect, and the only rational way of getting the recommended amount is in supplement form or as a food additive, such as the stanol esters in the Benecol products. There are also legal and regulatory concerns on how to promote and market these products, to determine exactly which ingredients have a pharmacological activity, to standardize these products so that they will have known amounts of active principles with known activity, to determine actual efficacy, and to devise appropriate claims.[15] The WHO's *World Medicines Situations Report 2011*,[16] noted that despite the growing popularity of natural products or traditional medicines, consumer understanding of potential risks of using them is low, and they are not always aware that products may be contaminated due to poor manufacturing practices, or may cause side effects in interaction with other herbs or drugs. Additionally, the decrease in consumer confidence has been fuelled by the many negative outcomes portrayed in the media with these products, especially those with falsely labeled claims. Unlike drug products that must be proven safe and effective for their intended use before marketing, there are no provisions in the law for FDA to "approve" dietary supplements for safety or effectiveness before they reach the consumer. By law (DSHEA), the manufacturer is responsible for ensuring that its dietary supplement products are safe before they are marketed. More recently, the FDA has established regulations to require Good Manufacturing Practices (GMPs), necessary for activities related to manufacturing, packaging, labeling, or holding dietary supplements, thus bringing the industry under increased scrutiny and accountability.

Although there are many concerns, modern research has strongly supported and further developed the idea that certain foods and herbals can help maintain good health or serve as medicines (Tables 5.18 and 5.19). The FDA defines special classes of foods including Medical Foods which have exact concentrations of nutrients and appropriate labeling for use in certain medical conditions (e.g., certain hyperalimentations preparations),[17] and Foods for Special Dietary Uses (FSDU), which includes hypoallergenic foods, weight-reduction foods, foods for diabetics, reduced sodium foods, and infant formulas.[18] In addition, 80% of the world's population (primarily in developing countries) still rely on plant-derived medicines.[19] Therefore, quality healthcare needs to be a combination of these "alternative" approaches and traditional therapies; both have a great utility in maintaining proper health and treating disease. With these factors in mind, it is certainly worthwhile for all of those in the healthcare arena to be aware of and take advantage of the fast flowing information regarding natural products to help decide which findings can be used to provide quality healthcare to all patients.

In addition to the use of natural products, such as foods and herbals, to prevent and manage disease, 25% of all drugs prescribed today are still based upon substances derived from plants or plant-derived synthetic analogs. In fact, in the former Federal Republic of Germany, six phytochemicals were among the top 100 of the most prescribed drugs in 1990. Some 4.23 million prescriptions were written for standardized *Ginkgo biloba* preparation alone.[20]

Table 5.17 Herb–drug interactions

Herb	Drug(s)	Possible interactions
Digitalis	Antiarrhythmic agents: Quinidine (Quinidine Gluconate, Quinidine Sulfate), Amiodarone (Cordarone); Calcium channel blockers: Verapamil (Calan, Verelan)	Increased serum digoxin levels have been observed due to a decrease in renal and nonrenal clearance and in the volume of distribution of digoxin.[a] Caution is warranted when using digitalis with these pharmaceutical agents.
Ginkgo biloba	Antidiabetics/Hypoglycemic agents: Sulfonylureas-Glyburide (Diabeta), glipizide (Glucotrol), glimepiride (Amaryl), tolbutamide (Orinase), etc.	Ginkgo has been found to increase plasma insulin concentrations in healthy volunteers,[b] and to decrease these concentrations in subjects with type 2 diabetes.[c] Interactions are possible with antidibetics/hypoglycemic agents.
	Calcium-channel blocker: Nifedipine (Adalat, Procardia)	It is reported that the maximal plasma concentration of nifedipine was approximately doubled by concomitant use of ginkgo, resulting in severe and longer-lasting headaches, dizziness or hot flushes, and increased heart rate.[d]
Ginseng	Anticoagulant: Heparin, warfarin (Coumadin); and antiplatelet agents: clopidogrel (Plavix), ticlopidine (Ticlid)	*Panax ginseng* may inhibit the aggregation of platelets, reduce platelet adhesiveness, reduce INR, and reduce warfarin concentrations and increase its clearance.
	Antidiabetics/Hypoglycemic agents: Sulfonylureas-Glyburide (Diabeta), glipizide (Glucotrol), glimepiride (Amaryl), tolbutamide (Orinase), etc.	Ginseng may significantly reduce blood glucose levels;[e] therefore caution is warranted as combining ginseng with antidibetics may lead to additive effects.
Milk thistle	Glucuronidated agents: lorazepam (Ativan), lamotrigine (Lamictal), entacapone (Comtan)	Silymarin in milk thistle has been reported to inhibit beta-glucurondase,[f] and theoretically may decrease the clearance of glucuronidated agents.
Saw palmetto	Androgenic agents: testosterone (Androderm, methyltestosterone (Android, Testred), fluoxymesterone (Halotestin), and stanozolol (Winstrol)	Because of the anti-androgenic properties of saw palmetto, its concomitant use may decrease the effectiveness of therapeutic androgens.
St. John's wort	5HT1 agonists (triptans): Nartriptan (Amerge), rizatriptan (Maxalt), sumatriptan (Imitrex), and zolmitriptan (Zomig).	Interaction with various triptan medications, via enhanced serotonergic activity, is possible in theory.
	Monoamine oxidase inhibitors (MAOIs): Isocarboxazid (Marplan) phenelzine (Nardil), and tranylcypromine (Parnate)	Hypericin, a constituent of St. John's wort may inhibit monoamine oxidase (MAO) A and B,[g] thereby potentiating the effects of MAOIs, possibly leading to clinical toxicity, such as serotonin syndrome or hypertensive crisis.
	Selective serotonin reuptake inhibitors (SSRIs): Citalopram (Celexa), Escitalopram (Lexapro), Fluoxetine (Prozac, Sarafem), Paroxetine (Paxil, Pexeva), and Sertraline (Zoloft)	Concomitant use of St. John's wort may lead to increased adverse effects typically associated with SSRI antidepressants, including serotonin syndrome or mania.

[a] Bhatia SJ, Digitalis toxicity-turning over a new leaf? *West J Med*. 1986; 145:74–82.

[b] Kudolo GB, The effect of 3 month ingestion of *Ginkgo biloba* extract on pancreatic beta-cell function in response to glucose loading in normal glucose tolerant individuals. *J Clin Pharmacol*. 2000; 40(6):647–654.

[c] Kidolo GB, The effect of 3-month ingestion of *Ginkgo biloba* extract (EGb 761) on pancreatic beta-cell function in response to glucose loading in individuals with non-insulin-dependent diabetes mellitus. *J Clin Pharmacol*. 2001; 41(6):600–611.

[d] Yoshioka M *et al*. Effects of *Ginkgo biloba* leaf extract on the pharmacokinetics and pharmacodynamics of nifedipine in healthy volunteers. *Biol Pharm Bull*. 2004; 27(12):2006–2009.

[e] Sotaniemi EA *et al*. Ginseng Therapy in Non-Insulin- dependent diabetic patients: effects on psychophysical performance, glucose homeostasis, serum lipids, serum aminoterminalpropeptide concentration, and body weight. *Diabetes Care*. 1995; 18(10):1373–1375.

[f] Kim DH *et al*. Silymarin and its components are inhibitors of beta-glucuronidase. *Biol Pharm Bull*. 1994; 17(3):443–445.

[g] Suzuki O *et al*. Inhibition of monoamine oxidase by hypercin. *Planta Med*. 1984; 50(3):272–274.

Table 5.18 Current FDA qualified health claims

Product	Permitted health claim
Dietary supplements containing selenium	Some scientific evidence suggests that consumption of selenium may reduce the risk of certain forms of cancer or Some scientific evidence suggests that consumption of selenium may produce anticarcinogenic effects in the body
Dietary supplements containing vitamin E and/or vitamin C	Some scientific evidence suggests that consumption of antioxidant vitamins may reduce the risk of certain forms of cancer
Whole or chopped almonds, hazelnuts, peanuts, pecans, some pine nuts, pistachio nuts, and walnuts	Scientific evidence suggests but does not prove that eating 1.5 ounces per day of most nuts such as [name of specific nut] as part of a diet low in saturated fat and cholesterol may reduce the risk of heart disease
Dietary supplements containing the omega-3 long chain polyunsaturated fatty acids eicosapentaenoic acid (EPA) and/or docosahexaenoic acid (DHA)	Consumption of omega-3 fatty acids may reduce the risk of coronary heart disease
Dietary supplements containing vitamin B6, B12, and/or folic acid	As part of a well-balanced diet that is low in saturated fat and cholesterol; folic acid, vitamin B6, and vitamin B12 may reduce the risk of vascular disease
Dietary supplements containing soy-derived phosphatidylserine	Consumption of phosphatidylserine may reduce the risk of dementia in the elderly or Consumption of phosphatidylserine may reduce the risk of cognitive dysfunction in the elderly
Dietary supplements containing folic acid	0.8 mg folic acid in a dietary supplement is more effective in reducing the risk of neural tube defects than a lower amount in foods in common form

This may be attributed to the Commission E, which was established in 1978 by a German federal agency (Bundesgeundheitsamt) to determine the safety and efficacy of herbal products. So far, the Commission has produced about 400 monographs on various phytopharmaceuticals and combination products. These compendia probably represent the most complete and accurate modern body of scientific information on the subject today. The study of physical, chemical, biochemical and biological properties of drugs of natural origin has been named Pharmacognosy (*Greek, Pharmakon-drug; gnosis-knowledge*). A number of scientific organizations such as the American Society of Pharmacognosy (ASP), the Phytochemical Society of North America (PSNA), and the Society for Economic Botany (SEB) continue to encourage and stimulate research in the field of natural products.

Nature remains an extremely rich source of molecular diversity, and therefore, natural products continue to be used for drug discovery. Interest in the field of marine natural product appears to be growing. Marine bioprospecting or exploring the oceans for novel compounds with therapeutic potential from marine organisms is the recent addition to current efforts in drug discovery from natural products. In the past, collecting and processing natural compounds was both difficult and costly, especially for

Table 5.19 Popular herbal medicines – Their bases and source

Herbal product	Source	Active ingredient(s)	Common uses	Common side effects	Supporting evidence
Bilberry	*Vaccinium myrtillus*	Vitamins A and C, flavonoids, anthocyanin, and glucoquinine	Improve eyesight, increase blood flow, and treatment of diabetes	Fresh bilberry fruit may have laxative effects	Studies have indicated an improvement in eyesight, due mainly to the effects of vitamin A
Black Cohosh	*Actaea recemosa* aka. *Cimicifuga racemosa*	Remifemin (brand name of standardized extract) Triterpene saponins (expressed as 26-deoxyactein)	Menopausal symptoms, peripheral artery disease, and hypercholes-terolemia	Overdose: nausea, dizziness, visual disturbances, nervous system abnormalities, increased perspiration and bradycardia. Large doses may induce miscarraige	Studies have shown measurable effect on reproductive hormones. Studies have also shown that established breast tumor cell lines were not stimulated, leading scientists to consider Black Cohosh for studies as a substitute for hormone replacement therapy
Cat's Claw	*Uncaria tormentosa*	Several alkaloids including: rhynchophylline, mytraphylline, gambirine, and hirsutine; also six quinovic acid glycosides	Inflammation, as an astringent, gastric ulcer, rheumatism, contraception, and cancer	Use cautiously in cardiac disorders as hirsutine, an indole alkaloid, has been shown to exhibit antiarrhythmic activity	Studies have verified some anticancer claims, as well as some immunostimulant properties. The major effective ingredient, rhynchophylline may decrease blood pressure to the point of being hypotensive at certain doses
Chamomile	*Matricaria recutita*	Bisabolol and flavonoids	Inflammation, GI spasms, and as a sedative	Persons allergic to the Compositae family may experience anything from contact dermatitis to anaphylaxis	Anti-inflammatory and antipyretic claims are supported in animal models. Its main active ingredient, rhynchophylline, has also been shown to decrease blood pressure to the point of being hypotensive at certain doses
Chaste Tree	*Vitex agnuscastus*	Monoterpene derivatives (limonene, 1,8-cineol, bornyl acetate, α- and β-pinene, sabinene), flavonoids (castican, orientin, isovitexin), and iridoid glycosides (agnuside, aucubin)	Menstrual irregularities, hormone imbalance, breast pain, uterine pain, and decreased sex drive in males	GI symptoms, rash, itching, headaches, and menstrual abnormalities can occur	Progesterone/estrogen balance was improved in studies. Its inhibition of prolactin release has also been supported; this can aid in the correction of luteal phase defects
Cranberry	*Vaccinium macrocar-pon*	Hippuric acid, phenolic acids, flavonol glycosides	Treatment, or prevention of urinary tract infections	GI symptoms, such as diarrhea, can occur at very high doses	Significant decrease in urinary pH has been observed in studies. However, treatment is still unproven as bacterial susceptibility and minimum effective dose were unclear

(continued overleaf)

Table 5.19 *(continued)*

Herbal product	Source	Active ingredient(S)	Common uses	Common side effects	Supporting evidence
Echinacea	*Echinacea augustifolia* (common); *E. purpurea* (commerce)	Isobutylamides	To decrease the length of cold or prevent its contraction	Those allergic to the daisy family should avoid due to immune response symptoms	Some evidence points toward a shortening of duration for the common cold; however, prevention has been shown to be doubtful at best
Evening Primrose	*Oenothera biennis*	Gamma-linolenic acid (GLA)	Breast disorders, PMS, breast pain, cardiovascular disease, rheumatoid arthritis, multiple sclerosis, atopic eczema, and other dermatologic disorders	None known	Cholesterol-studies have shown that the active ingredient is successful in significantly lowering blood cholesterol; however, in the concentration found in primrose oil, such a decrease is substantially less, if any. Breast cancer-studies have indicated only a slight decrease in recurrence in those patients who have recovered from breast cancer. Premenstrual syndrome-studies have indicated a decrease in symptoms associated with primrose oil
Feverfew	*Tanacetum parthenium*	Parthenolide	Fever, migraine prophylaxis, arthritis, menstrual pain, asthma, and dermatitis	Abrupt discontinuation can result in a withdrawal syndrome; increased heart rate has also been reported. Should not be used in children < 2 years old, or in pregnant or lactating women	Severity and incidence of migraine headaches has shown to be decreased in those taking feverfew
Garlic	*Allium sativum*	Alliin[(+)-*S*-allyl-L-cysteine sulfoxide]	High blood sugar, hypercholes-terolemia, and hyperlipidemia	None known	Garlic has been shown clinically to increase HDL, decrease LDL and total cholesterol. It has also been shown to have antioxidant properties and to decrease platelet aggregation
Ginger	*Zingiber officinale*	Gingerols; shogaol	Prevent motion sickness, for cough, stomach ache, and gallbladder disease	In large amounts, CNS depression may occur. May affect cardiac function and anticoagulant activity	Ginger has been shown to dramatically increase the amount of time needed to reach a state of motion sickness. It also decreases cardiac workload by increasing vasodilation. It has a strong antimicrobial effect
Ginkgo	*Ginkgo biloba*	Flavonol and flavone glycosides (e.g., quescetin and kaempferol); rutin	Raynaud's disease, stress, tinnitis, dementia, cerebral insufficiency, anxiety, asthma, and circulation problems	Rare, but may include heart palpitations, dizziness, headache and dermatological reactions	Ginkgo has been shown to increase cerebral blood flow and decrease cerebral deficiency. It has also been shown to decrease inflammatory response in lungs reducing severity of asthma attacks. It also increases microcirculation and improvement in pathologic blood flow disease has been observed

(continued overleaf)

Table 5.19 *(continued)*

Herbal product	Source	Active ingredient(S)	Common uses	Common side effects	Supporting evidence
Ginseng	*Panax quinquefolius*	Ginsenosides (triterpenoid saponins glycosides)	Decreased energy, cancer, immune support, and cardiovascular problems	Nervousness is the most common side effect; also some breast nodulation and vaginal bleeding have been reported	An increase in CNS stimulatory and inhibitory effects has been observed in patients taking ginseng. An increase in overall cognitive function has been established as well. However, no studies to date have linked ginseng and improved physical performance
Goldenseal	*Hydrastis canadensis*	Isoquinolone alkaloids (hydrastine, canadine, and berberine)	Topical infections and as an anticatarrhal	Side effects are rare, but contraindicated in patients with hypertension or pregnancy. In very high doses, can cause nausea, anxiety and seizures	Clinically, it has been shown to have modest antimicrobial activity, most effective topically
Grape seed	*Vitus vinifera*	Proanthocyanidins, polyphenols	Antioxidant, venous insufficiency, edema	Hepatotoxicity in animal studies	Clinically, it has been shown to have anti-enzyme properties resulting in a decrease in breakdown of compounds important for tissue structure such as collagen, elastin, and hyaluronic acid
Green Tea	*Camellia sinensis*	Catechins and polyphenol components	Cancer, hyperlipidemia, prevention of dental carries, as an antimicrobial, antimutagenic, and an antioxidant	Caffeine in green tea may cause nervousness and increased heart rate, and should be avoided during pregnancy	Clinically it has been shown to decrease total cholesterol; however, triglycerides and HDL were unchanged. Also, antimicrobial activity has been shown especially against mouth flora. It also has been shown to inhibit GI pathogens, although the dose was 9 cups per day
Hawthorn	*Crataegus laevigata*	Oligomeric procyanidins (epicatechin and flavonoids)	Hypertension, abnormal heart rate, artherosclerosis, angina pectoris, and as an antispasmodic and a sedative	Hypotension and sedation can be experienced at high doses. May interfere with digoxin blood levels	Studies have shown that hawthorn increases vasodilation and coronary artery flow, as well as stabilize heart rate. It has also been shown to decrease lipid levels
Horse chestnut	*Aesculus hippocastanum*	Aesculin	Edema, inflammation, and venous insufficiency	Use should be avoided due to classification as an unsafe herb by the FDA because of toxicity. Topical products containing this herb may also be carcinogenic	Increased vascular resistance and tone has been indicated. A decrease in complaints and edema measures was shown in patients with peripheral edema. Anti-inflammatory properties have also been supported

(continued overleaf)

Table 5.19 *(continued)*

Herbal product	Source	Active ingredient(S)	Common uses	Common side effects	Supporting evidence
Kava Kava	*Piper methysticum*	Kava lactones	Mild to moderate anxiety and as a sedative	Should not be used during pregnancy or by patients with depression. Use should be limited to 3 months to avoid habit-forming tendencies. Also, problems with vision and a condition similar to pellagra have been reported	Studies have supported kava's positive effect on patients with mild to moderate anxiety. It has also been demonstrated as an effective anticonvulsant. In addition, kava has an antithrombotic effect on platelet aggregation
Licorice	*Glycyrrhiza uralensis*	Carbenoxalone	GI complaints	Lethargy and quadriplegia may result from long-term daily consumption	Licorice has been shown to increase the lifespan of gastric epithelia cells. It has been demonstrated to be less effective than Cimetidine at treating gastric and duodenal ulcers
Milk Thistle	*Silybum marianum*	Silymarins (flavano-lignanssilybin, isosilybin, dehydrosilybin, silydianin, and silychristin)	Liver damage prophylaxis, antitoxin	Mild allergic reactions and mild GI symptoms	Milk thistle has been shown to normalize liver enzymes; however, improvement in the evolution and mortality of cirrhosis is not supported
Saw Palmetto	*Serenoa repens*	Probable active compounds are: phytosterols, fatty acids and their ethyl esters, and monoacylglyc-erides	Symptoms associated with benign prostatic hyperplasia	Should be avoided during pregnancy, but no other side effects aside from mild GI symptoms	Clinically, several symptoms associated with benign prostatic hyperplasia have been shown to decrease in those taking saw palmetto. It has not been shown to have any effect on prostate size or presence of prostate specific antigen in the blood
St John's Wort	*Hypericum perforatum*	Hypericin, hyperforin, and related napthodi-anthrones	Depression and viral infection	Rare, but may include constipation, other GI symptoms, dry mouth, dizziness and photosensitivity. Mania and sexual disturbance occur even more rarely	Clinical trials have shown that patients taking St. John's Wort have a significant decrease in serotonin reuptake as well as an increased dopamine function. Also, several viruses (influenza, herpes simplex 1 and 2 and some retroviruses) have susceptibility to this compound. St. John's Wort has also demonstrated potent antimicrobial activity
Valerian	*Valeriana officinalis*	Valepotriates, valerenic acid, and valeranone	Restlessness and sleep disorders	Few to none	Valerian has been demonstrated to improve sleep disorders very effectively. Also, antianxiety studies have indicated efficacy in treating those symptoms

Data from DerMarderosian A, *et al. Guide to Popular Natural Products*, 2nd ed. St. Louis, MO: Facts and Comparisions, 2001; and *United States Pharmacopeia and National Formulary (USP 27-NF 22)*. Rockville, MD: The United States Pharmacopeial Convention, Inc., 2003.

compounds present in very low concentrations. However, this has been made easier by continued advances in extraction, concentration, and identification techniques. Bioassay guided fractionation, high throughput screening and availability of cell-based or enzyme assays have further simplified the process of analyzing and studying natural products. Since natural products already have a function in nature, and therefore, typically already display pharmacological activity, they are seen as improving the odds of synthesizing a good drug compared to starting with a completely new structure. Such compounds are proving to be very useful as starting points for combinatorial chemistry and the synthesis of lead drug compounds. Natural products are complex organic molecules and their synthesis usually involves multiple steps with low yields. However, recent advances such as small-molecule organic catalysis and cascade reactions performed in a single step may be valuable in achieving total synthesis of several complex natural molecules. Despite the difficulties, the renewed interest in natural source of new chemical entities has resulted in approval of a number of natural products and their analogs as new drugs (Table 5.20).

Structure–activity relationships and drug design

Introduction

For centuries, humans have observed that natural substances not only can be used for their nutritional value and for treatment of diseases, but also may bring about toxic or lethal effects. The Chinese Emperor Sheng Nang in 2735 BC compiled a book of herbs and employed "Chang Shan" in the treatment of malaria. Although the majority of the drugs used from antiquity to the nineteenth century came from natural sources, in the twentieth century a new era arose when it became possible to treat diseases with synthetic drugs. In addition, the modification of natural products through various synthetic processes has provided a range of useful semi-synthetic drugs.

The field of medicinal chemistry has evolved from an emphasis on the synthesis, isolation, and characterization of drugs to an increased awareness of the biochemistry of disease states and the design of drugs for the prevention of diseases. An important aspect of medicinal chemistry has been to establish a relationship between chemical structure and biological activity. An increased consideration in recent years has been to correlate chemical structure with chemical reactivity or physical properties, and these correlations can, in turn, be related to their therapeutic actions.

Although there has been a great deal of success in understanding the relationship between chemical structure and biological activity in a number of areas (e.g., for antibacterial drugs), there are still many human afflictions that require new and improved drugs. Cancer, viral infections, and cardiovascular and mental diseases need new agents and approaches for treating and preventing these maladies. One thing has become clear – many disease states (such as cancer) involve a disruption in the normal regulatory machinery of the cell, and present the daunting prospect of addressing multiple potential molecular targets that may be implicated in the development of the illness. This has only intensified our motivation to achieve a better understanding of the relationship between the structure, activity, and specificity of drug molecules acting on cellular targets, so that the effects of small molecules on the web of interactions that support the life of a cell can be more fully understood.

In developing drugs with specific activities, several approaches are used. Often, bioactive compounds are first identified by using a *high-throughput screen*,[21] an assay in which typically thousands to millions[22,23] of small molecules (sometimes taken from proprietary libraries) are presented to a target of interest, and assessed using a fast biological assay implemented in a compact format (e.g., 96-well plates). Once active library compounds are identified, the medicinal chemist and pharmacologist work together to improve the activity of these "lead molecules." This will usually involve the development of a structure–activity model derived from the initial data, which will suggest modifications to the lead compound that are predicted to increase activity. This initiates a cycle of synthesis–biological test–synthesis–biological test, which is iterated until a drug with the desired activity is obtained. Our enhanced understanding of receptor structure (at least for enzymes and other cytosolic

Table 5.20 Recent natural product analog drug approvals

Year	Drug name	Indication	Natural Product (NP) template	NP originally derived from
2010	Cabazitaxel (Jevtana)	Cancer	Paclitaxel (Taxol)	*Taxus brevifolia*
2010	Eribulin mesylate (Halaven)	Cancer	Helichondrin B	*Halichondria okadai*
2010	Rifaximin (Xifaxan)	Antimicrobial	Rifamycin	*Streptomyces mediterranei*
2009	Artemether (Coartem)	Antimalarial	Artemisinin	*Artemisia annua*
2009	Capsaicin (Qutenza transdermal patch)	Neuropathic pain	Capsaicin	*Capsicum* sp.
2009	Colchicine (Colcrys)	Gout / Mediterranean fever	Colchicine	Colchicum autumnale
2009	Everolimus (Afinitor, Zortress)	Cancer / Immunosuppressant (approved in 2004)	Rapamycin	*Streptomyces hygroscopicus*
2009	Telavancin (Vibativ)	Antibacterial	Teicoplanin	*Actinoplanes teichomyceticus*
2007	Ixabepilone (Ixempra)	Cancer	Epothilone	*Sorangium cellulosum*
2007	Retapamulin (Altabax)	Impetigo	Pleuromutilin	*Pleurotus mutilus*
2007	Temsirolimus (Torisel)	Cancer	Rapamycin	*Streptomyces hygroscopicus*
2007	Trabectedin (Yondelis)	Cancer	Ecteinascidin	*Ecteinascidia turbinata*
2006	Anidulafungin (Eraxis)	Antifungal	Echinocandin	*Aspergillus nidulans*
2005	Exenatide (Byetta)	Type 2 Diabetes	Exendins	*Heloderma suspectum*
2005	Micafungin (Mycamine)	Antifungal	Echinocandin	*Aspergillus nidulans*
2005	Tigecycline (Tygacil)	Antibacterial	Tetracycline	*Streptomyces* sp.
2004	Telithromycin (Ketek)	Antibiotic	Erythromycin	*Saccharopolyspora erythraea*
2003	Daptomycin (Cubicin)	Antibacterial	Lipopeptide	*Streptomyces roseosporus*
2002	Pimecrolimus (Elidel)	Immunosuppressant	Rapamycin	*Streptomyces hygroscopicus*
2001	Acemannan (Carrington patch)	Wound healing	Polysaccharide	*Aloe vera*
2001	Caspofungin acetate (Cancidas)	Antifungal	Echinocandin	*Aspergillus nidulans*

Data from: Beutler JA. Natural products as a foundation for drug discovery. *Curr Protoc Pharmacol*. 2009; 46: 9.11.1–9.11.21.

proteins or protein domains) also leads to the possibility of *virtual screening*,[24] where the interactions of a small molecule and a protein receptor are predicted solely on the basis of structure and energetic models. While experiment remains the "final word" as to the activity of a molecule, computational models have advanced to the point where virtual screens are routinely used to select compounds for initial testing, and to refine structure–activity relationships. Computational modeling has become a routine element of the drug discovery process, and a design team often will include a dedicated computational specialist.

Analog approach

Ligand-based design

In drug design, we recognize two broad approaches: receptor-based design and ligand-based design. *Receptor-based design* starts with the assumption that we have an atomic-resolution model of a receptor (found most often by x-ray crystallography or nuclear magnetic resonance (NMR)), usually a protein molecule that includes an active site at which small molecule ligands can bind. High-resolution models can often be determined for soluble proteins or protein domains, including many interesting targets such as enzymes, transcription factors, and cytoskeletal proteins. In receptor-based strategies, the goal is to identify molecules that are strongly complementary to the receptor, in both shape and electrostatics (especially positions of hydrogen-bond acceptors and donors). In contrast, in *ligand-based design* it is assumed that no initial information as to the structure of the receptor is available; instead, we begin with activity information for a panel of known bioactive compounds, and assume that molecules similar in shape and electrostatic properties to one of our known actives will likewise interact with the same target receptor.

Recognizing that similarity in shape and electrostatic profile implies similar biological activity, it is natural for us to abstract those features of a panel of active compounds that are most important for eliciting a response. The pharmacophore is the chemical segment of a molecule that is responsible for biological action. Usually a pharmacophore will feature a set of organic functional classes with a specific relative arrangement in space. An implicit assumption is that these groups must be positioned in this way to interact with complementary features of the receptor; for example, a hydrogen-bond donor in the *pharmacophore* is presumed to interact with a hydrogen-bond acceptor in the receptor, a bulky alkyl group with a hydrophobic pocket in the target active site, and so on. The potency of a compound can often be correlated with the number of features it shares in common with the hypothetical pharmacophore, and this can represent a rough but useful structure–activity relationship. Figure 5.3 illustrates several pharmacophore models[25] which abstract the features of compounds that exhibit selective agonism toward estrogen receptor subtypes α and β, along with some active molecules which fit the pharmacophores. The spheres in the models represent spatial tolerances for declaring a match between a candidate molecule and the pharmacophore. For a molecule to fully match a pharmacophore, it must be possible to flex and position it so that all of the pharmacophore sites enclose a requisite chemical feature of the compound; for example, a sphere labeled "HD" must enclose a hydrogen-bond donating functional group to contribute to a match.

Since drug activity is directly determined by the shape and electrostatic field of a molecule, a useful approach is to modulate these properties by obtaining or synthesizing *analogs* of a molecule known to be active. Often a series of substitutions can be effected to a parent compound by changing reagents used at various steps of the synthesis. By introducing independent substitutions at several sites on the parent compound, a large number of analogs can be constructed, and coupling this with an assay of biological activity provides a powerful mechanism to probe the structure–activity relationship. At the same time, structure–activity relationship studies often provide the raw data needed to infer the pharmacophore (using either computational tools or chemical intuition) and thus to obtain drugs with increased potency. After a collection of compounds with adequate potency has been obtained, additional properties can be measured, including selectivity, duration of action, toxicity, and metabolic stability, and these can serve as additional criteria when selecting a drug candidate.

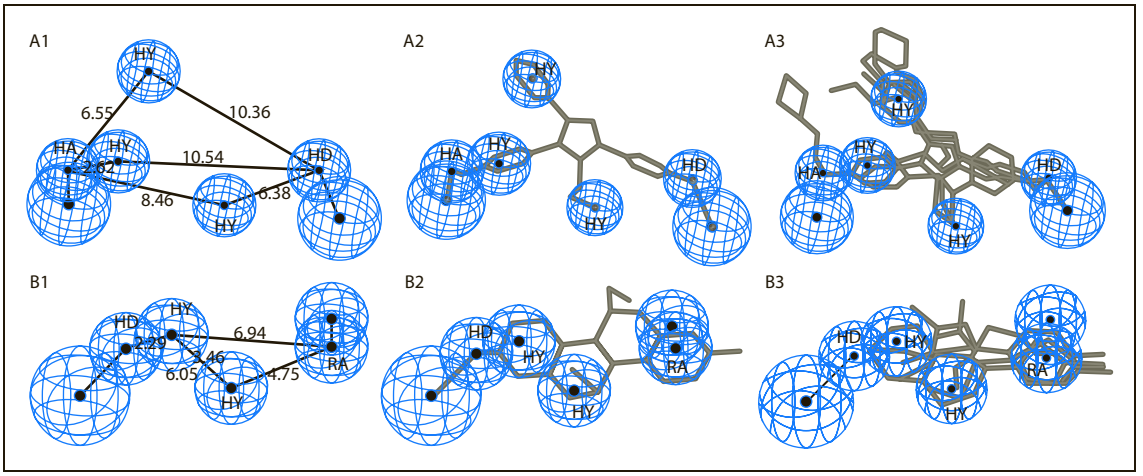
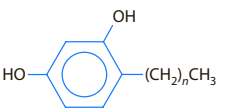


Figure 5.3 Pharmacophore models for selective ERα and ERβ ligands. (A1) ERαmodel with distance constraints (Å); (A2) ERα model mapped with the most active ligand 1 (RBA = 140, K_1 = 0.14 nM); (A3) ERα model mapped with selective ERα test set ligands 4′, 6′, 10′, 43′; (B1) ERβ model with distance constraints (Å); (B2) ERβ model mapped with the most active ligand 24 (RBA = 144, K_1 = 0.35 nM); (B3) ERβ model mapped with selective ERβ test set ligands 5″, 16″, 32″, 40″. (Reproduced from Fang J *et al*. Computational insights into ligand selectivity of estrogen receptors from pharmacophore modeling. *Mol Inform* 2011; 30: 539–549.)

Homologs

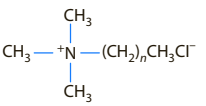
One approach to systematic modification is to adjust the size of a selected portion of the molecule in controlled steps. A *homologous series* refers to a series of analogs that differ in structure by a simple increment in the molecular formula. For example, these may be produced by sequential chemical change that includes increasing or decreasing the length of an akyl carbon chain. A series of homologs of this type is used to provide insight into the relationship of biological activity and chemical changes that involve only the number of methylene groups attached at a single site. This type of variation directly modulates the hydrophobic/hydrophilic partition coefficient, and consequently the biological action. Often, the compounds with short alkyl chains are low in activity; as the chain length is increased, the biological activity increases to an optimum point, and as more methylene groups are added, activity decreases. A classic example of this phenomenon is the activity of the *n*-alkylresorcinols in which the optimum biological activity, as measured by phenol coefficients against *Bacillus typhosus*, is hexylresorcinol.



Hexylresorcinol ($n = 5$)

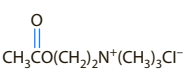
with six carbon atoms ($n = 5$) in the side-chain. If the alkyl chain is lengthened or decreased, a decrease in activity is observed relative to hexylresorcinol.

There are times when changing the number of methylene groups may lead to a change in the type of biological activity rather than its intensity. For example, it is known that alkyltrimethylammonium analogs



Alkyltrimethylammonium

possess different types of activity depending on the length of the alkyl group. If the alkyl group is up to six carbons (n = 5), the compounds are muscarinic agonists. Thus, these compounds have activity similar to acetylcholine.

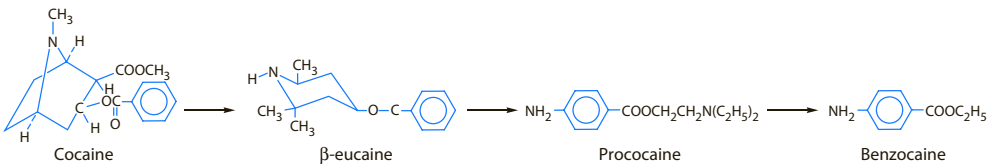


Acetylcholine chloride

on muscarinic receptors. With seven carbons (n = 6) to eight carbons (n = 7), these compounds are partial agonists; when the length is greater than nine carbons (n = 8), these compounds are muscarinic antagonists.

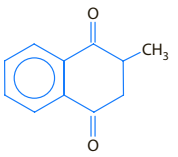
Fragment-based approaches

A very different tack is not to build molecules up, but rather tear them down, thus determining the functional groups responsible for activity. In recent years, *fragment-based approaches*[26] have enjoyed increasing popularity. This is in part motivated by the recognition that naturally occurring active molecules may include large components that are not required for activity. A classic example is cocaine, an alkaloid obtained from *Erythroxylon coca*, which has served as the prototype molecule for the development of a series of potent local anesthetics, produced by successive simplification of the starting structure:

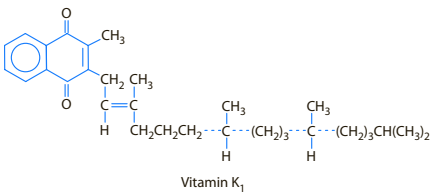


In this series, the carbomethoxy group of cocaine is first removed to produce tropacocaine, the tropane ring is next simplified to produce β-eucaine, and the six-member ring of β-eucaine can be broken to produce procaine without loss of activity (although procaine does introduce an additional amine group). It was demonstrated that the critical part of procaine required for activity was the hydrophilic amine segment attached to an intermediate chain, which in turn was attached to a lipophilic ester function. The key idea is that while the totality of a molecule may be involved in determining its overall biological profile, including bioavailability and metabolism, the portion actually responsible for target activity may be of limited extent, and point to lead compounds that are easier to synthesize. Moreover, smaller active compounds present superior *ligand efficiency*,[27] defined as the ratio of the free energy of binding to the number of heavy atoms in the compound, and this has become widely recognized as an important metric for evaluating drug molecules; smaller molecules are not only more economical to synthesize, they are demonstrated to have higher rates of success in surviving the clinical trial phase and eventually reaching the market.

An even more compelling classical example of improved ligand efficiency is provided by the anti-hemorrhagic menadione.



Menadione (vitamin K_3) is a precursor to the natural product vitamin K_1, which has similar action in reducing hemorrhage, but is a much larger molecule:



Menadione retains only the naphthoquinone ring of vitamin K_1, while maintaining the essential biological activity.

Modern fragment-based approaches[26,28] focus less on natural products or the deconstruction of known actives, and rely more on large chemical libraries as rich sources of structural diversity. While our emphasis here is on ligand-based approaches, we would be remiss not to mention some very productive experimental and computational strategies that utilize detailed knowledge of receptor structures. One approach to *de novo* design of new drugs is to first identify those sites on a target protein that will bind small molecules. The goal is not to immediately find lead compounds with drug-like properties, but rather to identify collections of fragment molecules (e.g., single rings with varying substituents, small acyclic molecules with one or two functional groups) which bind tightly enough to form one or more ad hoc scaffolds to develop larger molecules which *will* serve as leads. While fragments may only bind with millimolar affinity, it may still be possible to detect binding, and even to localize the bound fragment in the receptor.

Experimental techniques that support fragment-based drug discovery include x-ray crystallography and NMR. Crystallographic studies can be carried out after *co-crystallization* of the target protein structure with one or more fragment compounds. The electron-density map is studied for the presence of fragment occupancy in the vicinity of the active site, and it may be possible to resolve multiple fragments that bind close together with a mutual orientation that is consistent with a larger structure that links the two together:[29] alternatively, libraries of larger compounds involving two or more fragments may be employed at the outset.[30] In principle, it should be possible to develop a novel compound with binding affinity that reflects the sum of the binding energies of the individual fragments, and in fact this has been a useful strategy against several molecular targets. (There is evidence, however, that this process is not invertible, in the sense that a known binder comprising several fragments may not be "explained" on the basis of its component parts, which may prefer alternative binding sites when presented individually.[31])

NMR provides another route to detecting the binding of small fragments and to localizing them in the receptor. Chemical shifts in the receptor are very sensitive to the binding of small molecules, and moreover NMR structure-determination methods can be applied to determine a three-dimensional structure for the bound ligand in favorable circumstances, even in situations where fragments may overlap. Again, in favorable circumstances it may be possible to identify synthetic strategies that effect a merger of neighboring compounds, creating a larger molecule with higher potency that may serve as a novel lead.

Yet another approach to fragment-based design is to dispense with experiments for initial screening, and instead rely on computational tools to predict, solely on the basis of structure, the most likely binding sites for small fragments, and moreover to automatically assemble these to form larger compounds that might serve as useful lead molecules. A wide variety of such *de novo* drug design strategies[32] are available. While the approaches are diverse, all typically rely on libraries of chemical fragments to serve as raw material, a method to identify likely binding sites, a stochastic approach to explore possible positions and orientations of fragments, a scoring function to assess and rank the binding positions of the fragments, and finally some mechanism to merge fragments to construct larger molecules. While it is generally recognized that such theoretical calculations are far less reliable than experiment, the accuracy of the predictions made by such tools is steadily improving as the underlying algorithms are refined. It should also be noted that experimental screening of large numbers of fragments is expensive and sometimes difficult to carry out for specific targets; thus theoretical computations are increasingly seen as an attractive alternative.

Quantitative structure–activity relationships

A long-standing goal of workers in the area of *quantitative structure–activity relationships* (QSAR) has been the development of quantitative methods of determining the activities of a series of compounds. One of the earliest hypotheses that attempted to relate activity to a physicochemical parameter was the Meyer–Overton narcosis theory.[33] In 1901, both men working independently observed that, for general anesthetics, activity was related to the lipid/water partition coefficient; for example, cyclopropane with a value of 65 was far more effective than nitrous oxide with a coefficient of 2.2.

In the field of theoretical chemistry, Hammett[34] was the first to demonstrate that the pK_a values of substituted benzoic acids could be predicted as a function of the various substituents attached to the ring and their abilities to either donate or withdraw electrons from the carboxyl group. These results then were extended to other reactions and other series of compounds using the same substituent constants derived from the benzoic acid series. In the Hammet equation,

$$\log \frac{k}{k_0} = \rho\sigma \tag{5.43}$$

where k is the rate constant for the reaction of a substituted aromatic compound, k_0 is the rate constant for the unsubstituted aromatic compound, ρ is the reaction constant, and $\rho\sigma$ is the substituent constant. Later work led to substituent constants in which the electronic effect is separated into inductive and resonance terms; in the Taft equation, a term E_s is defined as a measure of the steric requirements of a substituent.

Contemporary QSAR approaches, despite their great diversity, share some broad features in common: the use of numerical *descriptors* to characterize the

molecules in a collection under study, and the development of a *functional model* between the descriptors and the measured bioactivity of the molecules in the set. This functional model is then used to predict the activities of molecules that lie outside the *training set* used to construct it.

Descriptors

A wide array of measures have been adopted to characterize the molecules in a series. The most familiar of these are the *physicochemical* descriptors, including molecular weight, dipole moment, and perhaps most importantly log *P*, the logarithm of the octanol–water partition coefficient:

$$\log P = \log_{10} \frac{[S_{oct}]}{[S_{aq}]} \tag{5.44}$$

where $[S_{oct}]$ and $[S_{aq}]$ are the equilibrium concentrations of the compound in the low-polarity octanol phase and aqueous medium, respectively. Log *P* is a measure similar to the lipid–water partition coefficient of Meyer–Overton theory, and this and other measures of hydrophobicity remain among the most important molecular descriptors, as they are indicative not only of the likelihood of binding to particular receptor sites, but also of transport across membranes (i.e., bioavailability) and other features of storage and disposition.

Other descriptors seek to capture more details of chemical structure. *Two-dimensional (2D) descriptors* depend on chemical connectivity alone; the simplest of these are counts of various functional groups, including hydrogen-bond donors and acceptors. These and other numerical counts may correlate with bioactivity. The approach may be extended to its logical limit to construct a *molecular hologram*, a histogram in which chemical fragments map to bin positions, and the histogram counts the number of occurrences of fragments that map to the same bin.[35] By decomposing an input molecule into all fragments within a range of sizes, and mapping these to a histogram of fixed length, a small descriptor is created which encapsulates much chemical information.

Other 2D descriptors are defined by treating the molecule as a mathematical *graph*, a tree structure consisting of vertices (atoms) connected by edges (bonds). With this perspective in place, many graph-theoretic concepts are available to inspire new descriptors, such as the classical Randic index:

$$r = \sum_{b \in B} \frac{1}{\sqrt{d_{b(i)} d_{b(j)}}} \tag{5.45}$$

Here the sum ranges over all bonds *b* (each bond connecting atoms b(i) and b(j)), and d_k is the *degree* of atom k, equal to the number of connections (bonds) including that atom. (We note that in all computations of 2D descriptors, it is customary to ignore hydrogens.) Graph-theoretic descriptors are fast to compute, capture structural information in non-obvious ways, and have been shown to strongly correlate with selected molecular properties. Taking a further step, we can use the graph depiction to construct a matrix representation of the molecule, where each off-diagonal position (row *i*, column *j*) signifies presence or absence of a bond between atoms i and j; an off-diagonal element that contains a nonzero value indicates a connection between the atoms, and perhaps also the order of the bond. Diagonal elements may hold a selected property of the atom corresponding to that row/column. By construction, these matrices will be symmetrical (swapping rows and columns leaves the matrix unchanged). The *eigenvalues*[36,37] of an $n \times n$ matrix are found by treating it as an operator in *n*-dimensional space and identifying "special" directions it leaves unchanged. In physical calculations, these often have special significance (e.g., vibrational frequencies); in QSAR they are simply numbers that have been shown to sometimes correlate strongly with bioactivity, and thus are useful as descriptors. While the connection between the eigenvalues of a molecular structure matrix and the molecule's properties may be opaque, the practical utility of these numbers as descriptors is undisputed.

Whereas 2D descriptors are completely defined by the elements in a compound and their pattern of bonding, *three-dimensional (3D)* descriptors require that all the atoms have assigned x–y–z coordinates. Computing atomic coordinates is not a trivial task; modeling packages such as Schrödinger and MOE include methods for coordinate generation, and there are specialized tools like CORINA[38] dedicated to this purpose. Coordinates may be stored with the compounds in a chemical library, depending on its

format and intended purpose, or we may choose to compute them as needed.

Three-dimensional QSAR descriptors include those involving surface area, since this geometrical measure is a function of the specific conformation of a molecule. Surface descriptors include total polar and nonpolar surface areas, where each portion of the surface is assigned to one or the other category based upon the chemical types of the atoms underlying the surface, and can be extended to a histogram approach where surface contributions are tallied over a range of a selected hydrophobicity index (such as atomic contributions to the log *P*).

The 3D descriptors with the greatest potential explanatory power are *grid-based descriptors*, which are generated by enclosing a molecule, or a set of molecules, in a rectangular lattice of points. Each grid point can sample the steric volume presented by each molecule, as well as its electrostatic potential or other properties. It is important to stress that every grid point is an *individual descriptor*, and a QSAR study involving a grid may imply the presence of hundreds or even thousands of descriptors, with important implications for the reliability of predictive models.

Models

The universal concern of QSAR studies is to construct a function that will predict the bioactivity of molecules against a given target, or other measurable properties of interest (such as bioavailability). The classical approach is to build a *linear regression model*, a linear function that maps a collection of descriptor values (potentially large in number) to a single real number, the predicted activity/property (e.g., the log of the IC_{50}). The output of the model is called the *response*. There are a number of mathematical approaches to construct this function, and all recognize some typical difficulties that arise when there are a large number of input variables to a predictive function, and where many of these may be poorly correlated with variation in the response. All of the approaches, which include principal components analysis (PCA) and partial least squares (PLS), seek to collapse together those variables whose variation is strongly correlated, so as to reduce the effective number of inputs to the regression model and increase its robustness.

In more recent studies, a variety of novel methods have been used to construct predictive models, often borrowed from the world of data mining. These include *k* nearest neighbor (*k*NN) and "lazy learning" approaches[39] where the activity of a compound is predicted on the basis of the training compounds it is closest to (as measured in the space of descriptors), and neural networks have also been applied to construct predictive models (these have the advantage of readily modeling nonlinear relationships). Methods have been developed that use data-mining techniques in conjunction with traditional PLS, for example using a genetic algorithm to select the best set of descriptors for building a predictive model.[40] For some series of active compounds, such hybrid methods may succeed where traditional PLS fails. Indeed, the ways in which different methodologies from different fields can be mixed and recombined provides a fertile ground for experimentation and development, and ensures that QSAR will continue to be an important and evolving area of work.

An important concern with any predictive method is that when the number of descriptors is much greater than the training set of active compounds (a common scenario in 3D QSAR), the algorithm may automatically pick out a subset of descriptors whose variation correlates with activity purely by chance, and produce what appears to be a valuable predictive model. This model will only work on the original set of training molecules, and will likely fail miserably when validated on another set of compounds. To guard against this, it is important to always employ a *cross-validation technique*. This may mean dividing a set of compounds of known activity into distinct training and validation sets, with the training compounds used to construct the model, which is then verified by using it to predict the activities of the validation molecules. A widely used and simple alternative to this is called *leave-one-out (LOO)*. In LOO, each active compound is selected in turn to be removed from the training set; the remaining compounds are used to construct the predictive model, which is then used to compute the activity of the compound removed. The residuals for the compounds (differences between measured and predicted activities) are collected and used to compute the correlation coefficient, which in this context is termed the cross-validated r^2, or q^2. A widely used rule-of-thumb is to consider a q^2 value

of 0.5 or greater as indicative of a useful model (the non-cross-validated r^2 for such a model might actually be close to unity, and is not a good measure of the model's utility). In the end, a non-cross-validated model is constructed using all the compounds in the training set.

Applications

Many successful applications of QSAR to the design of bioactive molecules are available in literature. They range from "classical" studies that employ physicochemical and 2D descriptors, to more current 3D QSAR methods, usually involving a grid-based approach. An illustrative example of classical QSAR model development is given by the rational design of a series of 1-(*X*-phenyl)-3,3-dialkyl triazenes as antitumor agents.[41] While these compounds were extensively investigated because of their potent antitumorigenic effects, they also exhibited significant mutagenicity.[42] QSAR studies were successfully conducted on a congeneric series of triazene derivatives to identify structural modifications that reduced the mutagenic properties of these compounds, while leaving unaffected their desirable antitumor activities.

Also, QSAR studies have been extensively applied to the rational design of anti-HIV inhibitors active against HIV-related biological targets.[43–45] Other pertinent examples include the implementation of QSAR models to design novel zinc-containing inhibitors of matrix metalloproteinases[46] as well as to the use of sulfonamide derivatives as potential inhibitors of carbonic anhydrase.[47]

In the course of the 1980s the computing power available to researchers engaged in drug discovery increased by orders of magnitude, greatly expanding the number of descriptors that could be considered in a QSAR analysis. This enabled the introduction of powerful methodologies such as comparative molecular field analysis (CoMFA),[48] a 3D QSAR approach[49] developed by Tripos[50] in 1988. CoMFA measures the electrostatic and steric (van der Waals) interactions between a series of aligned molecules (the training set) and a probe atom, which is placed at all the vertices of a regular grid of points that enclosed the aligned molecules. In this way, the electrostatic and steric properties of the set are sampled throughout the enclosing volume. Each point records individual field values for all the molecules, and each training molecule has a measured activity against the target of interest. It can be seen that each grid point thus serves as a *separate descriptor*, analogous to log *P* or molecular weight in "classical" QSAR. The difference of course is that while a traditional QSAR study may entail dozens of descriptors, a grid with a fine spacing can easily lead to thousands of descriptors. Fortunately, fast computers coupled with an appropriate implementation of the PLS regression method[51] can produce a useful model in this situation, one which automatically de-emphasizes unimportant descriptors (e.g., grid points at which activity does not correlate with measured field values).

In CoMFA, the structures of the training set need to be correctly superimposed in a consistent manner. Alignments can be realized by reference to crystallographic data for a series of actives in complex with a common receptor or by using molecular docking. When no receptor-based information is available, structural alignments are often built according to a pharmacophore hypothesis, or by relying on a shared scaffold if the active molecules form a congeneric series (often the case). Interactions between the aligned molecules and the probe atom presume existing steric and electrostatic force-field parameters. An important advantage of CoMFA is that the significant grid points (those where variations in steric and/or electrostatic fields correlate well with activity) are identified immediately by the PLS procedure, and moreover the *kind* of variation associated with increased activity (e.g., increasing steric bulk or negative electrostatic potential) is also known. This allows the grid to be "color coded" by the strength of correlation (intensity) and the kind of variation (color), leading to isocontour maps that inform the medicinal chemist as to where the addition or removal of steric bulk, or the modulation of electric charge, is likely to lead to increased activity.

The first implementation of CoMFA refers to a series of steroid molecules binding to two different globulin targets.[48] Since then, significant progress has been made in the application of CoMFA, and several noteworthy examples are available, including the CoMFA analysis for the design of p38 MAP kinase inhibitors[52,53] and the synthesis and characterization of novel cyclic sulfamide inhibitors of HIV-1 protease.[54] CoMFA remains one of the most powerful and popular QSAR methods ever devised.

Although not a QSAR method *per se*, another important 3D tool is GRID,[55] a structure-based ligand design tool that involves the prediction of binding pockets on protein surfaces by calculating interaction energies, using a set of empirical energy functions. Similar to CoMFA, GRID relies on the use of a regular lattice of points which, in this case, is overlaid against the binding pocket. Again, a selection of chemical probes is distributed throughout the grid volume, while empirical scoring functions are used to calculate specific interaction energies between each probe and the receptor atoms. Lastly, a 3D map is obtained where molecular interaction fields (MIF) are visualized and used to locate favorable interaction regions and protein-binding sites. One of the most successful applications of GRID in the field of structure-based drug design is its role in the discovery of the drug Relenza[56] (GlaxoSmithKline), a potent inhibitor of the influenza virus replication. The natural evolution of the GRID maps led to their use as descriptors in CoMFA analyses for the successful development of QSAR and 3D QSAR approaches. More recent applications have been reported in the field of ADME and metabolism, in particular through the software tool VolSurf.[57,58]

As already noted, in typical CoMFA and CoMFA/GRID analyses, a very large number of variable descriptors can be easily computed for each compound. However, many of these variables are likely to be uninformative as to activity or binding, and many will be tightly correlated (e.g., two neighboring grid points may sample nearly identical field values). Indeed, any structural variation in the compounds generally affects only a *subset* of related variables; thus a selection procedure is needed to enhance the overall quality of the PLS model by neglecting redundant and uninformative descriptors. GOLPE[59] (generating optimal linear PLS estimations) is a powerful tool introduced in 1993 that achieves this goal, and which has been widely applied in combination with other tools. GOLPE implements a procedure of preselection of nonredundant variables with high degree of orthogonality in the multidimensional space defined by the descriptors. A fractional factorial design (FFD) approach is then used to choose different subsets of descriptors used to generate PLS models. Lastly, the predictive abilities of these models are estimated (and cross-validated) and a selection of the meaningful variables, which significantly explain the predictive power of the model, is finally performed. Over the past few years, several applications of the GRID/GOLPE combination have been implemented to successfully guide the design of new bioactive molecules against a number of targets, including inhibitors of glycogen phosphorylase b,[60] histone deacetylase inhibitors,[61] and the design of novel putative inhibitors of the tyrosine kinase Abl.[62]

Pharmaceutical profiling

Introduction

According to *Mosby's Medical Dictionary*, 8th edn,[63] a drug profile is an outline or summary of the characteristics of a drug or drug family, listing dosage types, pregnancy category, prescription or over-the-counter forms, generics (if available), contraindications, and classification if covered by controlled-substance laws. Therefore, pharmaceutical profiling may be simply defined as pharmaceutical and biomedical research activities undertaken in order to identify and/or predict a drug profile in the early drug discovery and development phase to ensure future clinical success in terms of patient outcomes (e.g., efficacy and safety). This topic is becoming increasingly important as underscored in a recent series of comprehensive manuscripts following the Pharmaceutical Research and Manufacturers of America (PhRMA)'s initiative on predictive models of efficacy, safety, and compound properties.[64–68] Traditionally, the process of drug discovery has been directed by target generation from observation of the biological activity of a natural or synthetic chemical entity on a physiological or pathological process.[69] This "one molecule at a time" approach which is based on trial and error, serendipity, scientific intuition, genius, and luck, has achieved several noteworthy therapeutic successes. The availability of new molecular approaches to the selection of drug therapy is an emerging need and the traditional approach based on the evaluation of patient characteristics is clearly far from optimal. In many cases the majority of treated patients do not have significant benefits from treatment and they often experience moderate to severe toxicities.[70]

Paul Ehrlich's pioneering experiments with cells and body tissue revealed the fundamental principles of the immune system and established the legitimacy of chemotherapy – the use of chemicals to treat disease. Moreover, recent advances in genomics, proteomics and informatics, and analytical techniques have allowed the development of pharmaceutical profiling. For example, as we better understand how biological processes unfold in real time through advances in chronobiology and related fields, we are able to create safer, more effective drugs, drug delivery systems, and disease monitoring and prevention systems.[71,72] Tests that predict clinical outcome for patients (e.g., cancer therapy) on the basis of the genes expressed by their tumors are likely to increasingly affect patient management, heralding a new era of personalized medicine.[73]

The use of direct-to-consumer genome-wide profiling to assess disease risk is controversial, and little is known about the effect of this technology on consumers. In a selected sample of subjects who completed follow-up after undergoing consumer genome-wide testing, such testing did not result in any measurable short-term changes in psychological health, diet or exercise behavior, or use of screening tests. Potential effects of this type of genetic testing on the population at large are not known.[74] Advances in analysis techniques, such as mass spectrometry (MS), high-resolution liquid phase separations, and informatics/bioinformatics for large-scale data analysis have enabled pharmaceutical profiling at different levels.

To complete the already long list of issues facing the pharmaceutical industry, we should also note that unused pharmaceuticals are posing unknown risks for the environment and take a toll on human health.[75] In an effort to elucidate and predict pharmaceutical profile, the *in silico*, *in vitro*, and *in vivo* tools for prediction, measurement, and application of compound properties to select and improve potential drug candidates have been reported elsewhere.[76]

Pharmaceutical profiling in drug discovery

Computational methods for the prediction of "drug-likeness"

Early drug discovery efforts relied on the screening of natural product extracts, pure serendipity, the "me-too" philosophy, or a mixture of all three. High-throughput screening (HTS), robotics, and automation now allow assays to be performed using very small volumes with novel liquid-handling technologies. These technologies had little, if any, impact on facilitating the discovery of new clinically successful drugs. To this end, HTS and computational technologies can be easily combined to improve chances of hit discovery and lead selection.[77] These include docking (e.g., DOCK programs such as AutoDock and Glide, a crude combination of computational chemistry and parallel synthesis), similarity search (e.g., Network Conceptor, Inc.'s COMPARE algorithm to identify molecules with similar effect), pharmacophores (3D arrangement of molecular features necessary for bioactivity using the Catalyst program), quantitative structure–activity relationship (QSAR), and *de novo* design which is based on crystal structure of the molecular target.

Docking has gained great importance for rational drug design. This approach is relevant in drug discovery where the drug function is computationally assessed by protein–drug interaction. The results of docking can be used to find inhibitors for specific target proteins and thus to design new drugs. In addition to molecular docking,[78] two of the most successful methods described in the literature for computational drug design are *in silico* screening (e.g., inhibitor discovery[79,80]) and molecular dynamics simulations (e.g., for dynamic models of protein–ligand interactions to aid in lead optimization[81,82]).

There are several comprehensive review papers[83–88] and books[76,89] on these topics. Ligand similarity-based lead identification is a technique that follows the principle of similarity. It does not require information about the 3D structure of the target protein. It is assumed that molecules with similar structures will have similar chemical properties. Hence, the information provided by a compound, or set of compounds, known to bind to the desired target is used to identify new compounds from the external databases of chemical compounds using virtual screening approaches. The most commonly used methodologies for ligand similarity-based lead identification are shown in Table 5.21.

The QSAR process quantitatively correlates structural molecular properties (descriptors) with functions

Table 5.21 Selected softwares in QSAR analysis

Software/webserver name	Description
ACD/Log P Freeware	Fragment-based algorithm for log *P* prediction
Carcinogenic Potency Database (CPDB)	Unique and widely used international resource of the results of 6540 chronic, long-term animal cancer tests on 1547 chemicals
COMPARE	HP NonStop NSK-only utility program that identifies the differences between files or segments of files. It can be used to compare text files, entry-sequenced files, object or unstructured files. The product has two different modes of comparison: uses extensive correlation technology to reduce false matches and miscompares that tend to "confuse" other similar utilities. NCI's COMPARE can identify additions, deletions and modifications
DALTON	Program for *ab initio* calculation of molecular properties
DSSTox	Distributed Structure-Searchable Toxicity (DSSTox) Public Database
MoKa	*In silico* computation of pK_a values
Molinspiration	Calculation of Molecular Properties and Drug-likeness
PK Tutor	Free Excel Tools for PK and ADME Research and Education
PreADMET ADMET Prediction	Predict permeability for Caco-2 cell, MDCK cell and BBB (blood–brain barrier), HIA (human intestinal absorption), skin permeability and plasma protein binding
PreADMET Toxicity Prediction	Predict toxicological properties from chemical structures, such as mutagenicity and carcinogenicity
RCDK	Allows the user to load molecules, evaluate fingerprints, calculate molecular descriptors and view structures in 2D
Steric	A program to calculate molecular steric effects

Adapted from Computational Resources for Drug Discovery website (http://crdd.osdd.net/qsar.php).

(e.g., physicochemical properties, biological activities, toxicity) for a set of similar compounds. The main objectives of QSAR models are to allow the prediction of biological activities of untested or novel compounds to provide insight into relevant and consistent chemical properties or descriptors (2D/3D) that define the biological activity. Once a series of predicted models is collected, these can be used for database mining for the identification of novel chemical compounds; particularly for those having drug-like properties following Lipinski's "Rule of Five"[90] along with suitable pharmacokinetic properties. The Rule of Five states that any oxygen (O) and nitrogen (N) atoms are defined as hydrogen-bond acceptors, and N–H or O–H groups are considered as hydrogen-bond donors. Log *P* refers to the octanol–water partition coefficient of a compound and is used as a measure of lipophilicity. Other important drug properties include molecular weight, pK_a, permeability, and species of the drug molecules (acids, bases, zwitterions, and neutrals), plasma protein binding, volume of distribution, intravenous or oral clearance, half-life, and preclinical bioavailability. These properties for the 108 drug dataset have been extensively analyzed using predictive methods such as those of Mahmood,[91] Obach *et al.*,[92] Hosea *et al.*,[93] and PhRMA.[64]

Energy minimization is very widely used in molecular modeling and is an integral part of techniques such as conformational search procedures. It is also used to prepare a system for other types of calculations. For example, it may be used prior to a molecular dynamics or Monte Carlo simulation in order to relieve any unfavorable interactions in the initial configuration of the system. This is especially recommended for simulations of complex systems such as macromolecules or large molecular assemblies.[94] The molecular mechanics or quantum mechanics energy at an energy minimum corresponds to a hypothetical, motionless state at 0 K. Experimental measurements are made on molecules at a finite temperature when the molecules undergo translational, rotational, and vibrational motion. To compare the theoretical and experimental results, it is necessary to make appropriate corrections to allow for these motions. These corrections are calculated using a standard molecular mechanics formula. The internal energy $U(T)$ at a temperature T is given by:

$$U(T) = U_{\text{trans}}(T) + U_{\text{rot}}(T) + U_{\text{vib}}(T) + U_{\text{vib}}(0) \quad (5.46)$$

If all translational and rotational modes are fully accessible in accordance with the equipartition theorem, then $U_{\text{trans}}(T)$ and $U_{\text{rot}}(T)$ are both equal to 3.2 $k_{\text{B}}T$ per molecule (except that $U_{\text{rot}}(T)$ equals $k_{\text{B}}T$ for a linear molecule) where k_{B} is Boltzmann's constant.[94] Aqueous solubility is a critical physicochemical property and must be addressed early during drug discovery research. Due to the difficulty in accurately predicting aqueous solubility *in silico*, high-throughput experimental determination of aqueous solubility is in great demand. Chen *et al.*[95] evaluated a method using a multi-wavelength UV plate reader and disposable 96-well UV plates for fast solubility determination. In addition to excellent sensitivity and reproducibility, a UV plate reader method also offers the flexibility of being able to determine thermodynamic solubility in the presence or absence of dimethyl sulfoxide, a solvent widely used for combinatorial compounds during HTS.[95] According to the previous analysis, the solubility (S_{w}), melting point (mp), and permeability are related using equation (5.5)[96]

$$\log S_{\text{w}} \approx -\log P - 0.01\,\text{mp} + 1.05 \quad (5.47)$$

Although many successful QSAR and quantitative structure–property relationship (QSPR) models are available, these models have inherent disadvantages. By their very nature, they tend to find the most generalized relationships that smooth over interesting substructural effects and tend to be limited in the precision of prediction. Such generalizations in the prediction of primary potency, and other properties, are often insufficient for guiding design in a lead optimization phase. Precision and accuracy are further limited by the quality of descriptors used in the model. Although many thousands of descriptors can be generated, the value of each is not always clear and can lead to misleading relationships and chance correlations depending on the data and modeling technique used. Descriptors frequently describe chemical structure incompletely, and so information about the structure–activity relationship is lost. To solve this problem, recently matched molecular pairs analysis (MMPA) has been proposed.[97] For example, MMPA was used for the optimization of pharmaceutical properties such as a drug's aqueous solubility and plasma protein binding.[98]

New methods of synthesis, screening small and large molecules, and drug reprofiling

Over the past 10 years, a handful of academic and industrial research groups have developed strategies for the synthesis of DNA-encoded small-molecule libraries. The DNA-encoded library field holds the potential to address the general problem of biological ligand discovery, including pharmaceutical lead generation.[99]

Many processes in the human body have evolved to regulate the transport of various molecules, cells, or particles across epithelial barriers. To take advantage of this biology, total gene expression analysis (TOGA) gene expression profiling, a systematic multistep process, was used to identify receptor or transporter molecules to target delivery vehicles for transport across an epithelial barrier.[100] Discoveries made by this process will provide targets for development of new vaccines and new insights into the biology of transepithelial transport.

The number of diabetic patients has recently been increasing worldwide. In many cases, diabetes is asymptomatic for a long period and the patient is not aware of the disease. Therefore, the potential

biomarker(s) leading to the early detection and/or prevention of diabetes mellitus should be identified. The biomarker candidates related to diabetes mellitus were recently extracted from a multivariate statistical analysis (orthogonal partial least squares discriminant analysis) followed by a database search. *N*-Acetyl-L-leucine is an endogenous compound found in all biological specimens (plasma, hair, liver, and kidney) and appears to be a potential biomarker candidate related to diabetes.[101] Several drugs have been withdrawn from the market or received black box labeling following clinical cases of QT interval prolongation, ventricular arrhythmias, and sudden death. Other drugs have been denied regulatory approval because of their potential for QT interval prolongation. Since clinical arrhythmia risk is a major cause for compound termination, preclinical profiling for off-target cardiac ion channel interactions early in the drug discovery process has become common practice in the pharmaceutical industry. An assay development for three cardiac ion channels was demonstrated as a reliable pharmacological profiling tool for cardiac ion channel inhibition to assess compounds for cardiac liability during drug discovery.[102]

Combinatorial, automated HTS of small molecules has revolutionized modern drug discovery.[103] By using these methods, a library of 2350 structurally unique, degradable, cationic polymers has been synthesized. High-throughput cell-based screening identified 46 new polymers that transfected with a higher efficiency than conventional nonviral delivery systems, such as poly(ethyleneimine).[103] Each branch in complex macromolecules, such as low-density polyethylene (LDPE), can have a wide range of molecular weights and can be positioned arbitrarily along other branches, so the number of distinct species within an LDPE melt is extremely large. If the molecular species in such a melt cannot even be fully inventoried, how can one hope to model its flow properties (rheology), which depend on how these branches tangle? As a step in solving such limitations, prediction of the real flow of a polymer by making simplifying assumptions about the distribution of branches and how they transfer force through the molecule have been reported.[104] These ongoing efforts may lead to better profiling of pharmaceutical inactive ingredients functionalities based on physicochemical properties.

The focus on drug reprofiling as a new strategy for drug discovery and development is a way to identify new treatments for diseases.[105] In this strategy, the actions of existing medicines, whose safety and pharmacokinetic effects in humans have already been confirmed clinically and approved for use, are examined comprehensively at the molecular level and the results used for the development of new medicines. This strategy is based on the fact that we still do not understand the underlying mechanisms of action of many existing medicines, and as such the cellular responses that give rise to their main effects and side-effects are yet to be elucidated. To this extent, identification of the mechanisms underlying the side-effects of medicines offers a means for us to develop safer drugs. The results can also be used for developing existing drugs for use as medicines for the treatment of other diseases. Promoting this research strategy could provide breakthroughs in drug discovery and development.[106]

Drug formulation screening

One of the major changes in the pharmaceutical industry has been the integration of development activities into the early phases of drug discovery. The goal of this paradigm shift is the prompt identification and elimination of candidate molecules that are unlikely to survive later stages of discovery and development. The growing role of computational methods in this filtering process has been reported.[107] In the context of preformulation and formulation, predictive analyses are related to the physical chemical characterization of the preferred solid states of the active pharmaceutical ingredient (API), optimal formulation variables, and process parameters. To genuinely enhance the API's physicochemical properties for targeted formulation, a good knowledge of all possible salt forms and polymorphs is required.

The physicochemical characterization of the solid state of new drug substances in development requires the isolation of all forms to be considered first. The most important task is the selection of the best solvent for the salt generation[48] and early recognition of the thermodynamically stable form.[49] For example, it has been reported that an organic solvent may adversely influence the ionization of drug due to a decrease in dielectric constant as compared to water. While assessing the influence of organic solvents on

salt formation of drugs, one should consider their effects on the ionization of counterion species used. For example, in forming salt of a basic drug with a carboxylic acid, the organic solvent may not only decrease the pK_a of the base, it may also increase the pK_a of the conjugate acid compared with its value in water. This will have a negative impact on salt formation.[108] The selection of this thermodynamically stable form is generally preferred since it allows a robust manufacturing process and delivers a constant quality for the manufacturing of the drug product. However, the stabilization of metastable forms, and especially the amorphous state, increases the challenging task of development. The solid properties of the salt forms and polymorphs have to be studied in a thermodynamic and kinetic context. Highly sophisticated automated combined analysis techniques and modeling tools are required to achieve this goal.[109]

To increase the success rate of the drug product on the market, it is preferable to examine experimentally the contribution of salt/crystal screening and formulation study as early as possible in the drug discovery/development process. High-throughput formulation screening (HTFS) methods can enable this,[110,111] and have been recently reported in the literature.[112,113] For example, the formulation of protein drugs is a difficult and time-consuming process, mainly due to the complexity of protein structure and the very specific physical and chemical properties involved. Understanding protein degradation pathways and the factors affecting solubility is essential for the success of a biopharmaceutical drug. Basically, the HTFS platform consists of two parts: (1) an automated sample preparation systems for dispensing the drug and the formulation ingredients in both liquid and powder form; and (2) sample analysis using specific methods developed for each protein to investigate physical and chemical properties of the formulations in microplates.[114]

In the biotechnology industry it is well known that protein solubility is a critical attribute in monoclonal antibody formulation development, as insolubility issues can negatively impact drug stability, activity, bioavailability, and immunogenicity. A high-throughput adaptation of an experimental method previously established in the literature to determine apparent protein solubility has been described, where polyethylene glycol (PEG) is used to reduce protein solubility in a quantitatively definable manner. Utilizing an automated, high-throughput system, an immunoglobulin in a variety of buffer conditions was exposed to increasing concentrations of PEG and the amount of protein remaining in solution was determined. Based on these comparisons, it was concluded that rapid, high-throughput determinations of relative protein solubility profiles can be used as a practical, experimental tool to compare monoclonal antibody preparations and to rank order buffer and pH conditions during formulation development.[115]

To accelerate the choice of appropriate excipients in drug microencapsulation process, coarse-grained computer simulations of polymer–drug interactions to study the encapsulation of hydrophobic drugs (e.g., prednisolone, paracetamol) and hydrophilic drug (isoniazid) have been performed. The comparison of these simulations with experimental data showed good correlation with these data for hydrophobic encapsulation within polylactide microspheres and predicted the experimental data within certain concentration limits (e.g., paracetamol levels exceeding 5 mg/mL). However, the mesoscale technique was unable to model the hydrophilic drug encapsulation.[116]

Molecular dynamics simulation was recently combined with docking calculations to model and predict polymer–drug interactions in self-assembled nanoparticles consisting of ABA-type triblock copolymers, where A-blocks are PEG units and B-blocks are low-molecular-weight tyrosine-derived polyarylates. The model compounds tested were nutraceutical curcumin, the anticancer drug paclitaxel, and prehormone vitamin D3. The study suggests that computational calculations of polymer–drug pairs can potentially be a powerful prescreening tool in drug development and optimization of new drug delivery systems, therefore reducing both the time and the cost of the process.[117]

Degradant profiling in active pharmaceutical ingredients and drug products

The roles of degradant profiling in active pharmaceutical ingredients (API) and drug products have been extensively reviewed[118] to fulfill development and regulatory needs. Alsante *et al.*[118] provided a roadmap for when and how to perform studies, helpful tools in designing rugged scientific studies, and

guidance on how to record and communicate results. Forced degradation studies are used to facilitate the development of analytical methodology, to gain a better understanding of API and drug product stability, and to provide information about degradation pathways and resulting products.[118] Degradant profiling is now possible due to advances in analytic techniques such as thin-layer chromatography (TLC) and spectroscopy. Recently, impurity profiling of pharmaceuticals by TLC has been reviewed as well.[119] Despite the current tendency in different pharmacopeias for high-performance liquid chromatography (HPLC) to be favored, TLC remains a very popular analytical method in the pharmaceutical industry. The possibilities of TLC in the different areas of pharmaceutical analysis, such as process and intermediate control, illustrated by impurity testing of API and final products have been highlighted.[119]

Fourier transform infrared–attenuated total reflection (FTIR-ATR) is a well-established standard method used to study *in vitro* drug release in semisolid formulations, drug penetration, and influence of penetration modifiers. It is also capable of characterizing drug effects in *in vivo* studies. Photoacoustic spectroscopy (PAS) has been applied to measure drug content in semisolid and solid formulations to determine drug penetration into artificial and biological membranes. The big advantage of this technique is the possibility of spectral depth profiling. However, FTIR-PAS is so far limited to *in vitro* investigations. Raman spectroscopy can be used to characterize the structure of colloidal drug carrier systems. It is readily applicable to *in vivo* studies, but such investigations must fulfill the relevant laser safety guidelines. With recent technical improvement in vibrational microspectroscopy, FTIR imaging shows great promise in its ability to visualize the drug and excipient distribution in pharmaceutical formulations, such as tablets and therapeutic transdermal systems, as well as to reveal the mechanism of drug release. For example, macro-ATR-IR images of a pharmaceutical tablet showing the distribution of sugar, starch, and magnesium stearate have been reported.[120] Furthermore, this unique technique offers completely new possibilities to study the lateral diffusion of drugs.[121] The topic of accelerated stability profiling in drug discovery has been extensively reviewed elsewhere.[122]

With regard to quality, one should not assume that moderate- to high-throughput assays produce poor-quality data. One should continue to strive for precise and accurate data and to implement methods that correlate well to critical drug success parameters such as half-life and stability during storage. Quantity and speed continue to improve with innovation in parallel and integrated analytical technologies (e.g., liquid chromatography mass spectrometry [LC-MS]) and should be supported. Effective decision-making benefits from (1) data that provide insights for important questions (e.g., kinetics, mechanisms), (2) effective communication of this information, (3) application of the information by integration of profiling scientists into discovery teams, and (4) knowledge by medicinal chemists and biologists about compound properties and their effects. A discovery process that effectively integrates properties (property-based design with activity–structure-based design) to select and optimize compounds is an ongoing goal.[122]

Conclusions and perspectives

In recent news on the jobs market,[123] the industry journalist Ed Silverman said that, "It's a whole big mess the pharmaceutical industry is in, … It's an unfortunate set of circumstances . The companies have had fewer new drugs in their product pipelines and … at the same time they're facing expiring patents on the biggest sellers." In fact, the pharmaceutical industry relies mainly on long-established products for revenues; just 5% of the US$856 billion in 2010 drug sales was attributable to products launched within the previous 5 years. Most importantly, the industry is approaching what many people call "the big patent cliff" – the imminent expiration of a large number of patents, which will allow generic drug manufacturers to produce cheaper versions of blockbuster drugs. In the US alone, the patent exclusivity of more than 110 products is set to expire between 2012 and 2014, among them 14 blockbuster drugs.

The world's leading pharmaceutical companies face considerable risk to their revenue streams in the next 3 years. The global economic crisis that started in late 2007 and pressure from governments and consumers to lower drug prices will worsen the crisis.[123]

In the same news article,[123] it was also stated that "The era of people working for a large company for 20 to 30 years is over." Some analysts viewed the research and development employees of the future working for a series of smaller research-intensive innovator companies. It is also recognized that the demand for new drugs remains, with many important unanswered scientific questions. This crisis warrants a new rethinking of the research and development process in the industry.

It was reasonably speculated that pharmaceutical profiling will continue to be a critical topic in this new era for a better and continuous integration of genomics, proteomics, and disease dynamics taking circadian rhythm into consideration in cases such as cancer and hypertension[71] to enhance drug safety and efficacy and the prevention of disease. Profiling will contribute to the better use of available and limited resources with better control over production cost to maximize drug success rate on the market. Since a successful profiling process requires professionals from many disciplines (e.g., medicinal chemist, formulation scientist, market analyst, clinicians, regulators), all healthcare professionals (academics, basic scientists, educators, or industrialists) should identify effective means to collaborate toward this common goal.

The regulatory systems and requirements need to be better harmonized and reinforced across the world by agencies such as the International Conference on Harmonization, or novel global regulatory models. To solve some of these crises of the pharmaceutical industry, it is reasonable to envision a new model of pharmaceutical companies and/or ecology-friendly services (for drug recycling or reprofiling) to better make use of unused or old pharmaceuticals for new uses either to treat unmet medical needs or for developing countries, thereby generating affordable medications for all on global scale with a better impact on global health and the environment. It is also anticipated the combination of vigorous and genuine implementation of emerging concepts such as pharmaceutical profiling, quality by design, and innovative approach to clinical trials will dramatically help to reduce failure rates in the future.

Prodrugs

The term "prodrug," or "proagent," was first used by Albert[124] to indicate pharmacologically inactive compounds that could be used to modify the physicochemical properties of drugs to increase their usefulness and/or decrease associated toxicity.[125] Albert mentioned that the substance can be only a prodrug if it is broken down *in vivo* to give the active drug. Examples of this theory were phenacetin, chloral hydrate, pamaquin, and proguanil (Fig. 5.4). This concept has been used by medicinal chemists as a tool to solve issues with problematic drugs. Prodrugs must undergo a chemical or enzymatic transformation to the active forms and promoieties within the body to exert desired pharmacological actions (Fig. 5.5).[126] The promoiety is not necessary for pharmacologic activity but is carefully selected to pass on a desirable property to the drug, resulting in prodrug with desired physicochemical properties. The promoiety should be safe and rapidly excreted from the body.[127]

Prodrugs can exist naturally, such as many phytochemicals/botanical constituents and endogenous substances, or they can be produced by synthetic or semisynthetic processes either intentionally as part of a rational drug design or unintentionally during drug development.[128] Release of the active drug is controlled and can occur before, during, or after absorption, or at the specific site of action within the body, depending on the purpose for which prodrug is designed.[129,130]

Almost all drugs have some undesirable physicochemical and biological properties. Their therapeutic efficacy can be improved by eliminating the undesirable properties, while retaining the desirable ones. This can be achieved through biological, physical, or chemical means.[131] The major goal in prodrug design is to overcome the various physicochemical, pharmaceutical, biopharmaceutical, and pharmacokinetic limitations of the parent drug, which otherwise could hinder its clinical use.[132–136] For example, prodrugs provide possibilities for overcoming drug delivery challenges, such as poor aqueous solubility, formulation, insufficient oral absorption, chemical instability, inadequate brain penetration, toxicity, and local irritation. Prodrugs can also improve drug targeting, and

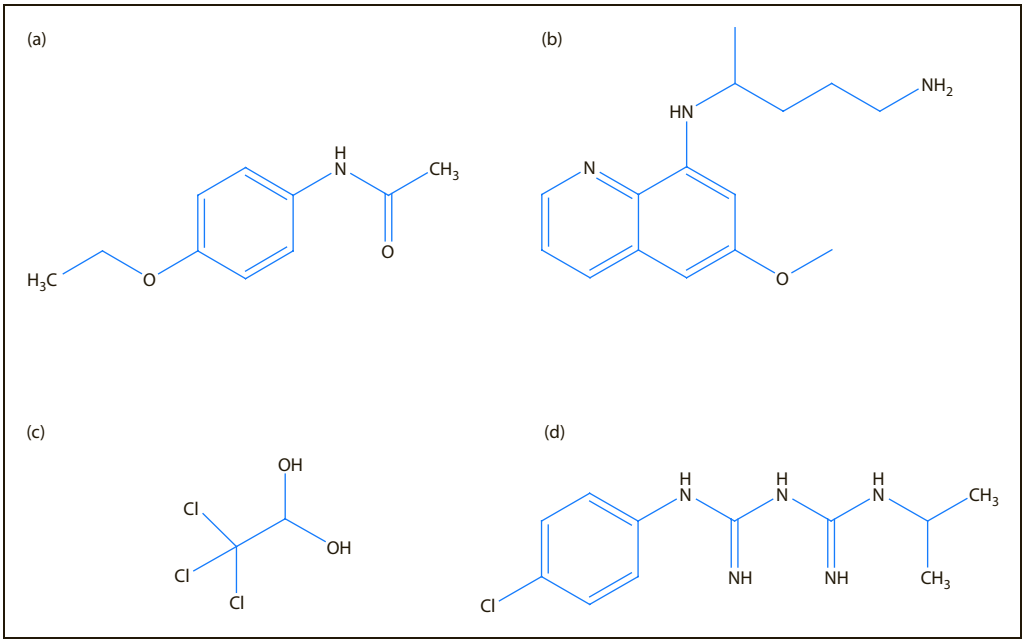


Figure 5.4 Structures of A) phenacetin, B) pamaquin, C) chloral hydrate, and D) proguanil.

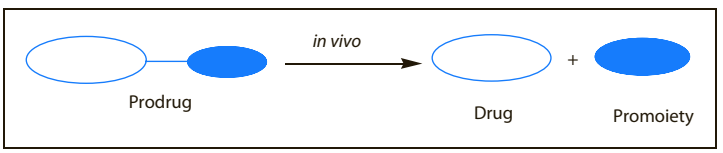


Figure 5.5 Illustration of prodrug concept.

the development of a prodrug of an existing drug with improved properties may represent a life-cycle management opportunity.[137]

The prodrug concept has found a number of useful applications in drug research and development. There are a number of subcategories of prodrugs. The most common category is one in which additional chemical substituents have been attached covalently to the drug molecule. Release of the free drug is then accomplished either enzymatically or chemically.[137] Earlier examples of prodrugs include methanamide (hexamine), aspirin, and prontosil (Fig. 5.6).[138] Methanamide was used in 1899 as a urinary tract prodrug that delivers the antibacterial formaldehyde. It is a stable, inactive compound at pH greater than 5. However, in acidic environment, the compound disintegrates to form formaldehyde. Aspirin (acetyl salicylic acid) is a common non-steroidal anti-inflammatory drug used for treatment of pain and arthritis; a less irritating form of sodium salicylate.[131,139] In the body, aspirin is rapidly deacetylated to form salicylic acid and acetic acid. Aspirin and salicylic acid have been proposed as anti-inflammatory agents.[140] Acetic acid can be acted on rapidly by metabolic enzymes, thus, is basically a non-toxic by-product.[141] Prontosil is an example of an accidental prodrug. It is the first commercially available antibacterial antibiotic and a prodrug of sulfanilamide. Prontosil is inactive as an antibacterial, but it is turned *in vivo* to pharmacologically active sulfanilamide by the enzyme azo reductase. These studies led to discovery of the sulfonamides as antibacterial agents.[127]

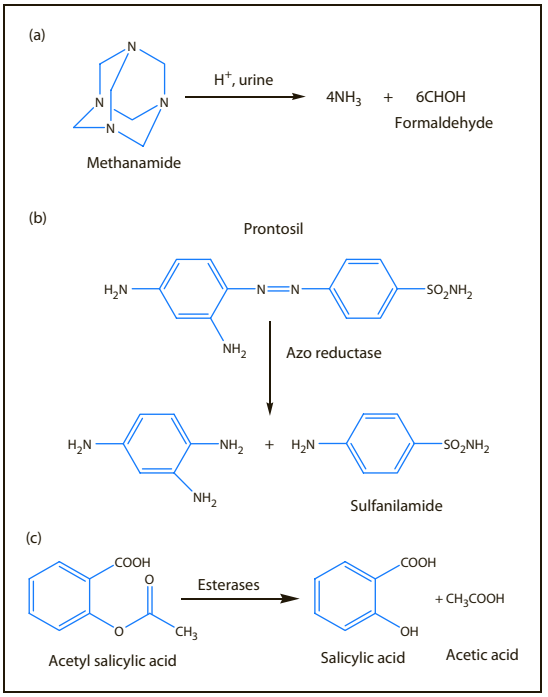


Figure 5.6 *In vivo* conversion of A) methanamide, B) prontosil, and acetyl salicylic acid to their active compounds.

There are currently a number of prodrugs in clinical trials. Classification can be based on the therapeutic categories; for example, anticancer, antiviral, antibacterial, non-steroidal anti-inflammatory, cardiovascular, etc., or based on the categories of moiety that attach to the active drug; for example, esters, carbonates and carbamates, amides, and oximes prodrugs;[142–144] or based on the delivery method; for example, oral, topical, or parenteral delivery.

There are a number of ways that drugs can be modified. What is necessary is that the parent drug has a functionality that is amenable to modification. Functional groups that are amenable to prodrug design include carboxylic, hydroxyl, amine, phosphate, and carbonyl groups. Modifications of these groups can lead to esters, carbonates, carbamates, amides, phosphates, and oximes. This creates the prodrugs that can provide drug release triggered by esterases, phosphatases, proteases, hypoxia, pH changes, reducing, oxidizing, and light conditions.[137]

Prodrugs are usually used with the aim of increasing drug permeation by enhancing lipophilicity or water solubility. The prodrug must display enough aqueous solubility and stability, adequate lipophilicity, sufficient safety, and reasonable conversion to the parent drug *in vivo*. Unmet needs that require addressing remain, for example, with respect to protein and macromolecular drug delivery. Wide-ranging research in this field and a growing knowledge of drug delivery should generate more new marketable prodrugs in the future.

Fundamentals of medical radionuclides

Applications of radionuclides in medicine and pharmacy

Radium has the distinction of being the first radionuclide used in medicine, employed as early as 1901. This nuclide was the most important medical radionuclide in use until approximately 1946, when artificially produced radionuclides became available in quantity. Since that date, growth in the medical applications of radionuclides has been very rapid, as their usefulness has become more and more apparent in medical diagnosis, therapy, and research and as greater numbers of physicians and other scientific personnel have been trained in their use. Current medical procedures employ more than 50 radionuclides in a wide variety of chemical and physical forms.

Other than for basic research, radionuclides are used in medicine and pharmacy in two different ways: as (1) sealed radiation sources or (2) radiopharmaceuticals.

As sealed radiation sources, their principal roles are in (1) therapy and (2) calibration of radiation detection instrumentation. For therapy, the choice of the radionuclide for a given application is governed largely by the properties of the radiation required for treatment; the type and energy of the radiation and range in tissues are prime considerations. For therapeutic applications, the radiation sources are either (1) externally beamed into cancerous tissue (teletherapy) or (2) implanted in the form of seeds, wires, or ribbons (or other physical forms) within, or in proximity to, cancerous tissue for specified periods of time (brachytherapy). For these purposes, the chemical properties or chemical form of the radionuclide are relatively unimportant. Likewise, for calibration

purposes, the nature of the radiation emitted is usually pertinent, whereas the chemical properties are not.

A radiopharmaceutical is a preparation, intended for *in vivo* use that contains a radionuclide in the form of a simple salt or a complex. It may exist as a solid, liquid, gas, or pseudogas. The chemical and physical identity and form of a radiopharmaceutical are very important, because, in each case, once administered, the radiopharmaceutical is intended to target certain tissues, binding sites and/or biochemical pathways. Depending on its specific physicochemical and radiation properties, a radiopharmaceutical can be used for either diagnostic or therapeutic purposes, and, in a few cases, both. For diagnostic applications, a radiopharmaceutical should not be pharmacologically active, in that it should not produce a physiologic effect. It is administered in extremely small (tracer) quantities, so it does not alter the physiologic or pathophysiologic process being measured. The nature of the radiation emitted by a diagnostic radiopharmaceutical is important, primarily for its ease of detection (i.e., to obtain an image or other diagnostic data). Conversely, for a therapeutic radiopharmaceutical, the type and energy of the radiation, as well as its range in tissues, are very important considerations, as was the case with sealed sources used for therapy. A radiopharmaceutical preparation designed for therapeutic purposes must contain enough radioactivity to produce the intended tissue effects.

The development, evaluation, preparation, testing, and clinical use of radiopharmaceuticals have led to the introduction of the specialty disciplines, known as nuclear medicine and nuclear pharmacy. In the United States alone, practitioners in these specialties are responsible for the care of approximately 40,000 to 50,000 patients each day, on average.

Production of radionuclides

Most, if not all, radionuclides used in medicine and pharmacy are produced artificially. Table 5.22 is a compilation of medical radionuclides along with their physical properties. These radionuclides are produced by three general methods: (1) as a fission by-product in a nuclear reactor; (2) as the product of a neutron reaction – either by activation or transmutation; and (3) by use of a particle accelerator, such as a cyclotron.

Fision by-products

Fission is a radioactive process in which a relatively heavy nucleus is divided into two new nuclei of nearly equal size with the simultaneous emission of two or three neutrons. Fission may be spontaneous, but the reaction is normally induced by bombardment of the parent nucleus with a neutron:

$$^{235}_{92}\mathrm{U} + \ ^{1}_{0}\mathrm{n} \rightarrow X + Y + 2.5\ ^{1}_{0}\mathrm{n},$$

where X and Y are fission products (new nuclei) with a Z value between 30 and 65 and a sum of 92. Fission reactions may be self-sustaining. For each neutron consumed, an average of 2.5 new neutrons are produced that may initiate the fission of other nuclei. Such a reaction is called a chain reaction. If at least one of the 2.5 neutrons produced is used to sustain the reaction, the reaction is said to be critical.

The following illustrates one of many combinations of fission reactions that are possible:

$$^{238}_{92}\mathrm{U} + ^{1}_{0}\mathrm{n} \rightarrow ^{131}_{50}\mathrm{Sn} + ^{106}_{42}\mathrm{Mo} + ^{1}_{0}\mathrm{n} + ^{1}_{0}\mathrm{n}.$$

The ^{131}Sn and the ^{106}Mo are very radioactive and have very short half-lives. They immediately decay by a series of beta decay processes:

$$^{131}_{50}\mathrm{Sn} \rightarrow ^{131}_{51}\mathrm{Sb} \rightarrow ^{131}_{52}\mathrm{Te} \rightarrow ^{131}_{53}\mathrm{I}$$
$$^{106}_{46}\mathrm{Mo} \rightarrow ^{106}_{43}\mathrm{Tc} \rightarrow ^{106}_{44}\mathrm{Ru} \rightarrow ^{106}_{45}\mathrm{Rh}.$$

Both ^{131}I and ^{106}Ru are available commercially as fission-produced radionuclides, although ^{106}Ru is not routinely used for medical applications.

Before use, the desired nuclide must be chemically separated from a large number of other fission-produced radionuclides. For many of the radionuclides produced by fission, separation of the desired nuclide from the mixture of fission products is too difficult or costly.

Neutron reactions

Many radioactive nuclides used in radiopharmaceuticals are prepared by neutron activation (n, λ) or transmutation (n, p) reactions, by placing a suitable target material in a nuclear reactor, where it is bombarded by neutrons. By means of (n, λ) and (n, p) reactions, reactors produce radionuclides having a high neutron-to-proton ratio that typically decay by emission of a negatron. For example, radioactive

Table 5.22 Physical characteristics of radionuclides commonly used in medicine

Nuclide	Common production	Half-life	Decay mode	Principle emissions (MeV)	Gamma ray constant (R/mCi hour at 1 cm)
^{11}C	$^{14}N(p, \alpha)^{11}C$	20.4 minutes	β^+	0.97 β^+ (100%)	5.9
				0.511 γ (200%)	
^{13}N	$^{16}O(p, \alpha)^{13}N$	10.0 minutes	β^+	1.2 β^+ (100%)	5.9
				0.511 γ (200%)	
^{14}C	$^{14}N(n, p)^{14}C$	5730 years	β^-	0.156 β^- (100%)	
^{15}O	$^{14}N(d, n)^{15}O$	2.05 minutes	β^+	1.74 β^+ (100%)	5.9
				0.511 γ (200%)	
^{18}F	$^{18}O(p, n)^{18}F$	110 minutes	β^+, EC[a]	0.635 β^+ (97%)	5.7
				0.511 γ (194%)	
^{32}P	$^{31}S(n, p)^{32}P$	14.3 days	β^-	1.71 β^- (100%)	
^{51}Cr	$^{50}Cr(n, \gamma)^{51}Cr$	27.8 days	EC	0.320 γ (9%)	0.18
^{57}Co	$^{56}Fe(p, \gamma)^{57}Co$	271 days	EC	0.014 γ (9%)	0.57
				0.122 γ (86%)	
				0.136 γ (10%)	
^{60}Co	$^{59}Co(n, \gamma)^{60}Co$	5.27 years	β^-	0.31 β^- (99%)	13.2
				1.173 γ (100%)	
				1.332 γ (100%)	
^{67}Ga	$^{68}Zn(p, 2n)^{67}Ga$	78.3 hours	EC	0.093 γ (38%)	1.6
				0.184 γ (20%)	
				0.300 γ (16%)	
				0.394 γ (5%)	
^{68}Ga	^{68}Ge daughter	68.3 minutes	β^+, EC	1.9 β^+ (88%)	5.4
				0.511 γ (176%)	
^{81m}Kr	^{81}Rb daughter	13 seconds	IT[a]	0.191 γ (66%)	1.6

(continued overleaf)

Table 5.22 *(continued)*

Nuclide	Common production	Half-life	Decay mode	Principle emissions (MeV)	Gamma ray constant (R/mCi hour at 1 cm)
^{82}Rb	^{82}Sr daughter	75 seconds	β^+, EC	3.15 β^+ (96%)	6.1
				0.511 γ (192%)	
^{89}Sr	$^{88}Sr(n, \gamma)^{89}Sr$	50.5 days	β^-	1.46 β^- (100%)	
^{90}Y	^{90}Sr daughter	64 hours	β^-	2.27 β^- (100%)	
^{99}Mo	fission	2.75 days	β^-	0.45 β^- (18%)	
				1.23 β^- (82%)	1.8
				0.181 γ (6%)	
				0.74 γ (13%)	
				0.778 γ (5%)	
^{99m}Tc	^{99}Mo daughter	6.02 hours	IT	0.140 γ (89%)	0.7
^{111}In	$^{112}Cd(p, 2n)^{111}In$	67.3 hours	EC	0.171 γ (90%)	3.2
				0.246 γ (94%)	
^{123}I	$^{127}I(p, 5n)^{123}Xe$ daughter	13.2 hours	EC	0.159 γ (83%)	1.6
				0.127 x (71%)	
^{125}I	$^{124}Xe(n, \gamma)^{125}Xe$ daughter	60.2 days	EC	0.036 γ (7%)	1.4
				0.027 x (110%)	
^{131}I	fission	8.04 days	β^-	0.61 β^- (90%)	2.2
				0.284 γ (6%)	
				0.364 γ (82%)	
				0.637 γ (7%)	
^{133}Xe	fission	5.25 days	β^-	0.35 β^- (100%)	0.5
				0.081 γ (36%)	
				0.031 x (39%)	

(continued overleaf)

Table 5.22 *(continued)*

Nuclide	Common production	Half-life	Decay mode	Principle emissions (MeV)	Gamma ray constant (R/mCi hour at 1 cm)
^{137}Cs	fission	30 years	β^-	0.51 β^- (94%)	3.3
				1.18 β^- (6%)	
				0.662 γ (84%)	
^{153}Sm	^{152}Sm(n, γ)^{153}Sm	46.3 hours	β^-	0.640 β^- (30%)	0.9
				0.71 β^- (50%)	
				0.81 β^- (20%)	
				0.103 γ (29%)	
^{186}Re	^{185}Re(n, γ)^{186}Re	3.72 days	β^-, EC	1.07 β^- (77%)	0.08
				0.93 β^- (23%)	
				0.137 γ (9%)	
^{201}Tl	^{203}Tl(p, 3n)^{201}Pb daughter	73 hours	EC	0.135 γ (3%)	0.47
				0.167 γ (10%)	
				0.07 × (94%)	
				0.08 × (20%)	

[a]EC, electron capture; IT, isomeric transition.

phosphorus (^{32}P) can be prepared from stable phosphorus (^{31}P) by neutron capture:

$$^{31}_{15}\mathrm{P} + {}^{1}_{0}\mathrm{n} \rightarrow {}^{32}_{15}\mathrm{P} + \gamma.$$

The disadvantage of this method is that the radioactive phosphorus (^{32}P) is highly diluted with stable ^{31}P. Phosphorus-32 of low specific activity can be used for certain purposes, such as the investigation of phosphate fertilizers, but would be less useful for many biological and medical applications.

Radioactive phosphorus can be made by transmutation, if high specific activities are required:

$$^{32}_{16}\mathrm{S} + {}^{1}_{0}\mathrm{n} \rightarrow {}^{32}_{15}\mathrm{P} + {}^{1}_{1}\mathrm{p}.$$

In this case, the radioactive phosphorus can be separated from the unreacted sulfur by chemical procedures. Where ^{32}P is made from ^{31}P, such chemical separations are not practical.

Transmutation is useful for the preparation of many radioactive nuclides, especially those of low atomic number. As the atomic number increases, (n, γ) reactions are favored over (n, p) reactions. For example, cobalt-60 is produced by the reaction ^{59}Co(n,γ)^{60}Co, because the reaction ^{60}Ni(n, p)^{60}Co does not occur with sufficient frequency to make the process commercially feasible. ^{125}I($t_{1/2}$ = 60 d) is produced from ^{124}Xe,

$$^{124}\mathrm{Xe(n,\gamma)}^{125}\mathrm{Xe}\ \ \mathrm{EC} \rightarrow\ {}^{125}\mathrm{I}.$$

Secondary neutron capture results in the side reaction $^{125}I(n,\gamma)^{126}I$. Because $^{126}I(t_{1/2}$ 314 d) is an undesirable impurity in ^{125}I, it is removed through its own decay.

Cyclotron-produced radionuclides

Certain radionuclides are cyclotron-produced. The cyclotron and similar particle accelerators can be used only with charged particles, such as electrons, protons, alpha particles, or deuterons, because the operation of such machines depends on the interaction of magnetic and/or electrostatic fields with the charge (either + or −) of the particle undergoing acceleration. When the particles have been accelerated to a high velocity, even approaching the velocity of light and representing enormous energies, they are caused to strike a target containing the atoms to be bombarded. Sodium-22 is prepared this way, by the interaction of high-velocity deuterons with magnesium. The nuclear equation is

$$^{24}Mg(d,\alpha)^{22}Na.$$

Cyclotrons produce neutron-deficient isotopes; that is, the neutron-to-proton ratio is low. These nuclides decay by positron emission or electron capture. Cyclotron-produced radionuclides are carrier-free, because they are normally produced by transmutation.

The following reactions are typical for the cyclotron production of some medically useful nuclides:

$$^{10}B(d,n)^{11}C$$

$$^{11}B(p,n)^{11}C$$

$$^{14}N(p,\alpha)^{11}C$$

$$^{14}N(p,\alpha)^{11}C$$

$$^{10}B(\alpha,n)^{13}N$$

$$^{12}C(d,n)^{13}N$$

$$^{16}O(p,\alpha)^{13}N$$

$$^{14}N(d,n)^{15}O$$

$$^{15}N(p,n)^{15}O$$

$$^{16}O(p,pn)^{15}O$$

$$^{18}O(p,n)^{18}F$$

$$^{20}Ne(d,\alpha)^{18}F$$

$$^{70}Zn(p,\alpha)^{67}Cu$$

$$^{66}Zn(d,n)^{67}Ga$$

$$^{68}Zn(p,2n)^{67}Ga$$

$$^{69}Ga(p,2n)^{68}Ge$$

$$^{82}Kr(p,2n)^{81}Rb \rightarrow ^{81m}Kr$$

$$^{111}Cd(p,n)^{111}\ In$$

$$^{112}Cd(p,2n)^{111}\ In$$

$$^{203}Tl(p,3n)^{201}\ Pb \rightarrow ^{201}Tl$$

Usually, a nuclide can be made by more than one reaction. For example, ^{123}I can be prepared either directly or indirectly. Direct reactions include the following:

$$^{123}Te(p,n)^{123}I$$

$$^{121}Sb(^{4}He,2n)^{123}I$$

$$^{122}Te(d,n)^{123}I$$

$$^{124}Te(p,2n)^{123}I.$$

Indirectly, the intermediate ^{123}Xe (or ^{123}Cs, which decays to ^{123}Xe) is prepared, which then decays to ^{123}I:

$$^{122}Te(^{3}He,2n)^{123}Xe \rightarrow\ ^{123}I$$

$$^{122}Te(^{3}He,2n)^{123}Xe \rightarrow\ ^{123}I$$

$$^{123}Te(^{3}He,3n)^{123}Xe \rightarrow ^{123}I$$

$$^{127}I(p,5n)^{123}Xe \rightarrow\ ^{123}I$$

$$^{124}Xe(p,2n)^{123}Cs \rightarrow\ ^{123}Xe \rightarrow ^{123}I.$$

Radionuclide generators

When clinical procedures require that a radionuclide be administered internally, it is advantageous to use a nuclide with a short half-life, to minimize the radiation dose received by the patient. It is evident, however, that the shorter the half-life, the greater the problem of supply. One answer to this problem is the radionuclide generator, which uses the phenomenon of sequential decay. A radionuclide generator provides a mechanism for separating a clinically useful, short half-life daughter nuclide from a long-lived parent nuclide. Radioactive decay of the long-lived parent results in the production of a short-lived radioactive daughter nuclide that is eluted or milked from the generator, by means of an appropriate eluant. Characteristics of a number of parent–daughter systems used in radionuclide generators are found in Table 5.23.

The molybdenum-99/technetium-99m generator (Fig. 5.7) consists of an alumina (Al_2O_3) column on which molybdenum-99 is adsorbed as ammonium molybdate. Radioactive decay of ^{99}Mo produces ^{99m}Tc, which is eluted from the column with 0.9%

Table 5.23 Selected radionuclide generators

Parent isotope	Half-life	Daughter isotope	Half-life	Mode of decay
^{68}Ge	271 d	^{68}Ga	68 minutes	β^+
^{81}Rb	4.7 h	^{81m}Kr	13 seconds	IT[a]
^{82}Sr	25 d	^{82}Rb	1.3 minutes	β^+
^{87}Y	80 h	^{87m}Sr	2.8 hours	IT
^{90}Sr	28 y	^{90}Y	64 hours	β
^{99}Mo	67 h	^{99m}Tc	6.0 hours	IT
^{109}Cd	453 d	^{109m}Ag	39.2 seconds	IT
^{113}Sn	118 d	^{113m}In	1.7 hours	IT
^{115}Cd	53.4 h	^{115m}In	4.5 hours	IT
^{122}Xe	20 h	^{122}I	3.6 minutes	β^+
^{132}Te	3.2 d	^{132}I	2.3 hours	β^-
^{137}Cs	30 y	^{137m}Ba	2.6 minutes	IT
^{144}Ce	285 d	^{144}Pr	17.3 minutes	β^-
^{178}W	21.5 d	^{178}Ta	9.4 minutes	β^+
^{191}Os	16 d	^{191m}Ir	4.9 seconds	IT
^{195m}Hg	41 h	^{195m}Au	30.6 seconds	IT
^{225}Ac	10 d	^{213}Bi	45.6 minutes	α, γ, β^-

[a] IT, isomeric transition.

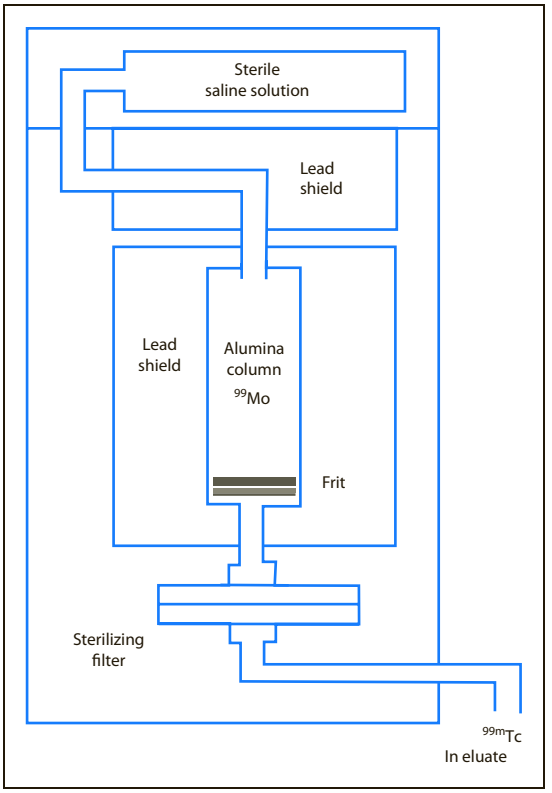


Figure 5.7 Schematic diagram of a radionuclide generator for the production ob technetium-99m by elution from molybdenum-99 absorbed on an alumina column.

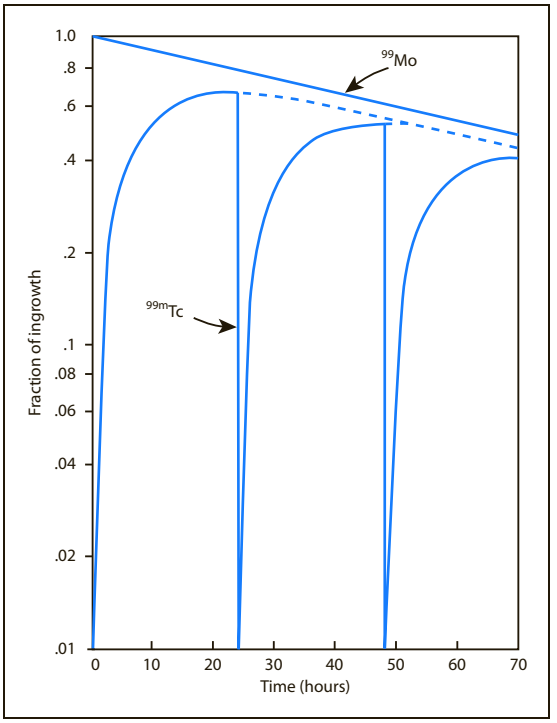


Figure 5.8 Elution curve. The lower solid lines show the theoretical activity of ^{99m}Tc in the generator as a result of in-growth followed by elution of ^{99m}Tc at 24-hour intervals. If the generator were not eluted, in-growth would follow the broken line and a transient equilibrium would be established. The upper solid line represents decrease in activity of ^{99}Mo, the parent nuclide, due to radioactive decay.

Sodium Chloride USP. Upon elution, the ^{99m}Tc is in the form of sodium pertechnetate ($Na^{99m}TcO_4$). Elution, repeated every 24 hours, provides a satisfactory balance between concentration and quantity of eluted ^{99m}Tc. If a high activity of ^{99m}Tc is not required, the generator can be eluted more frequently. Figure 5.8 shows a typical elution curve for a ^{99}Mo/^{99m}Tc generator. The generator must be replaced about once per week, due to the decay of ^{99}Mo.

Drug nomenclature

Advances in the scientific disciplines continue to occur at such an accelerated rate that the processing of information has become a separate and distinct discipline in its own right. Precise and current terminology is an important tool of science, and nowhere is it more important than in medicine and pharmacy. Drug nomenclature, particularly, would become confusing, meaningless, and incomprehensible without a well-developed system of rules.

It is not unusual for each drug entity to be known by several chemical names, more than one code number, several trivial designations, a formally selected nonproprietary name, and one or more trademarks. Therefore, it is essential that a logical, well-defined nonproprietary nomenclature system is available to facilitate the exchange of drug information.

This section describes the mechanisms for creating nonproprietary drug names that are used in the United States. It includes history, scope, function, and operation of the nomenclature system devised by the United States Adopted Names (USAN) Council. A brief introduction of the liaison relationship between the USAN Council and the US Food and

Drug Administration (FDA) and policies of the World Health Organization (WHO) International Nonproprietary Name (INN) program are also included. The majority of the information in this section has been obtained with permission directly from the USAN Council website maintained by the American Medical Association (AMA) at http://www.ama-assn.org/ama/pub/physician-resources/medical-science/united-states-adopted-names-council.page. The authors of the current edition of this scetion have edited the information provided by the authors of previous editions for clarity, have provided updated information as necessary, and have added information useful for this topic.

Drug name types

The term *drug nomenclature* implies that drugs may have several types of names, each having its own function, and indeed this is the case. Although some names are scientifically precise, others may be ambiguous or misleading.

The first type of name, usually applied to compounds of known composition, is the *chemical name*. Among the several conventions that exist for creating chemical names, the most widely established is the American Chemical Society's Chemical Abstracts Services (CAS) Index naming system. Use of this system results in the creation of systematic (CAS Index) names for chemical entities that serve as a key to the chemical literature of the world. The CAS system is used by the USAN program.

For substances of plant or animal origin that cannot be classified as pure chemical compounds, scientific identification is given in terms of precise *biochemical, botanical*, or *zoological* names. Such designations are also scientifically exact, but like their chemical counterparts, they tend to be complex, unwieldy, and generally not useful to the physician, pharmacist, or other users of drug nomenclature.

Most drugs acquire a *code designation* as a convenient means of referring to the compound before it has been assigned either a nonproprietary name or a trademark. Such codes are generally a letter and number combination, such as SC-40230 (bidisomide, *Searle*), Ro 4–3780 (isotretinoin, *Roche*), or RP 56976 (docetaxel, *Rhone-Poulenc Rorer*). The letter(s) generally represent an abbreviation of the research laboratory name; the numbers are assigned by the firm in an arbitrary manner or following some internally created convention. Codes may be acronyms or letter combinations derived from portions of the chemical or common name (e.g., AZT for azidothymidine or TPA for tissue plasminogen activator).

Code designations usually are considered as convenient "shop labels" and are meant to be discarded when a more appropriate name is selected. However, many of these codes appear in early scientific literature dealing with investigative work prior to the selection of a nonproprietary name. Frequently they are used in clinical studies in the absence of a nonproprietary name to identify the chemical entity. Code designations, therefore, must be considered a part of drug nomenclature, but they are not acceptable for general use. In themselves, these codes give no information about the compounds they represent.

The use of acronyms instead of the proper nonproprietary names may also be dangerous because many contractions are extremely similar, such as DDI (didanosine) and DDC (zalcitabine). Similarly, AZT is commonly used for the antiviral zidovudine (derived from *azidothymidine*, its shortened chemical name). However, AZT can just as readily represent the immunosuppressant azathioprine. Medication errors due to use of acronyms have been reported both by the Institute for Safe Medication Practices and the USP Medication Errors Reporting Program.

Trivial names occasionally are assigned to a new compound, usually by researchers working on it. Nomenclature agencies strongly discourage the use of trivial names as generally they are coined haphazardly and are usually not suited for adoption as official nonproprietary names. Too frequently, trivial names are similar to existing names, which may lead to confusing them with established nonproprietary names.

When a new drug has successfully survived the successive research stages and testing to the point where it appears it may become a marketable product, a *trademark* is developed by the manufacturer. Properly registered trademarks become the legal property of their owners and cannot be used freely in the public domain. Selected for their brevity and ease of recall, trademarks usually give little or no scientific information about the drug.

Each type of name described thus far aims to serve its specific purpose; however, none fulfills the need for a single, simple, informative designation available for unrestricted public use. The *nonproprietary name* is the only name intended to function in this capacity. The nonproprietary name often is referred to as the *generic name*, but this practice is inaccurate, as each nonproprietary name is specific for a given compound, even though it may possess a stem that is common to a related group of drugs.

Throughout this section, the term *nonproprietary name* applies to those names that have been selected by the formal process of negotiation between the drug manufacturer and the USAN Council.

History

The *United States Pharmacopeia* (USP) has been supplying standards for pharmaceutical preparations since the first edition appeared in 1820. Because there was a need for titles for monographs included in the USP that described the drugs for which standards were being prepared, the USP was one of the first publications to recognize the necessity for a standardized system of drug nomenclature and the first to take action to establish such a system.

The American Pharmacists Association (APhA) began publication of a second compendium, the *National Formulary* (NF) in 1888 and established quality standards for drugs included in the NF. The editor of the NF quickly became involved with providing nonproprietary names for the monographs published in the NF.

In 1906, the US government legally recognized the significance of the work being done by the USP and the NF by declaring both publications *official* compendia. Since that time, monograph titles have had the status of official nonproprietary names.

As new pharmaceutical products increased in number, other organizations recognized the need for formally approved names while the drug entity was still in its investigational stages. The AMA Council on Pharmacy and Chemistry (CPC), later known as the Council on Drugs, was created in 1905 as an advisory body to the Board of Trustees to encourage rational drug use by physicians. In conjunction with screening and evaluating new remedies, the CPC initiated a nomenclature program to provide nonproprietary names for individual drugs available commercially under more than one trademark. This activity continued until the early 1940s when the Council on Drugs began to require a nonproprietary name for every active compound listed in all AMA publications.

The 1938 Food, Drug and Cosmetic (FDandC) Act stipulated that the *common or usual name* should be used as part of drug labeling to identify the drug entity. In the absence of such a name (or until a name attained such status), a chemical name was to be used.

The Drug Amendments of 1962 replaced the "common or usual" terminology with the more meaningful requirement that nonproprietary names must be "simple and useful." Also, for the first time, the Commissioner of the FDA was given the authority to designate the official name if he determined that such action was necessary or desirable.

Despite the nomenclature activities of the AMA, USP, and APhA, large numbers of drug products did not become the subject of either the NF, the USP, or the Council on Drugs monographs and continued to be identified by their chemical names, trivial names, or trademarks selected by the manufacturers. As medicine and pharmacy advanced and drugs became more specific in their actions and structurally more complex, other nomenclature-related needs were recognized that made it apparent that each new drug needed a nonproprietary name selected early in its development. A systematic approach to assure drug name appropriateness and acceptability to AMA, USP, NF, and the drug manufacturer now became more obvious. Each new drug also needed a *global name* – one name used and accepted worldwide.

A significant step toward supplying this need was taken in June 1961, with the formation of the AMA-USP Nomenclature Committee. The names adopted by this committee were deemed acceptable as potential compendia monograph titles, and the acronym *USAN* (United States Adopted Name) was coined to designate names formally processed and approved by the Committee. The APhA participated in the program from its inception but did not become a full and official sponsor until January 1964, at which time the name of the committee was changed to the USAN Council.

The USAN council

The agency responsible for the selection of nonproprietary names for single-entity drugs marketed in the US is the United States Adopted Names (USAN) Council. This expert committee on drug nomenclature is jointly sponsored by the AMA, the USP, and APhA. All three agencies were involved in the selection of drug names for many years prior to the establishment of the USAN Council in the 1960s. The aim of USAN is the global standardization and unification of drug nomenclature and related rules to ensure that drug information is communicated accurately and unambiguously. The Council conducts its negotiation activity by correspondence. Twice a year, the Council convenes to discuss nomenclature policy, liaison activity, and new nomenclature strategies.

Today, the USAN Council comprises of five members: one member is appointed by each of the three sponsoring organizations, one is a liaison member from the FDA, and one is a member-at-large who must be approved by the three sponsoring organizations. Council members are nominated by their sponsoring organizations annually. Every year their nominations must be approved by the boards of trustees of the other sponsoring organizations, who also approve the nominees for the FDA liaison and the member-at-large positions. Council members may serve for up to 10 consecutive years.

At an early stage in the development of the USAN Council, it was anticipated that occasional disagreements might arise between the Council and a manufacturer over the selection of a particular nonproprietary name. In the majority of such cases, the Council and the firm can, in time, work out an acceptable compromise. However, in rare instances, an impasse may develop that needs adjudication by someone not directly involved with the USAN Council or the drug manufacturer. The USAN Review Board was established as the final arbitrator of nomenclature disputes when normal procedures have failed. Each sponsoring organization nominates two members to the Review Board annually; nominations must be approved annually by the Boards of Trustees of the other sponsoring organizations. No term limits have been placed on member's participation on the Review Board.

The USAN Review Board Secretariat is supported by the USP. At the time of any appeal to the Board, representatives of the drug firm involved in the specific case can participate in the deliberations, but they have no voting privileges. The USAN Council Secretariat becomes the spokesperson for the Council. The determination of the USAN Review Board is final and not subject to appeal.

The USAN Council Secretariat is located at the AMA headquarters in Chicago, Illinois. The agency works closely with the WHO INN Committee, and various national nomenclature groups. In addition, the USAN program has liaison organizations all over the world. These organizations include the following:

Chemical abstracts service

2540 Olentangy River Road, P.O. Box 3012, Columbus, OH 43210

WHO INN program manager

World Health Organization, Avenue Appia 20, 1211 Geneva 27, Switzerland

Belgium

L'Inspecteur en chef-Directeur, Ministère de la Santé Publique et de l'Environement, Inspection générale de la Pharmacie, Cité administrative de l'Etat, Quartier Vésale 333 B1010, Bruxelles Belgium

China

The Deputy Chief, Drug Standard Division II, The Chinese Pharmacopeia Commission, Ministry of Health, Temple of Heaven, Beijing 100050, People's Republic of China

France

DCF – Dénominations Communes Françaises, Agence du Médicament, Direction des Laboratoires et des Controles, Unité Pharmacopée, 145–147 boulevard Anatole France, F-93285 Saint-Denis Cedex, France

Hungary

Director-General, National Institute of Pharmacy, P.O. Box 450, 1372 Budapest 5, Hungary

Italy

DCIt – Commission – Denominazione Communi Italiane, Director-General, Pharmaceutical Division, Ministero della Sanità, Viale della Civiltà Romana 7, I-00144 Roma, Italy

Japan

JAN –Japanese Accepted Names, Japanese Ministry of Health and Welfare, New Drugs Division, Pharmaceuticals Affairs Bureau, 1-2-2, Kasumigaseki, Chiyoda-ku, Tokyo 100, Japan

United Kingdom

BAN – British Approved Names, The Secretary, British Pharmacopoeia Commission, Market Towers, 1 Nine Elms Lane, London SW8 5NQ, United Kingdom

USAN council and FDA Liaison

The USAN Council and the FDA conducted an unofficial liaison until early 1967 when it was determined that a formal cooperative effort in the development of nonproprietary names would be more beneficial to both. In June 1967, an official agreement was signed between the sponsors of the USAN Council and the FDA to appoint annually one voting member to the Council. This contract stipulated that the FDA would accept as the "official or established" name any drug name the USAN Council adopted. In this agreement, the Commissioner of the FDA reserved the right to select the official name in those instances in which the USAN Council could not reach consensus. It should be noted that the designation of a name as an "official or established" name by the FDA did not follow automatically but was accomplished by publication, subject to public comment, in the *Federal Register*. All parties upheld this agreement until it was modified 17 years later.

On November 26, 1984, the Commissioner of Food and Drugs and the Secretary of Health and Human Services published in the *Federal Register* an amendment to the FDandC Act that stated in part that "... the Food and Drug Administration agrees with "*Guiding Principles for Coining US Adopted Names for Drugs*," published in *USAN and the USP Dictionary of Drug Names* ... "and that ... the established name ... will ordinarily be either the compendia name of the drug or, if there is no compendia name, the common or usual name of the drug. Interested persons, in the absence of the designation of an official name, may rely on the USAN listed in *USAN and the USP Dictionary of Drug Names* as being the established name in accordance with the Federal Food, Drug, and Cosmetic Act."

The FDA also plays a role when a manufacturer seeks to register a trademark (proprietary name) for a drug entity that has been assigned a USAN. Within the Center for Drug Evaluation and Research (CDER) of the FDA, the Office of Surveillance and Epidemiology (OSE) within the Division of Medication Error Prevention and Analysis (DMEPA) reviews proposed proprietary names. DMEPA consults with the Division of Drug Marketing, Advertising, and Communications (DDMAC) and receives input from pertinent disciplines involved with the review of the application and determines the acceptability of proposed proprietary names. In reviewing proposed proprietary names, both promotional and safety aspects of a name are considered.

WHO and international nonproprietary names

The USAN Council functions primarily to serve the health professions in the United States. However, at a time when drug manufacturers market their products in many countries and medical and pharmaceutical literature is widely translated around the world, the need for cooperation in nomenclature activities among the major drug-producing countries clearly is evident.

To prevent the confusion that arises when several nonproprietary names are used for a single drug, either in the same country or in different countries, the WHO has assumed the responsibility for coordinating drug nomenclature at the international level. In 1915 the International Pharmaceutical Federation established a Committee on International Nomenclature and assigned it the responsibility for identifying each

pharmaceutical substance by a globally available and unique nonproprietary name. The WHO Constitution in 1946 relegated the duty of drug nomenclature to the WHO. By 1953, the WHO initiated the selection and publication of INNs for pharmaceutical substances.

The present INN Program is administered by the INN Program Manager in Geneva, Switzerland. Nonproprietary names are selected biannually by members of the WHO Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations. This advisory panel is composed of representatives from national nomenclature groups.

Through its Committee on Nonproprietary Names, whose members are drawn from representatives of the national nomenclature agencies, WHO has developed procedures and formulated guiding principles for the selection of INNs. National nomenclature agencies usually act as agents for the drug manufacturers by referring mutually selected designations (usually *prior* to national adoption) to the WHO with a request that these names be selected as an INN.

A drug manufacturer located in a country without a nomenclature agency is permitted to make a direct submission for a nonproprietary name to the INN Committee or, alternatively, to an established nomenclature agency in another country, preferably a country in which the pharmaceutical preparation is likely to be marketed.

INNs are selected for substances that can be characterized unequivocally by a chemical name or formula, and exceptions to this rule are rare. The INN is designated for the active part of the molecule only. The INN Program does not select names for mixtures or herbal substances.

The process of INN selection is similar to that utilized to select a USAN. After the manufacturer submits an application, review and objections periods are followed by selection of the INN. Details of the process are explained below.

Under its charter, the WHO is empowered simply to *recommend* specific actions or procedures to its Members States. The WHO INN Committee initially publishes in *WHO Drug Information* the selected names as "proposed International Nonproprietary Names (pINN)." From the date of publication, four months are allowed for member states or other interested parties to submit comments or objections to any proposal. An objection generally reflects a belief that the proposal is confusingly close to (i.e., conflicts with) a name already in use. If no objection is received, the proposed INN will attain the status of recommended INN. Subsequently, WHO will publish the name as a "recommended International Nonproprietary Name (rINN)." The WHO publishes lists of rINN on a biannual basis. Many member states then recognize the rINN as the sole or preferred nonproprietary name for use in their respective countries.

A cumulative list of INNs and the guidelines for coining an INN (*INN for Pharmaceutical Substances*) can be obtained from the WHO in Geneva, Switzerland or on their website at www.who.int/medicines/services/inn/en/. The INN Cumulative List now contains more than 7000 names for drug entities. The INN Committee adds 120 to 150 new designations each year.

Guidelines on the Use of International Nonproprietary Names (INNs) for Pharmaceutical Substances is available online at: http://whqlibdoc.who.int/hq/1997/WHO_PHARM_S_NOM_1570.pdf.

Procedure for obtaining a USAN

The criteria set by the USAN Council for initiating the process for selection of a USAN states that if a substance is regarded as an Investigational New Drug (IND) within the terms of the federal Food, Drug and Cosmetic Act, selection of a USAN should begin during clinical trials, so that the USAN will be adopted before the relevant New Drug Application (NDA) is filed. USAN application forms may be obtained online at www.ama-assn.org/ama/pub/physician-resources/medical-science/united-states-adopted-names-council.page or by writing to the USAN Secretariat at AMA Headquarters, 515 N State Street, Chicago, IL 60654.

In practice, firms usually apply for a USAN when the investigational therapy is in Phase I or Phase II clinical trials. By then the sponsor's patents or intellectual property covering the substance are in place, and it is early enough in clinical trials that the risk of not having a name for the NDA is low. The earliest time that US firms may request a USAN is during Phase I clinical studies. The typical time for US firms to apply for a USAN is during Phase II clinical studies.

Before most USANs are adopted, three parties (i.e., the sponsor, the USAN Council and the INN Expert Group) must accept the name. This process is facilitated by the USAN Program staff. All negotiations are conducted throughout the year by USAN Council member correspondence and electronic balloting or at either of the biannual USAN meetings, typically occurring in January/February and July. The purpose of these meetings is to review and set policy, review the INN Expert Group decisions, discuss multiple-round negotiations and address negotiations where a consensus has not yet been reached. New negotiations are accepted on a space-available basis.

When considering an acceptable name the following criteria are constantly kept in mind by the USAN Council: usefulness to healthcare providers, patient safety, adherence to the nomenclature rules, absence of conflicts with existing names, suitability for use internationally, ease of pronunciation, and other factors. The USAN Council does not choose names based on specific marketing considerations.

Immediately after receiving a submission, the USAN Program Secretariat verifies that the application is complete (payment must be received) and that the substance meets all prerequisites to apply. Two important requirements are that the substance has entered clinical trials and has an IND number. If the requirements are met the submission is considered a complete application.

Each complete application is assigned a file number and a USAN Program staff member as the "negotiator." The negotiator serves as the manufacturer's contact for all questions and correspondence. Following assignment of these, the applicant receives an acknowledgment letter, which confirms receipt of the submission and application fee, and includes the USAN file number and the name of the assigned negotiator.

Before submitting an application to the USAN Council, the negotiator verifies the chemical information listed on the application and searches databases for drug information. The negotiator determines how the drug may be classified using the nomenclature scheme and whether the proposed names appropriately reflect its action. A detailed check to verify that the submitted names are free of conflicts with nonproprietary or proprietary names and an analysis of the stem assignment requested by the applicant are performed. A ballot is prepared with the firm's proposed names and alternative suggestions, if any, and any conflicts with nonproprietary or proprietary names are noted for the USAN Council.

Next, the USAN Council reviews the names. Review criteria include absence of conflicts with nonproprietary or proprietary names, appropriate use of the nomenclature scheme, and usefulness of the proposed names to the healthcare providers. Names too similar to existing nonproprietary or proprietary names are rejected. The FDA's opinion on the proposed name(s) is sought through the FDA representative on the USAN Council. When consensus is reached, USAN Program staff forwards the name selected to the firm.

After the USAN Council completes deliberation and recommends a name, it is sent to the sponsor for acceptance or rejection. Once the USAN Council recommendation letter is sent to the applicant, the name under consideration is published online on the USAN website for public comment. If the firm accepts the name, it proceeds through international review before adoption as a USAN. When accepting a name, the applicant will need to notify their assigned negotiator and, depending upon the type of submission, include a check made out to WHO for their application fee and to process the submission through the WHO-INN Expert Group to ultimately receive a recommended INN (rINN).

When rejecting a name, the notification must include new name suggestions for the USAN Council and explain the reasons for rejection. Rejection leads to another round of review by the negotiator and the USAN Council and can add about six months to the timeline. The applicant should carefully weigh whether to reject the name and subsequently delay adoption. The negotiator will review potential alternative suggestions before they are submitted to the USAN Council, as this will expedite further balloting. When an alternative is finalized, the negotiator prepares a new ballot accompanied by the sponsor's letter describing reasons for rejecting the names and any new supporting information. If the USAN Council deems a proposed name unacceptable due to conflicts or patient safety concerns, the name will not be reconsidered. If a new stem is deemed unacceptable, additional, *new* data and information are required

to support the case for a new stem. New stems are assigned only when no existing stem is appropriate. Additional rounds of USAN Council balloting are conducted as many times as necessary to reach an acceptable name. There is no charge for additional rounds of balloting.

At the completion of the USAN Council review and after a name is accepted, the USAN Program staff request an INN on behalf of the sponsor (depending on the type of submission). The INN Expert Group, which is composed of scientists and regulatory experts from around the world, reviews and accepts the proposed name, or suggests an alternative. INN review criteria include conflicts with non-US nonproprietary names or trademarks, connotations in languages other than English, and conformity to international nomenclature schemes. Many firms seeking a USAN are multinational companies with subsidiaries outside the United States. It is highly desirable to the drug firms, the various nomenclature committees and the medical community that a global name be established for each new substance. To prevent confusion with the use of multiple nonproprietary names in different counties, the INN Program coordinates drug nomenclature internationally. US drug sponsors should submit to the USAN Council first, but drug firms in countries where there are no national nomenclature agencies may apply directly to the INN Program.

Input from other countries is very valuable because it prevents selection of a USAN that could possibly have unacceptable and unintended negative connotations in other languages. The INN Expert Group evaluates suggested names following procedures somewhat similar to those of the USAN Council; however, the deliberation and actual name selection occurs at each of their biannual meetings, not through a year-round balloting process. Also, there are some things, such as contact lens polymers and cell therapies, which are named by the USAN Council but not the INN Expert Group.

The firm and the USAN Council are notified of the INN Expert Group's decision by the USAN Program staff. If the INN Expert Group has made alternative suggestions, the firm and the USAN Council may accept or reject the suggestions. Once the USAN Council, firm, and the INN Expert Group reach a consensus, the name is adopted. Per standard USAN policy, adoptions occur the last Wednesday of each month. A letter and adoption statement formally notify the applicant that the negotiation has been completed and a USAN assigned. A firm may begin using a USAN when it receives an adoption statement. There is no need to wait until publication, which would normally occur 60 days later. Upon publication the adoption statement is published on the USAN website and forwarded to both USP for inclusion in the *USP Dictionary of USAN and International Drug Names* and CAS for inclusion in their databases. Internationally, names are published twice, as proposed INN and recommended INN, in the journal *WHO Drug Information*. A firm may request a publication deferral for up to six months.

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6

Pharmaceutical analysis and quality control

Analysis of medicinals

Specifications

The pharmaceutical manufacturer is responsible for ensuring the quality, purity, identity, and strength of each lot of drug product manufactured. One mandatory control strategy is to ensure that the lot "conforms to specification," which means that the drug product (formulated preparation), when tested to the listed analytical procedures, will meet the listed acceptance criteria.[1] Specifications are critical quality standards.

A specification is a document that is defined as a list of tests, references to analytical procedures, and appropriate acceptance criteria (numerical range or limit).[1] The pharmaceutical manufacturer justifies the information on the specification, which is approved by regulatory authorities. Examples of specifications for hypothetical drug products are provided in Appendix A.

Specifications can be categorized in a couple of manners. One way is by the intended use of the product. For example, is the medicinal an investigational product intended for use in a clinical study, or is it a commercial product that will be marketed? Let's consider the evolution of a hypothetical oral drug product as it enters the clinic for single- and multiple-ascending dose safety studies during Phase I clinical studies, then multiple-ascending dose efficacy studies in Phase IIa, and confirmatory efficacy studies in Phase IIb and Phase III. In order to enter the clinic rapidly, a simple drug product called a drug-in-capsule was chosen for Phase I. This dosage form consists of neat drug (no excipients) that has been accurately weighed into gelatin capsules. The manufacturing process meets the volume demand for Phase I, but the dosage form must be changed prior to scaling-up to Phase II. Hence,

the drug-in-capsule is a "lame duck" dosage form. Specifications for investigational products tend to have acceptance criteria that reflect the early life of the product. Here, the acceptance criteria for dissolution of our drug-in-capsule may be "record result."

Now let's say that our drug-in-capsule drug product will be replaced with a dosage form that is manufactured using a scalable manufacturing process – a tablet for Phase II. The tablet will first be used in Phase II ascending-dose clinical studies, so several dose strengths will need to be manufactured. Let's say that these dose strengths are 10, 25, and 100 mg. The acceptance criterion for the dissolution test may remain as "record result" because the dosage form is new, or the criterion may be a "disaster check" criterion. Although the analytical chemist may not be able to assign a strict acceptance criterion because of the limited data, a slow-dissolving drug from an immediate-release tablet may jeopardize the interpretation of the clinical results. So a criterion like 70 percent of the drug dissolved after 60 minutes may be appropriate for the 100-mg tablet. The lower dose strengths are usually assigned the same acceptance criterion.

Finally, the tablet has entered late development and will be used for confirmatory studies. The dose ranging Phase IIa studies determined that the efficacious dose was 60 mg, so a new 60-mg tablet was developed for use in the Phase III studies. During Phase III, a robust manufacturing process has been developed at suitable scale, a robust dissolution test also has been developed and validated, and many lots of tablets have been manufactured and analyzed. Now, a suitable acceptance criterion at the time of New Drug Application (NDA) or Medicare Modernization Act (MAA) submission may be 70% of the drug dissolved after 30 minutes.

Another common categorization involves using different acceptance criteria for release testing and stability testing in order to account for changes that may occur during the shelf life. For example, a topical cream may become less viscous upon storage at 25°C to 30°C for two years. The cream may be too fluid to apply when its viscosity is less than 1000 mPa·s. A suitable acceptance criterion for a stability specification may be 2000 mPa·s. Let's say that the development data indicate that in order to ensure a viscosity of 2000 mPa·s at the end of the shelf life, the cream must have a viscosity of 10,000 mPa·s at the time of release. Therefore, the acceptance criteria for the release and stability specifications would be not less than (NLT) 10,000 mPa·s and NLT 2000 mPa·s, respectively, in order to ensure a quality product for its entire shelf life.

Compendia

All drug products, whether commercial or investigational, must meet standards that have been established by Pharmacopeial Conventions or Regulatory Agencies. The United States Pharmacopeial (USP) Convention is a scientific nonprofit organization that sets standards for the quality, purity, identity, and strengths of medicines, food ingredients, and dietary supplements manufactured, distributed, and consumed worldwide.[2–4] USP drug standards are enforceable in the United States by the Food and Drug Administration (FDA), and these standards are developed and relied upon in more than 130 countries.[2,4]

The European Directorate for Quality of Medicines and Healthcare (EDQM), which publishes the *European Pharmacopoeia*, establishes official standards that provide a legal and scientific basis for quality control during the development, production, and marketing of medicines in all signatory states of the European Union Convention on the Elaboration of a European Pharmacopoeia (i.e., 37 member states and the European Union).[5,6] In addition to the signatory states, seven European countries, 16 non-European countries (including Australia, Brazil, Canada, China, the Russian Federation, and the United States) and the World Health Organization are listed as observers. Consequently, the standards developed by Ph. Eur. have an impact on the quality of medicines across the globe.[5,6]

The USP and Ph. Eur. publish books of pharmacopeial standards. The thirty-fifth revision of the USP and the thirtieth edition of the National Formulary, USP 35/NF 29, became official on May 1, 2012. The USP-NF is continuously revised. Standard revisions are found in supplements to the USP-NF that are published twice yearly. Accelerated revisions are published in Pharmacopeial Forum (PF) and on the USP website, http://www.usp.org. A new edition of USP/NF becomes official each year on May 1.

Chapters <1> through <999> are enforceable chapters, while Chapters <1000> through <1999> are informational chapters.[3]

The seventh edition of the *European Pharmacopoeia* (Ph. Eur 7.0) became official on January 1, 2011. This edition will be augmented with eight supplements over a three-year period.[5] The eighth edition of Ph. Eur. will become official on January 1, 2014. The *European Pharmacopoeia* is published in English and French.

The *British Pharmacopoeia* (BP) is the official collection of standards for UK medicinal products and pharmaceutical substances.[7] The standards are established by the British Pharmacopeia Commission. Canada and Australia also use the BP is as their official standards. The BP is recognized in over 100 countries as an internationally acceptable standard and remains an essential reference for all individuals and organizations working within pharmaceutical research, development, manufacture, and testing across the globe.[8] A new edition of the BP becomes official each year on January 1.

Japan's Ministry of Health, Labor, and Welfare (MHLW) publishes the *Japanese Pharmacopoeia* (JP), which provides an official standard to ensure the quality of medicines in Japan.[9–11] The *Japanese Pharmacopoeia*, 16th edition (JP 16) became official on April 1, 2011. JP 16 is printed in Japanese only at the time of publication of this chapter. JP 15, however, is available in English. Both editions can be found on the *Japanese Pharmacopoeia* website (http://jpdb.nihs.go.jp/jp16e/) and are free of charge.

Monographs

A monograph is written after a drug product has been registered and established in the marketplace and usually before its patent expires. The USP defines a monograph as a written standard that describes an article (e.g., drug substance, drug product, excipient, compounded preparation).[12] A monograph published in any USP compendium provides the name of a substance; its definition; package, storage, and labeling requirement; and information on tests needed to ensure the substance is of the appropriate identity, strength, quality, and purity.[3] The later part of a monograph is similar in scope to a specification.

The monograph gives manufacturers, governments, and scientists a public standard by which to judge an article's quality. Monographs play an important role in meeting the USP's mission by providing standards for substances consumed in a global marketplace – standards that help maintain public health. The USP-NF comprises more than 4000 monographs.[12] The USP contains monographs for drug substances and preparations (drug products); excipient monographs are in the NF.

The *European Pharmacopoeia* contains more than 2000 general and specific monographs, including chemical substances, antibiotics, vaccines, dosage forms, herbal drugs, and homeopathic preparations.[5] One major difference between the Ph. Eur. and USP is illustrated by this example: the USP has monographs for tablets of a specific drug (e.g., amoxine), whereas Ph. Eur. will have only a general monograph for tablets. The BP and JP also contain monographs of drug substances and drug products. The BP, which contains over 3000 monographs, incorporates monographs of the *European Pharmacopoeia*.[13]

Release and stability testing

Release and stability testing can be classified in a couple of practical ways. One is by the nature of the testing performed: chemical, physical, and microbial. For example, the assay for the amount of active ingredient in a gel would be a chemical test, the viscosity measurement and the *in vitro* release test would be physical tests, and the microbial limits test would be a microbiological test. This classification system is often used in analytical laboratories that are specialized by the type of test being performed. The chapters in pharmacopoeias are also organized by the nature of the test.[3,5,9,10]

Another classification system that is used is based on the attribute that is being tested. For example, the International Conference on Harmonization (ICH) Guidances and the USP provide two categories for the system: analytical tests and acceptance criteria for assessing (1) general quality attributes and (2) product performance.[1, 14–17] Using the previous gel example, the assay, viscosity, and microbial limits tests would be examples of tests that assess general quality attributes. while the *in vitro* release test would assess product performance.

Universal tests

There are four tests that are generally applicable to all drug products: description, identification, assay, and impurities.

Description

This test is often called "appearance" on a specification and is a qualitative description of the dosage form. For example, the description of a tablet on a specification may read: white, round, biconvex, film-coated tablet, imprinted with "400" on one side.

Identification

The purpose of an identification or identity test is to verify the identity of the active pharmaceutical ingredient(s) (API) in the dosage form. This test should be able to discriminate between compounds of closely related structure that are likely to be present. Infrared and Raman spectroscopy are commonly used techniques. A more practical technique, however, is high-performance liquid chromatography (HPLC) because the identity and assay can be determined using the same analytical method. The ICH Q6A Guidance,[1] however, does not regard identification solely by a single chromatographic retention time as being specific, the definition of which is the ability of the method to assess unequivocally the analyte in the presence of the sample matrix (excipients, impurities, and degradation products). Thus, some laboratories will couple a diode array or mass spectrometric (MS) detector to the HPLC system. The diode array detector provides a UV spectrum of the drug; the MS detector gives the nominal mass of the drug.

Assay

This test determines the strength or content of the API in the dosage form and is sometimes called a content test. The method should be stability-indicating, which means that the method is quantitative and specific and can detect chemical changes with respect to time, so that the quantity of the active ingredient(s) can be accurately and precisely measured in the presence of the sample matrix. HPLC is the most common technique used for stability-indicating methods.

Impurities

ICH Guidance Q6A[1] defines an impurity in a drug product as any component that is not the API or an excipient. The most common type of impurities that are measured is related substances, which are process impurities from the new drug substance synthesis, degradation products of the API, or both. The test for related substances is often referred to as a purity test and must be stability-indicating. The method can be the same as that used for assay, or it can be a different method that has been developed for measuring low-level impurities. An additional method to measure chiral purity may be used to quantify enantiomeric impurities in the drug product. In cases in which an organic solvent is used during the manufacture of the drug product, a method for measuring residual solvents is also used.

Future direction

The biggest change in the analysis of medical products in the coming years will likely be in the implementation of the Quality by Design (QbD) paradigm and corresponding ICH Guidelines into everyday pharmaceutical development. The information and knowledge gained from pharmaceutical development studies and manufacturing experience provide scientific understanding to support the establishment of the design space, specifications, and manufacturing controls. The use of meaningful analytical methods and specifications will be an integral part of QbD because quality is expected to be built into the design of the product. Analytical tests, especially those that test product performance, will be expected to be discriminating. For example, dissolution tests will be expected to tell when a manufacturing or formulation change will affect the product performance.

Biological testing

Introduction

Biological testing includes the quantitative assay of drugs by biological methods as well as the application of qualitative biological tests. Such testing uses intact animals, animal preparations, isolated living tissues and cells, or microorganisms. In addition to drugs, biological tests are a requirement for plastics to be used as containers or closures for ophthalmic and parenteral preparations or to be used as implants, devices, or other related systems.

The practices of the USP are a good index of the state of biological testing. The USP/NF[18] is a combination of chapters describing current assays or procedures using USP reference standards, as well as monographs of drug substances. The monographs are developed by researchers and contain the name of the drug or preparation; the definition; packaging, storage, and labeling requirements; and the series of tests, procedures for the tests, and acceptance criteria for the drug.[19] Currently there is a trend to use fewer animals in research and biological testing and to use alternatives such as cells and microorganisms in culture. This decrease in animal use can be observed in the decreased requirement for animal testing by the USP as documented in their monographs. Wherever possible, *in vitro* procedures should be used to complement or replace *in vivo* tests for evaluating the suitability of plastics.

The majority of currently available therapeutic agents are substances of known chemical composition that can be assayed by quantitative chemical or physical analyses. However, there are a limited number of useful drugs that cannot be assayed satisfactorily by chemical or physical means. Such drugs, which are primarily of natural origin, are assayed by biological methods. Biological standardization procedures are generally less precise, more time consuming, and more expensive to conduct than are chemical assays; therefore, they generally are reserved for use:

1. If the chemical identity of the active principle has not been elucidated fully.
2. If no adequate chemical assay has been devised for the active principle, although its chemical structure has been established (e.g., insulin).
3. If the drug is composed of a complex mixture of substances of varying structure and activity (e.g., extracts of digitalis leaf, posterior pituitary gland).
4. If purification of the crude drug, sufficient for the performance of a chemical assay, is not possible or practical (e.g., the separation of vitamin D from certain irradiated oils).
5. If the chemical assay is not a valid indication of biological activity, due, for example, to lack of differentiation between active and inactive isomers.

There are several situations in which factors such as specificity, sensitivity, or practicality dictate the use of a biological rather than a chemical assay procedure.

A chemical assay quantitatively determines the amount of a specific compound or structural moiety present in a given sample. Once the concentration has been established, an assumption is made relative to the biological activity of the sample. In contrast, a biological assay measures the actual biological activity of a given sample, which may represent the algebraic sum of the interaction of a number of chemical and physical-chemical factors. For example, the data obtained from a chemical assay will not provide information concerning the contribution to the net biological activity of trace amounts of substances that do not influence the chemical analysis. Such substances may produce qualitative variations in biological activity that may be responsible for unexpected side effects or toxic reactions. Furthermore, the enhancing or inhibiting influences of variations in the physical state of the active principle are not reflected in the results of a chemical assay. The safety, efficacy, and dependability of dosage of drugs are contingent upon standardization, and biological assays must be employed in some instances even though the chemical identities of the active principles in the preparation may be known.

Animal testing

As animals are an important *unknown* factor in most biological assays, the need for their proper selection and adequate care is self-evident. Most laboratories seek a reliable source of animals that can supply their needs from colonies maintained for this purpose. In any one test it is desirable to use animals of only one strain. Usually bioassayists adopt a specified strain for all work of a particular type. This enables the bioassayist to gain experience concerning the expected normal variation. For some assays a specific sex must be employed (e.g., estrogenic tests); in other assays either sex may be used, but the effect that sex may play in the response should not be overlooked. The male rat, for instance, has a faster growth rate than the female; therefore, indiscriminate use of both males and females in a rat growth test should be avoided. Differences in the response of the sexes may extend into other categories, such as response toward toxic materials. Animals used in these biological assays

should always be handled according to the National Institutes of Health guidelines.[20]

Bioassay procedures

Bioassays are conducted by determining the amount of a preparation of unknown potency required to produce a definite effect on suitable test animals or organs under standard conditions.

Reference standards

To minimize the source of error resulting from animal variation, standard reference preparations are used in certain bioassay procedures. The principle of the using a reference standard consists of successively testing the unknown and standard preparations on two groups of similar animals, or, in some cases (e.g., epinephrine, posterior pituitary) on the same animal or organ. The amount of the unknown preparation required to produce an effect equal to that produced by a defined amount of the standard will be inversely proportional to their relative potencies. The potency of the unknown therefore can be expressed as a percentage of that of the reference standard.

In some assays it is necessary to adopt precise methods of calculating potency based on observations of relative, but not necessarily equal, effects. Likewise, methods of computation have been devised to determine the statistical reliability of the results. The chapters on Biological Tests and Assays in the USP 35/NF 30[21] also present a detailed consideration of factors germane to the chapter on Design and Analysis of Biological Assays.[22]

When reference standards are required for use in assays, they are available as a service from USPNF Reference Standards, 12601 Twinbrook Parkway, Rockville, MD 20852. These references are standardized in terms of the appropriate existing international standards.

Disadvantages of bioassays

Biological assays leave much to be desired in several respects. Although some are extremely sensitive in detecting small differences in concentration, their quantitative accuracy usually falls considerably below that obtainable with most chemical analyses. The techniques and interpretations involved often can vary with different operators, in spite of the rigid requirements specified by the USP 35/NF 30;[18] hence, there is a considerable subjective element present.

Furthermore, the effect measured in the test animals often is not that which the drug is intended to produce in treating patients. The importance of this discrepancy was minimized formerly, but recent studies have shown that when several active principles are present in a crude drug, those producing the maximal therapeutic effect are not necessarily the ones chiefly responsible for the action measured in the assay. As a result, samples found to be of equal strength by assay may show different potencies when employed clinically. An example of this situation is found in the discussion on digitalis.

Classification of bioassay procedures

Bioassays are classified in three groups according to whether the effect produced is all or none (as death), graded (as rise in blood pressure), or is characterized by developing in a measured period of time (as the curative response to thiamine). It should be noted that in all three types, with few exceptions, the calculations of potency are based on the sizes of doses necessary to produce approximately equal effects and not on the magnitude of the responses. Furthermore, *the results derived from all are quantitative* in that the potency of the unknown is expressed in terms of the standard.

Clinical analysis

The characterization and quantitation of the various components of blood, urine, and other body fluids are the primary functions of the clinical laboratory. The major divisions of clinical analysis are clinical biochemistry, hematology, blood-bank technology, histopathology, immunology, and microbiology. The accurate diagnosis of disease and determination of a potential therapeutic regimen frequently are based on the laboratory analysis of blood, urine, feces, gastric secretions, or cerebrospinal fluid. Modern medical practice is tending toward greater reliance on laboratory results as definitive measures of pathological or normal states.

Pharmacists should familiarize themselves with the basic principles involved in sample collection, analysis, and diagnostic significance of the various clinical parameters. Their role in community health

necessitates comprehension of the methodology and diagnostic value of clinical laboratory procedures. The influence of various drugs and drug interactions on these parameters must be considered in both the clinical and drug-abuse situation.

Quality assurance and control

The pharmaceutical industry, as a vital segment of the healthcare system, conducts research and manufactures and markets pharmaceutical and biological products and medical devices used for the acute/chronic treatment and diagnosis of disease. Recent advances in drug discovery, primarily in the field of biotechnology and in the required controls over manufacturing processes, are presenting new challenges to the control of quality and to the systems that operate internally in the industry. The external regulations established by the federal FDA and other regulatory bodies also add to these challenges. The evolving role of the industrial quality professional requires more extensive education including food and drug law, business, as well as the traditional science/technology coursework.

The pursuit of quality is being approached through the application of quality systems including risk-based assessment and continuous improvement, whereby management and labor join forces to build quality into products while helping to ensure the company's financial success. This changed emphasis is directed toward defect prevention (proactive) rather than defect detection (after the fact).

Quality assurance (QA) and quality control (QC) departments develop and follow standard internal operating procedures directed toward assuring the quality, safety, purity, and effectiveness of drug products. The FDA has issued a primary regulation to the industry entitled *Current Good Manufacturing Practice for Finished Pharmaceuticals* (commonly referred to as the cGMPs or GMPs) (see Appendix B). Numerous guidelines have been issued relative to specific dosage forms and operations such as aseptic manufacturing, validation and stability testing, etc., which impose significant compliance requirements. These guidelines also serve as the basis for compliance investigations conducted by the FDA and are used in regulatory agency inspections of facilities and operations. Emphasis is being placed on the inspection of quality systems as part of the regulatory pre-approval program when reviewing NDAs and Biological License Applications (BLAs).

QA and QC: organization/responsibilities

Industry, to ensure compliance with these government regulations and with their own internal policies and procedures, has developed very sophisticated quality organizations with well-defined responsibilities. It has been accepted that QA and QC have different functions within an organization; although both are considered part of the Quality Unit as identified in the *Code of Federal Regulations* Title 21 (CFR) (see Appendix B). QC most commonly functions to test and measure material and product. QA establishes systems for ensuring the quality of the product. Firms must decide upon the exact roles they wish QC and QA to perform in operations and put these definitions in writing.

QA functions and responsibilities

The QA department within any organization, because of its responsibilities, normally will report to a relatively high-level administrator within a company, depending on its size. In smaller companies they may report to the chief executive officer or the president. In larger corporations, they will sometimes report to the president or executive vice-president or chief of operations. In any case, however, responsibility for quality, as currently dictated by the FDA, ultimately resides with top management which has responsibility for ensuring that appropriate resources are provided to meet all quality and compliance requirements. In all cases, the QA department will be independent of the economic issues associated with manufacturing and distribution of the product.

The QA department is responsible for ensuring that the quality policies adopted by a company are followed. In some organizations, QA serves as the primary contact with regulatory agencies and is the final authority for product acceptance (release) or rejection. It is customary for QA to play a major role in the identification and preparation of the necessary policies and standard operating procedures (SOPs) relative to the control of quality. Where QA has responsibility for final product release, it must determine that the

product meets all the applicable specifications and that it was manufactured according to internal standards and cGMPs. QA departments now tend to work as a team member with the other functional groups within the firm rather than simply to serve a police function, a largely outdated role of QA.

A second major responsibility of the QA department is the quality monitoring or audit function. Through this activity, it is able to determine if operations have adequate systems, facilities, and written procedures to control the quality of products produced. Thus, the QA function not only determines that the procedures are current and correct, but that properly trained operators are following them. Combining this review of SOPs with an audit of facilities and operations, including those of contract manufacturing and testing subcontractors, will give company management an inside report on its level of compliance and will allow the necessary changes and/or corrections to be made prior to a product failure or being reported as a deficiency during an inspection by an FDA investigator. This is consistent with the top-level management review component of the quality systems approach currently emphasized by FDA during inspections. Senior management of a company looks to the QA function to assess operations continually and to advise and guide them toward full compliance with all applicable internal and external regulations. Organizationally, the Quality department(s) should report, as directed by the GMPs, to someone other than the person responsible for production.

QC functions and responsibilities

QC is responsible for the day-to-day control of quality within a company. This department is staffed with scientists and technicians responsible for the sampling and analytical testing of incoming raw materials and inspection of packaging components, including labeling. QC conducts in-process testing when required, performs environmental monitoring, inspects operations for compliance, and conducts the required release tests on finished dosage form. Finally, QC is responsible for monitoring product quality through distribution, including testing of product complaint samples, evaluating product stability, and so on.

Many companies have the heads of QC and production report to a common higher level of management, but with QC being independent of production. This higher-level management may be the same or different individuals, but it allows independent operation of both functions without direct conflict arising when reaching a final decision on the acceptability of final products.

The analytical control laboratory must be staffed with persons who are trained academically and are, through experience, capable of performing the often complex analyses used to evaluate the acceptability of the materials tested. The equipment and instrumentation in the laboratory must be suitable for performing the testing in an accurate and efficient manner. Detailed specifications must be available, as well as validated test methods against which products and raw materials will be evaluated. The specifications detail the limits for acceptance of the article, based on identified critical parameters.

The testing and acceptance of only high-quality raw materials is essential for the production of uniformly acceptable products. QC plays a major role in the selection and qualification of vendors from whom these materials are purchased. Testing of representative samples is required, and in many cases, an audit of the vendor's operation is necessary to determine their suitability and degree of compliance with GMPs and other relevant standards prior to their being approved. The vendor audit frequently is organized by QA, with technical support from research, QC, and manufacturing.

At various critical in-process steps in production, it may be necessary to sample and test product against criteria previously established. Often, in-process alert or action levels will be identified for the critical in-process parameters as a means of process control. These alert or action levels are normally set such that they are more restrictive than the final acceptance limits, but serve as an in-process control by providing early warnings of conditions that could lead to an out-of-control situation and thus will allow timely corrective action before such conditions occur. The acceptance criteria for such testing are established using QbD approaches which identify the Design Space within which the process will perform satisfactorily. Trending of analytical data is also useful in providing early warning signals that the process is moving out of control. It should be noted, however, that materials, which have reached the alert or action

level criteria, are still acceptable for use in manufacturing, since they have not exceeded an out-of-limit rejection level.

QC is responsible, as part of its testing and inspection functions, for monitoring the environmental conditions under which products are manufactured and/or held. Different levels of control are established depending on the intended use of the dosage form. Parenteral and ophthalmic products must be produced in a controlled environment that is designed to ensure their sterility. Monitoring of air and water systems is critical in confirming that they are being controlled and that the levels of particulates, microbial matter, and other contaminants are within pre-established limits. The USP contains monographs and specifications on Water Used for Pharmaceutical Purposes. Formerly, the Federal Government Standard 209E, Airborne Particulate Cleanliness Classes in Cleanrooms and Clean Zones, established acceptable limits for particulates in a controlled environment, but it is no longer considered applicable to the pharmaceutical industry, having been replaced by international standards. Federal standards are currently not enforced for environmental quality, but guidance is available in the FDA Concept Paper, Sterile Drug Products Produced by Aseptic Processing, published in September 2004.[23] In addition, reference is made to the Baseline Pharmaceutical Engineering Guide, Vol. 3, Sterile Manufacturing Facilities, published by the International Society of Pharmaceutical Engineering (ISPE) in partnership with the FDA, in June 2000.[24] Generally, conditions listed as Class ISO 5 (formerly Class 100) (or equivalent) are maintained in areas where parenteral products are filled into clean, sterile containers. The ISO 5 classification is defined as an area that can be controlled to contain fewer than 100 particles, 0.5 microns and larger, per cubic foot of air. In addition, manufacturers must establish limits for the presence of viable microorganisms in the environment and appropriately monitor the air quality in the filling area.

Another major element of control is the environmental monitoring of the areas in which nonsterile products are manufactured, such as liquids, tablets, and capsules. The objective here is first to determine an acceptable level of particulates and microbial contaminates and then to control them to this level. If particulate levels are found to be excessive, steps must be taken to bring them within acceptable limits so as not to compromise the quality of the product. This monitoring and control of the environment will further ensure the quality and stability of the product by preventing the products from being exposed to a hostile environment.

Control of packaging components, especially those that come into direct contact with a product, is required. These materials must be inspected and tested against rigid specifications to ensure that they meet predetermined functional standards. This includes evaluation of compatibility of the product with the packaging materials. Labeling is understandably a critical component, not just in its original design and acceptance, but also with regard to secure storage and issuance to ensure accountability. Furthermore, final product labeling must be 100% inspected to ensure that it is correct. Often automated imaging methods are employed to conduct these inspections.

Stability of pharmaceutical products

Introduction

Stability of a pharmaceutical product may be defined as the capability of a particular formulation, in a specific container/closure system, to remain within its physical, chemical, microbiological, therapeutic, and toxicological specifications at a defined storage condition. Pharmaceutical products are expected to meet their specifications for identity, purity, quality, and strength throughout their defined storage period at specific storage conditions. Assurances that the packaged product will be stable for its anticipated shelf life must come from an accumulation of valid data on the drug in its commercial package. These stability data include selected parameters that, taken together, form the stability profile.

The stability of a pharmaceutical product is investigated throughout the various stages of the development process. The stability of a drug substance is first assessed in the preformulation stage. At this stage, pharmaceutical scientists determine the drug substance and its related salts stability/compatibility with various solvents, buffered solutions and excipients considered for formulation development. Suitable

analytical methods must be employed in order to ensure the likelihood that this assessment will be successful. Optimization of a stable formulation of a pharmaceutical product is built (using statistical design) upon the information obtained from the preformulation stage and continues during the formulation development stages.

Typically, the first formulation development stage may be for preclinical studies or as late as the preparation of a "first in human" formulation which is often a non-elegant formulation optimized for short-term dose-ranging clinical studies. The second major formulation development stage occurs to support Phase II clinical studies (proof of concept phase). The pharmaceutical product developed at this stage is usually the prototype for the commercial product. Therefore, the pharmaceutical product will be formulated based in part on the stability information obtained from the previous formulations and must meet stability requirements for longer-term clinical studies. In the final formulation development state for Phase III clinical studies, the formulation must be truly representative of what the commercial pharmaceutical product will be in order to avoid delays in approval. In addition to building on the clinical requirements of the drug, the commercial pharmaceutical product must also incorporate the commercial or the final market image of the product, which includes the container closure system. The stability of this product must be demonstrated to the appropriate regulatory agencies in order to assign an expiration period and date for the product. This expiration period allows for the assignment of an expiration date based on the manufacture date of each lot of drug product.

Once a pharmaceutical product has gained regulatory approval and is marketed, the pharmacist must understand the proper storage and handling of the drug. In some cases, a pharmacist may need to prepare stable compounded preparations from this product.

Most drug products are not shipped directly from the manufacturer to a pharmacy. Typically, a drug product is shipped from a manufacturer to a distribution center. From the distribution center the drug product is then shipped to a wholesaler. From the wholesaler, the drug product may be shipped to the distribution center for a pharmacy chain or directly to the pharmacy. Finally, the drug product is dispensed by the pharmacy to the patient. Dispensing of the drug product may be at a hospital, a clinic, and a traditional "brick and mortar" pharmacy or from a mail-order pharmacy. Therefore, the stability typically must also assess the robustness of the drug product through its supply chain. It is not unusual for temperature excursions to occur during these transfers of control.

Inventory control, or holding, of each drug is important for a wholesaler or pharmacy. A drug must be within its expiration dating throughout its use by the patient. Solid oral dosages may be dispensed in the commercial packaging or in a pharmacy supplied container closure system. Most prescriptions are supplied to patients for up to 30 or 90 days by traditional and mail-order pharmacies, respectively. Inventory control of product by wholesalers and pharmacies must assess how much dating must remain on a product for it to be useful for its customer. This causes the actual holding of a product to be shorter than the expiration date. Under normal circumstances it is unusual for a pharmacy to accept any product with less than 6 month dating remaining on a product.

Much has been written about the development of a stable pharmaceutical product. Comprehensive treatments of all aspects of pharmaceutical product stability have been published by Connors *et al.*[25], Carstensen[26] and more recently by Allen.[27] This will cover the applicable topics from preformulation to drug approval to assure that the pharmaceutical product developed is stable. Requirements for compounded products will also be discussed.

The USP General Chapter <1191>[4] defines the stability of a pharmaceutical product as "extent to which a product retains, within specified limits, and throughout its period of storage and use (i.e., its shelf life), the same properties and characteristics that it possessed at the time of its manufacture." There are five types of stability that must be considered for each drug (Table 6.1).

The use of kinetic and predictive studies for establishing credible expiration dating for pharmaceutical products is now accepted worldwide. Scientifically designed studies using reliable, meaningful, and specific stability-indicating assays, appropriate statistical concepts, and a computer to analyze the resulting data are used to determine an accurate and realistic shelf life. In this way the maximum amount of valid information is obtained to establish a reliable, defendable

Table 6.1 Types of stability

Type of stability	Conditions maintained throughout the shelf life of the drug product
Chemical	Each active ingredient retains its chemical integrity and labeled potency, within the specified limits.
Physical	The original physical properties, including appearance, palatability, uniformity, dissolution, and suspendability are retained.
Microbiological	Sterility or resistance to microbial growth is retained according to the specified requirements. Antimicrobial agents that are present retain effectiveness within the specified limits.
Therapeutic	The therapeutic effect remains unchanged.
Toxicological	No significant increase in toxicity occurs.

expiration date for each formulation. The assigned expiration date is a direct application and interpretation of the knowledge gained from the stability study.

Although there are exceptions, 90% of labeled potency generally is recognized as the minimum acceptable potency level over the shelf life of a drug product. Exceptions to this minimum potency include drugs with active pharmaceutical ingredients that have a narrow therapeutic thresholds and biologics.

The stability of a commercial pharmaceutical product is expressed as an expiration date (expiry). Expiration dating is defined, therefore, as the time in which a drug product in a specific packaging configuration will remain stable when stored under recommended conditions. This date is usually calculated by adding the established expiration period to the date of manufacture. The date of manufacture is many times defined as the date in which the active pharmaceutical ingredient is first combined with a drug product excipient.

An expiration date, which is expressed traditionally in terms of month and year, denotes the last day of the month. In the United States, the expiration date shall appear on the immediate container and the outer retail package. However, when single-dose containers are packaged in individual cartons, the expiration date may be placed on the individual carton instead of the immediate product container. If a dry product is to be reconstituted at the time of dispensing, expiration dates are assigned to both the dry mixture and the reconstituted product. Tamper-resistant packaging is to be used where applicable.

Product stability

Many factors affect the stability of a pharmaceutical product including the intrinsic stability of the active ingredient(s), the potential interaction between active and inactive ingredients, the manufacturing process, the dosage form, the container-liner-closure system and the environmental conditions encountered during shipment, storage and handling, and length of time between manufacture and usage.

Classically, pharmaceutical product stability evaluations have been separated into studies of chemical (including biochemical) and physical stability of formulations. Realistically, there is no absolute division between these two arbitrary divisions. Physical factors – such as heat, light, and moisture – may initiate or accelerate chemical reactions, whereas every time a measurement is made on a chemical compound, physical dimensions are included in the study.

One type of time-related chemical stability failure is a decrease in therapeutic activity of the preparation to below some arbitrary labeled content. A second type of chemical stability failure is the appearance of a toxic substance, formed as a degradation product upon storage of the formulation. The numbers of published cases reflecting this second type are few. However, it is possible, though remote, for both types of stability failures to occur simultaneously within the same pharmaceutical product. Thus, the use of stability studies with the resulting application of expiration dating to pharmaceuticals is an attempt to predict the approximate time at which the probability of occurrence of a stability failure may reach an intolerable level. This estimate is subject to the usual Type 1 or alpha error (setting the expiration too early so that the product will be destroyed or removed from the market appreciably earlier than actually is necessary) and the Type 2 or beta error (setting the date too

late so that the failure occurs in an unacceptably large proportion of cases). Thus, it is obligatory that the manufacturer clearly and succinctly defines the method for determining the degree of change in a formulation and the statistical approach to be used in making the shelf life prediction. An intrinsic part of the statistical methodology must be the statements of value for the two types of error. For the safety of the patient a Type 1 error can be accepted, but not a Type 2 error.

One type of time related physical stability failures may affect the availability or rate of drug release of a product. This type of physical stability failure may cause the active ingredient not to be released or a higher rate of drug release (dose dumping). Another type of time related physical stability failures are appearance related. These may just cause the drug product not to appear pharmaceutically elegant or may be an artifact of another physical or chemical stability failure.

In this treatment, physical and chemical stability are discussed along with those dosage form properties that can be measured and are useful in predicting shelf life. The effect of various physical and chemical phenomena of pharmaceuticals also is treated.

Knowledge of the physical stability of a formulation is very important for three primary reasons. First, a pharmaceutical product must appear fresh, elegant, and professional, for as long as it remains on the shelf. Any changes in physical appearance such as color fading or haziness can cause the patient or consumer to lose confidence in the product. Second, since some products are dispensed in multiple-dose containers, potency of the active ingredient over time must be ensured for each individual dose. A cloudy solution or a broken emulsion can lead to a non-uniform dosage pattern. Third, the active ingredient must be bioavailable to the patient throughout the expected shelf life of the preparation. A breakdown in the physical system can lead to non-availability or "dose dumping" of the medication to the patient. In the case of metered-dose inhaler pulmonary aerosols, particle aggregation may result in inadequate lung deposition of the medication.

The chemical causes of drug deterioration have been classified as incompatibility, oxidation, reduction, hydrolysis, racemization, and other mechanisms. In the latter category, decarboxylation, deterioration of hydrogen peroxide and hypochlorites, and the formation of precipitates have been included.

Pharmaceutical dosage forms

As the various pharmaceutical dosage forms present unique stability problems, they are discussed separately in the following section.

Tablets

Stable tablets retain their original size, shape, weight, and color under normal handling and storage conditions throughout their shelf life. In addition, the *in vitro* availability of the active ingredients should not change appreciably with time.

Excessive powder or solid particles at the bottom of the container, cracks or chips on the face of a tablet, or appearance of crystals on the surface of tablets or on container walls are indications of physical instability of uncoated tablets. Hence, the effect of mild, uniform, and reproducible shaking and tumbling of tablets should be studied. The recommended test for such studies is the determination of tablet friability as described in the USP. Tablet Friability USP <1216> describes the recommended apparatus and the test procedure. After visual observation of the tablets for chips, cracks, and splits, the intact tablets are sorted and weighed to determine the amount of material worn away by abrasion. In general, a maximum weight loss of not more than 1% of the weight of the tablets being tested is considered acceptable for most products. The results of these tests are comparative rather than absolute and should be correlated with actual stress experience. Packaged tablets also should be subjected to cross-country shipping tests as well as to various drop tests.

Tablet hardness (or resistance to crushing or fracturing) can be assessed by commercially available hardness testers. As results will vary with the specific make of the test apparatus used, direct comparison of results obtained on different instruments may not necessarily be made. Thus, the same instrument should be used consistently throughout a particular study.

Color stability of tablets can be followed by an appropriate colorimeter or reflectometer with heat, sunlight, and intense artificial light employed to accelerate the color deterioration. It is still not unusual for color assessment to be performed visually. Caution must be used in interpreting the elevated temperature

data, as the mechanism for degradation at that temperature may differ from that at a lower temperature. It is not always proper to assume that the same changes will occur at elevated temperatures as will be evidenced later at room temperature. Cracks, mottling, or tackiness of the coating indicates evidence of instability of coated tablets.

Typically, dissolution is the *in vitro* test performed to estimate bioavailability for a tablet regardless of the solubility of the active ingredients. Disintegration has been relegated to an in-process test or used to help dissolution. Dissolution tests should be run in an appropriate medium at 37°C. Actual dissolution conditions, including medium, are developed during the clinical development phase of a product. The dissolution method developed has to demonstrate a correlation that is relevant to the bioavailability of the dosage form. Dissolution profiles are examined during development to provide sufficient information to define a single sample time point with a minimum concentration for immediate release product. Controlled release drug products require a dissolution profile with concentration ranges at set sampling points for product assessment. When no significant change (such as a change in the polymorphic form of the crystal) has occurred, an unaltered dissolution-rate profile of a tablet formulation usually indicates constant *in vivo* bioavailability.

Uniformity of weight, odor, texture, drug and moisture contents, and humidity effect may also be studied during a tablet stability test.

Gelatin capsules

Hard gelatin capsules are the type used by pharmaceutical manufacturers in the production of the majority of their capsule products. The pharmacist in the extemporaneous compounding of prescriptions may also use hard gelatin capsules. Soft gelatin capsules are prepared from shells of gelatin to which glycerin or a polyhydric alcohol such as sorbitol has been added to render the gelatin elastic or plastic-like. Gelatin is stable in air when dry but is subject to microbial decomposition when it becomes moist or when it is maintained in aqueous solution. Normally hard gelatin capsules contain between 13% and 16% moisture. If stored in a high humidity environment capsule shells may soften, stick together or become distorted and lose their shape. On the other hand, in an environment of extreme dryness, gelatin capsules may harden and crack under slight pressure. Gelatin capsules should be protected from sources of microbial contamination. Encapsulated products, like all other dosage forms, must be packaged properly.

Because moisture may be absorbed or released by gelatin capsules depending on the environmental conditions, little physical protection is offered to hygroscopic or deliquescent materials enclosed within a capsule when stored in an area of high humidity. It is not uncommon to find capsules packaged in containers along with a packet of desiccant material as a precautionary measure.

Dissolution development and requirements for capsules are similar to tablets. The capsule shell can affect dissolution test results but not be relevant to bioavailability. Both hard and soft gelatin capsules exposed to excessive heat and moisture may exhibit delayed or incomplete dissolution due to cross-linking of the gelatin in the capsule shell. The cross-linking of gelatin capsules is an irreversible chemical reaction. Cross-linking may also occur in capsules that are exposed to aldehydes and peroxides. Although cross-linked capsules may fail dissolution due to pellicle formation, digestive enzymes will dissolve the capsules. For hard or soft gelatin capsules that do not conform to the dissolution specification, the dissolution test may be repeated with the addition of enzymes. Where water or a medium with a pH less than 6.8 is specified as the medium in the individual monograph, the same medium specified may be used with the addition of purified pepsin that results in an activity of 750,000 units or less per 1000 mL. For media with a pH of 6.8 or greater, pancreatin can be added to produce not more than 1750 USP units of protease activity per 1000 mL.

Suspensions

A stable suspension can be redispersed homogeneously with moderate shaking and can be poured easily throughout its shelf life, with neither the particle size distribution, the crystal form, nor the physiological availability of the suspended active ingredient changing appreciably with time.

Most stable pharmaceutical suspensions are flocculated; that is, the suspended particles are bonded together physically to form a loose, semi-rigid structure. The particles are said to uphold each other while

exerting no significant force on the liquid. Sedimented particles of a flocculated suspension can be redispersed easily at any time with only moderate shaking.

In non-flocculated suspensions, the particles remain as individuals unaffected by neighboring particles and are affected only by the suspension vehicle. These particles, which are smaller and lighter, settle slowly, Once they have settled, they often form a hard, difficult-to-disperse sediment. Non-flocculated suspensions can be made acceptable by decreasing the particle size of the suspended material or by increasing the density and viscosity of the vehicle, thus reducing the possibility of settling.

When studying the stability of a suspension, a differential manometer is used to determine if the suspension is flocculated. If the suspension is flocculated, the liquid will travel the same distance in the two side arms. With non-flocculated suspensions, the hydrostatic pressures in the two arms are unequal; hence, the liquids will be at different levels.

The history of settling of the particles of a suspension may be followed by a Brookfield viscometer fitted with a Helipath attachment. This instrument consists of a rotating T-bar spindle that descends slowly into the suspension as it rotates. The dial reading on the viscometer is a measure of the resistance that the spindle encounters at various levels of the sedimented suspension. This test must be run only on fresh, undisturbed samples.

An electronic particle counter and sizer, such as a Coulter counter, or a microscope may be used to determine changes in particle size distribution. Crystal form alterations may be detected by microscopic, near-IR or Raman examination and, when suspected, must be confirmed by X-ray powder diffraction.

All suspensions should be subjected to cycling temperature conditions to determine the tendency for crystal growth to occur within the suspension. Shipping tests, namely transporting bottles across the country by rail or truck, are also used to study the stability of suspensions.

Solutions

A stable solution retains its original clarity, color, and odor throughout its shelf life. Retention of clarity of a solution is a main concern of a physical stability program. As visual observation alone under ordinary light is a poor test of clarity, a microscope light should be projected through a diaphragm into the solution. Undissolved particles will scatter the light, and the solution will appear hazy. Although the Coulter counter also can be used, light-scattering instruments are the most sensitive means of following solution clarity.

Solutions should remain clear over a relatively wide temperature range such as 4 to 47°C. At the lower range an ingredient may precipitate due to its lower solubility at that temperature, whereas at the higher temperature the flaking of particles from the glass containers or rubber closures may destroy homogeneity. Thus, solutions should be subjected to cycling temperature conditions.

The stability program for solutions also should include a study of pH changes, especially when the active ingredients are soluble salts of insoluble acids or bases. Among other tests are observations for changes in odor, appearance, color, taste, light-stability, pourability, viscosity, isotonicity, gas evolution, microbial stability, specific gravity, surface tension, and pyrogen content, in the case of parenteral products.

When solutions are filtered, the filter medium may absorb some of the ingredients from the solution. Thus, the same type of filter should be used for preparing the stability samples as will be used to prepare the production-size batches.

For dry-packaged formulations reconstituted prior to use, the visual appearance should be observed on both the original dry material and on the reconstituted preparation. The color and odor of the cake, the color and odor of the solution, the moisture content of the cake, and the rate of reconstitution should be followed as a part of its stability profile.

Emulsions

A stable emulsion can be redispersed homogeneously to its original state with moderate shaking and can be poured at any stage of its shelf life. Although most of the important pharmaceutical emulsions are of the oil in water (O/W) type, many stability test methods can be applied to either an O/W or water in oil (W/O) emulsion.

Two simple tests are used to screen emulsion formulations. First, heating to 50 to 70°C and observing its gross physical stability either visually or by turbidimetric measurements can determine the stability of an

emulsion. Usually the emulsion that is the most stable to heat is the one most stable at room temperature. However, this may not be true always, because an emulsion at 60°C may not be the same as it is at room temperature. Second, the stability of the emulsion can be estimated by the *coalescence time* test. Although this is only a rough quantitative test, it is useful for detecting gross differences in emulsion stability at room temperature.

Emulsions also should be subjected to refrigeration temperatures. An emulsion stable at room temperature has been found to be unstable at 4°C. It was reasoned that an oil-soluble emulsifier precipitated at the lower temperature and disrupted the system. An emulsion chilled to the extent that the aqueous base crystallizes is damaged irreversibly.

The ultracentrifuge also is used to determine emulsion stability. When the amount of separated oil is plotted against the time of centrifugation, a plateau curve is obtained. A linear graph results when the oil flotation (creaming) rate is plotted versus the square of the number of centrifuge revolutions per minute. The flotation rate is represented by the slope of the line resulting when the log distance of emulsion–water boundary from the rotor center is plotted against time for each revolution per minute.

For stability studies, two batches of an emulsion should be made at one time on two different sizes of equipment. One should be a bench-size lot and the other a larger, preferably production-size, batch. Different types of homogenizers produce different results, and different sizes of the same kind of homogenizer can yield emulsions with different characteristics.

Ointments

Ointments have been defined as high-viscosity suspensions of active ingredients in a non-reacting vehicle. A stable ointment is one that retains its homogeneity throughout its shelf life period. The main stability problems observed in ointments are *bleeding* and changes in consistency due to aging or changes in temperature. When fluid components such as mineral oil separate at the top of an ointment, the phenomenon is known as *bleeding* and can be observed visually. Unfortunately, as there is no known way to accelerate this event, the tendency to *bleed* cannot be predicted.

An ointment that is too soft is messy to use, whereas one that is very stiff is difficult to extrude and apply. Hence, it is important to be able o define quantitatively the consistency of an ointment. This may be done with a penetrometer, an apparatus that allows a pointed weight to penetrate into the sample under a measurable force. The depth of the penetration is a measure of the consistency of an ointment. Consistency also can be measured by the Helipath attachment to a high-viscosity viscometer or by a Burrell Severs rheometer. In the latter instrument the ointment is loaded into a cylinder and extruded with a measured force. The amount extruded is a measure of the consistency of the ointment.

Ointments have a considerable degree of structure that requires a minimum of 48 hours to develop after preparation. As rheological data on a freshly made ointment may be erroneous, such tests should be performed only after the ointment has achieved equilibrium. Slight changes in temperature (1 or 2°C) can affect the consistency of an ointment greatly; hence, rheological studies on ointments must be performed only at constant and controlled temperatures.

Among the other tests performed during the stability study of an ointment are a check of visual appearance, color, odor, viscosity, softening range, consistency, homogeneity, particle size distribution, and sterility. Undissolved components of an ointment may change in crystal form or in size with time. Microscopic examination or an X-ray diffraction measurement may be used to monitor these parameters.

In some instances it is necessary to use an ointment base that is less than ideal, to achieve the required stability. For example, drugs that hydrolyze rapidly are more stable in a hydrocarbon base than in a base containing water, even though they may be more effective in the latter.

Transdermal patches

A typical transdermal patches consist of a protective backing, a matrix containing active drug, an adhesive that allows the patch to adhere to the skin and a release liner to protect the skin adhering adhesive. Therefore, the transdermal patch must deliver drug as labeled, adhere properly to both the backing and to the patient's skin. In addition, the transdermal patch must be pharmaceutically elegant through the shelf life of the product. For a transdermal patch, this means that the release line peels easily with minimal

transfer of adhesive onto the release liner and that the adhesive does not ooze from the sides of the patch. Therefore, the typical stability related tests for transdermal patches are appearance, assay, impurities, drug release per USP<724>, and backing peel force.

Metered-dose aerosols drug products

A metered dose inhalation product comprises an aerosol can containing a propellant and drug, and a mouthpiece used to present an aerosolized drug to the patient. There are many drug contact components in a metered-dose inhalation product. Therefore, the drug may be in contact with materials that could allow plasticizer leach into the propellant. The typical stability related tests for metered-dose aerosols include appearance, assay, impurities, plume geometry, emitted dose, particle size distribution of the emitted dose, and number of doses per unit. In addition, stability studies on leachables may be required. Shelf life of metered-dose aerosols drug products may also be dependent on the orientation that the drug product is stored. Typically most canister type products are tested at least in the upright orientation.

Dry-powdered inhalation products

A dry-powdered inhalation product consists of drug with excipients delivered in a dry powdered form. The delivery system for a dry-powdered inhalation product may be a separate device or integrated with the active. A dry-powdered dosage must reproducibly deliver a specific amount of drug at a particle size that can be deposited into the lungs. Particles too large will get trapped in the throat and particles too small will just be carried out of the lungs on the next expiration. The typical stability related tests for dry powder inhalation products include appearance, assay, impurities, emitted dose, particle size distribution of the emitted dose, and water content.

Nasal inhalation products

A nasal inhalation product consists of drug with excipients delivered from a delivery system. The delivery system for a nasal inhalation product may be a separate device or integrated with the active. A nasal inhalation product must reproducibly deliver a specific amount of drug at a particle size and plume that can be deposited into the nasal membrane. Particles too large will not be absorbed into nasal membrane or run out of the nose and poor spray pattern will deposit the drug ineffectively in the nasal cavity. The typical stability related tests for nasal inhalation products include appearance, assay, impurities, spray content uniformity, particle (droplet) size distribution of the emitted dose, spray pattern or/and plume geometry, leachables, weight loss and preservative content. Sterility and microbial testing may be required periodically for stability testing.

Incompatibility

Typically, physicochemical stability is assessed at the preformulation stage of development. A drug substance candidate is treated with acid, base, heat, light, and oxidative conditions to assess its inherent chemical stability. Binary mixtures of the drug substance with individual excipients are also investigated at the preformulation stage. These tests are performed to determine the drug substance sensitivity to degradation or reactivity with common pharmaceutical excipients. The most common reactions observed for drug substances from these tests include: hydrolysis, epimerization (racemization), decarboxylation, dehydration, oxidation, polymerization, photochemical decomposition and addition. All drug substances have the potential to degrade by at least one of the reactions mentioned above. With an understanding of the stability/reactivity of a drug substance in the preformulation stage, it is possible to formulate the drug product to minimize drug decomposition. Numerous examples are described in other sections of this book, and the literature is replete with illustrations.

Although undesirable reactions between two or more drugs are said to result in a *physical, chemical*, or *therapeutic* incompatibility, physical incompatibility is somewhat of a misnomer. It has been defined as a physical or chemical interaction between two or more ingredients that leads to a visibly recognizable change. The latter may be in the form of a gross precipitate, haze, or color change.

On the other hand, a chemical incompatibility is classified as a reaction in which a visible change is not necessarily observed. Since there is no visible evidence of deterioration, this type of incompatibility requires trained, knowledgeable personnel to recognize it.

A therapeutic incompatibility has been defined as an undesirable pharmacological interaction between two or more ingredients that leads to:

1. Potentiation of the therapeutic effects of the ingredients.
2. Destruction of the effectiveness of one or more of the ingredients.
3. Occurrence of a toxic manifestation within the patient.

Chemical reactions

The most frequently encountered chemical reactions, which may occur within a pharmaceutical product, are described below.

Oxidation–reduction

Oxidation is a prime cause of product instability, and often, but not always, the addition of oxygen or the removal of hydrogen is involved. When molecular oxygen is involved, the reaction is known as autoxidation because it occurs spontaneously, though slowly, at room temperature.

Oxidation, or the loss of electrons from an atom, frequently involves free radicals and subsequent chain reactions. Only a very small amount of oxygen is required to initiate a chain reaction. In practice, it is easy to remove most of the oxygen from a container, but very difficult to remove it all. Hence, nitrogen and carbon dioxide frequently are used to displace the headspace air in pharmaceutical containers to help minimize deterioration by oxidation.

As an oxidation reaction is complicated, it is difficult to perform a kinetic study on oxidative processes within a general stability program. The redox potential, which is constant and relatively easy to determine, can, however, provide valuable predictive information. In many oxidative reactions, the rate is proportional to the concentration of the oxidizing species but may be independent of the concentration of the oxygen present. The rate is influenced by temperature, radiation, and the presence of a catalyst. An increase in temperature leads to an acceleration in the rate of oxidation. If the storage temperature of a preparation can be reduced to between 0 and 5°C, usually it can be assumed that the rate of oxidation will be at least halved.

The molecular structures most likely to oxidize are those with a hydroxyl group directly bonded to an aromatic ring (e.g., phenol derivatives such as catecholamines and morphine), conjugated dienes (e.g., vitamin A and unsaturated free fatty acids), heterocyclic aromatic rings, nitroso and nitrite derivatives, and aldehydes (e.g., flavorings). Products of oxidation usually lack therapeutic activity. Visual identification of oxidation, for example, the change from colorless epinephrine to its amber colored products, may not be visible in some dilutions or to some eyes.

Oxidation is catalyzed by pH values that are higher than optimum, polyvalent heavy metal ions (e.g., copper and iron), and exposure to oxygen and UV illumination. The latter two causes of oxidation justify the use of antioxidant chemicals, nitrogen atmospheres during ampoule and vial filling, opaque external packaging, and transparent amber glass or plastic containers.

Trace amounts of heavy metals such as cupric, chromic, ferrous, or ferric ions may catalyze oxidation reactions. As little as 0.2 mg of copper ion per liter considerably reduces the stability of penicillin. Similar examples include the deterioration of epinephrine, phenylephrine, lincomycin, isoprenaline, and procaine hydrochloride. Adding chelating agents to water to sequester heavy metals and working in special manufacturing equipment (e.g., glass) are some means used to reduce the influence of heavy metals on a formulation. Parenteral formulations should not come in contact with heavy metal ions during their manufacture, packaging, or storage.

Hydronium and hydroxyl ions catalyze oxidative reactions. The rate of decomposition for epinephrine, for example, is more rapid in a neutral or alkaline solution with maximum stability (minimum oxidative decomposition) at pH 3.4. There is a pH range for maximum stability for any antibiotic and vitamin preparation, which usually can be achieved by adding an acid, alkali, or buffer.

Oxidation may be inhibited by the use of antioxidants, called negative catalysts. They are very effective in stabilizing pharmaceutical products undergoing a free-radical-mediated chain reaction. These substances, which are easily oxidizable, act by possessing lower oxidation potentials than the active ingredient. Thus, they undergo preferential degradation or act as chain inhibitors of free radicals by providing an

electron and receiving the excess energy possessed by the activated molecule.

The ideal antioxidant should be stable and effective over a wide pH range, soluble in its oxidized form, colorless, nontoxic, nonvolatile, nonirritating, effective in low concentrations, thermostable, and compatible with the container-closure system and formulation ingredients.

The commonly used antioxidants for aqueous systems include sodium sulfite, sodium metabisulfite, sodium bisulfite, sodium thiosulfate, and ascorbic acid. For oil systems, ascorbyl palmitate, hydroquinone, propyl gallate, nordihydroguaiaretic acid, butylated hydroxytoluene, butylated hydroxyanisole, and alpha-tocopherol are employed.

Synergists, which increase the activity of antioxidants, are generally organic compounds that complex small amounts of heavy metal ions. These include the ethylenediamine tetraacetic acid (EDTA) derivatives, dihydroethylglycine, and citric, tartaric, gluconic, and saccharic acids. EDTA has been used to stabilize ascorbic acid, oxytetracycline, penicillin, epinephrine, and prednisolone.

Reduction reactions are much less common than oxidative processes in pharmaceutical practice. Examples include the reduction of gold, silver, or mercury salts by light to form the corresponding free metal.

Hydrolysis

Drugs containing the following functional groups: esters (e.g., cocaine, physostigmine, aspirin, tetracaine, procaine, and methyldopa), amides (e.g., dibucaine), imides (e.g., amobarbital), imines (e.g., diazepam), and lactam (e.g., penicillins, cephalosporins) are among those prone to hydrolysis.

Hydrolysis reactions are often pH dependent and are catalyzed by either hydronium ion or hydroxide ions (specific-acid or specific-base catalysis, respectively). Hydrolysis reactions can also be catalyzed by either a Brønsted acid or a Brønsted base (general-acid or general-base catalysis, respectively). Sources of Brønsted acid or base include buffers and some excipients. Sometimes it is necessary to compromise between the optimum pH for stability and that for pharmacological activity. For example, several local anesthetics are most stable at a distinctly acid pH, whereas for maximum activity they should be neutral or slightly alkaline. Small amounts of acids, alkalis, or buffers are used to adjust the pH of a formulation. Buffers are used when small changes in pH are likely to cause major degradation of the active ingredient.

Obviously, the amount of water present can have a profound effect on the rate of a hydrolysis reaction. When the reaction takes place fairly rapidly in water, other solvents sometimes can be substituted. For example, barbiturates are much more stable at room temperature in propylene glycol–water than in water alone.

Modification of chemical structure may be used to retard hydrolysis. In general, as it is only the fraction of the drug in solution that hydrolyzes, a compound may be stabilized by reducing its solubility. This can be done by adding various substituents to the alkyl or acyl chain of aliphatic or aromatic esters or to the ring of an aromatic ester. In some cases less-soluble salts or esters of the parent compound have been found to aid product stability. Steric and polar complexation has also been employed to alter the rate of hydrolysis. Caffeine reduces the rate of hydrolysis and thus promotes stability by complexation with local anesthetics such as benzocaine, procaine, or tetracaine.

Esters and beta-lactams are the chemical bonds that are most likely to hydrolyze in the presence of water. For example, the acetyl ester in aspirin is hydrolyzed to acetic acid and salicylic acid in the presence of moisture, but in a dry environment the hydrolysis of aspirin is negligible. The aspirin hydrolysis rate increases in direct proportion to the water vapor pressure in an environment.

The amide bond also hydrolyzes, though generally at a slower rate than comparable esters. For example, procaine (an ester) will hydrolyze upon autoclaving, but procainamide will not. The amide or peptide bond in peptides and proteins varies in the lability to hydrolysis. The lactam and azomethine (or imine) bonds in benzodiazepines are also labile to hydrolysis. The major chemical accelerators or catalysts of hydrolysis are adverse pH and specific chemicals (e.g., dextrose and copper in the case of ampicillin hydrolysis).

The rate of hydrolysis depends on the temperature and the pH of the solution. A much-quoted estimation is that for each 10°C rise in storage temperature, the rate of reaction doubles or triples. As this is an empiricism, it is not always applicable.

When hydrolysis occurs, the concentration of the active ingredient decreases while the concentration of the decomposition products increases. The effect of this change on the rate of the reaction depends on the order of the reaction. With zero-order reactions the rate of decomposition is independent of concentration of the ingredient. Although weak solutions decompose at the same absolute rate as stronger ones, the weaker the solution, the greater the proportion of active ingredient destroyed in a given time; i.e., the percentage of decomposition is greater in weaker solutions. Increasing the concentration of an active ingredient that is hydrolyzing by zero-order kinetics will slow the percentage decomposition.

With first-order reactions, which occur frequently in the hydrolysis of drugs, the rate of change is directly proportional to the concentration of the reactive substance. Thus, changes in the concentration of the active ingredient have no influence on the percentage decomposition.

The degradation of many drugs in solution accelerates or decelerates exponentially as the pH is decreased or increased over a specific range of pH values. Improper pH ranks with exposure to elevated temperature as a factor most likely to cause a clinically significant loss of drug, resulting from hydrolysis and oxidation reactions. A drug solution or suspension, for example, may be stable for days, weeks, or even years in its original formulation, but when mixed with another liquid that changes the pH, it may degrade in minutes or days. It is possible that a pH change of only one unit (e.g., from 4 to 3 or 8 to 9) could decrease drug stability by a factor of ten or greater.

A pH-buffer system, which is usually a weak acid or base and its salt, are common excipients used in liquid preparations to maintain the pH in a range that minimizes the drug degradation rate. The pH of drug solutions may also be either buffered or adjusted to achieve drug solubility. For example, pH in relation to pK_a controls the fractions of the usually more soluble ionized and less soluble nonionized species of weak organic electrolytes.

Interionic (ion N^+ – ion N^-) Compatibility

The compatibility or solubility of oppositely charged ions depends mainly on the number of charges per ion and the molecular size of the ions. In general, polyvalent ions of opposite charge are more likely to be incompatible. Thus, an incompatibility is likely to occur upon the addition of a large ion with a charge opposite to that of the drug.

As many hydrolytic reactions are catalyzed by both hydronium and hydroxyl ions, pH is an important factor in determining the rate of a reaction. The pH range of minimum decomposition (or maximum stability) depends on the ion having the greatest effect on the reaction. If the minimum occurs at about pH 7, the two ions are of equal effect. A shift of the minimum toward the acid side indicates that the hydroxyl ion has the stronger catalytic effect and *vice versa* in the case of a shift toward the alkaline side. In general, hydroxyl ions have the stronger effect. Thus, the minimum is often found between pH 3 and 4.

The influence of pH on the physical stability of two-phase systems, especially emulsions, is also important. For example, intravenous fat emulsion is destabilized by acidic pH.

Decarboxylation

Pyrolytic solid-state degradation through decarboxylation usually is not encountered in pharmacy, as relatively high heats of activation (25 to 30 kcal) are required for the reaction. However, solid *p*-aminosalicylic acid undergoes pyrolytic degradation to *m*-aminophenol and carbon dioxide. The reaction, which follows first-order kinetics, is highly pH-dependent and is catalyzed by hydronium ions. The decarboxylation of *p*-aminobenzoic acid occurs only at extremely low pH values and at high temperatures. Some dissolved carboxylic acids, such as *p*-aminosalicylic acid, lose carbon dioxide from the carboxyl group when heated. The resulting product has reduced pharmacological potency. Beta-K decarboxylation can occur in some solid antibiotics that have a carbonyl group on the beta-carbon of a carboxylic acid or a carboxylate anion. Such decarboxylations will occur in the following antibiotics: carbenicillin sodium, carbenicillin free acid, ticarcillin sodium, and ticarcillin free acid.

Racemization

Racemization, or the action or process of changing from an optically active compound into a racemic compound or an optically inactive mixture of corresponding *R* (*rectus*) and *S* (*sinister*) forms, is a

major consideration in pharmaceutical stability. Optical activity of a compound may be monitored by polarimetry and reported in terms of specific rotation. Chiral HPLC has been used in addition to polarimetry to confirm the enantiomeric purity of a sample.

Epimerization

Members of the tetracycline family are most likely to incur epimerization. This reaction occurs rapidly when the dissolved drug is exposed to a pH of an intermediate range (higher than 3), and it results in the steric rearrangement of the dimethylamino group. The epimer of tetracycline, epitetracycline, has little or no antibacterial activity.

In general, racemization follows first-order kinetics and depends on temperature, solvent, catalyst, and the presence or absence of light. Racemization appears to depend on the functional group bound to the asymmetric carbon atom, with aromatic groups tending to accelerate the process.

Photochemical reactions

Photolytic degradation can be an important limiting factor in the stability of pharmaceuticals. A drug can be affected chemically by radiation of a particular wavelength only if it absorbs radiation at that wavelength and the energy exceeds a threshold. Ultraviolet (UV) radiation, which has a high energy level, is the cause of many degradation reactions. Exposure to, primarily, UV illumination may cause oxidation (photo-oxidation) and scission (photolysis) of covalent bonds. Nifedipine, nitroprusside, riboflavin, and phenothiazines are very labile to photo-oxidation. In susceptible compounds, photochemical energy creates free radical intermediates, which can perpetuate chain reactions.

If the absorbing molecule reacts, the reaction is said to be photochemical in nature. When the absorbing molecules do not participate directly in the reaction, but pass their energy to other reacting molecules, the absorbing substance is said to be a photosensitizer.

As many variables may be involved in a photochemical reaction, the kinetics can be quite complex. The intensity and wavelength of the light and the size, shape, composition, and color of the container may affect the velocity of the reaction.

The photodegradation of chlorpromazine through a semiquinone free-radical intermediate follows zero-order kinetics. On the other hand, alcoholic solutions of hydrocortisone, prednisolone, and methylprednisolone degrade by reactions following first-order kinetics.

Colored-glass containers most commonly are used to protect light-sensitive formulations. Yellow-green glass gives the best protection in the UV region, whereas amber confers considerable protection from UV radiation but little from infrared (IR) radiation. Riboflavin is best protected by a stabilizer that has a hydroxyl group attached to or near the aromatic ring. The photodegradation of sulfacetamide solutions may be inhibited by an antioxidant such as sodium thiosulfate or metabisulfite.

A systematic approach to photostability testing is recommended covering, as appropriate, studies such as tests on the drug substance, tests on the exposed drug product outside of the immediate pack; and if necessary, tests on the drug product in the immediate pack. The ICH Q1B Guidance[28] discusses the minimum requirements for assessing photostability. Drug substance is first assessed by exposing sample powder having a depth of not more than 3 mm to an overall illumination of not less than 1.2 million lux hours and an integrated near-UV energy of not less than 200 watt hours/square meter. If the drug substance shows sensitivity to photodegration, then the drug product will need to be tested as well. The testing of drug product uses the same light exposure that was used to test drug substance. The drug product should be tested directly exposed to light and in its container closure system.

Ultrasonic energy

Ultrasonic energy, which consists of vibrations and waves with frequencies greater than 20,000 Hz, promotes the formation of free radicals and alters drug molecules. Changes in prednisolone, prednisone acetate, or deoxycorticosterone acetate suspensions in an ultrasonic field have been observed spectrometrically in the side chain at C-17 and in the oxo group of the A ring. With sodium alginate, in an ultrasonic field, it has been reported that above a minimum power output, degradation increased linearly with increased power.

Ionizing radiation

Ionizing radiation, particularly gamma rays, has been used for the sterilization of certain pharmaceutical products. At the usual sterilizing dose, 2.5 mRad, it seldom causes appreciable chemical degradation. In general, formulations that are in the solid or frozen state are more resistant to degradation from ionizing radiation than those in liquid form. For example, many of the vitamins are little affected by irradiation in the solid state but are decomposed appreciably in solution. On the other hand, both the liquid- and solid-state forms of atropine sulfate are affected seriously by radiation.

Predicting shelf life

ICH recommended evaluation

The shelf life of a commercial drug product must be determined in the commercial container closure at the defined storage conditions. The FDA and ICH Q1A (R2) Guidances[29] require at least 12 months stability data at the time of submission. Most products require at least 24 months shelf life to be commercially viable. The ICH Q1E Guidance[30] recommends how the 12 months data may be used to predict long-term stability. Figures 6.1 and 6.2 show trending graphs with double-sided and single-sided 95% confidence limits plots, respectively. The expiration of a product is the time where the confidence line intersects with the acceptance limit. Trend analysis of data need only be performed on test data that show a change related to time.

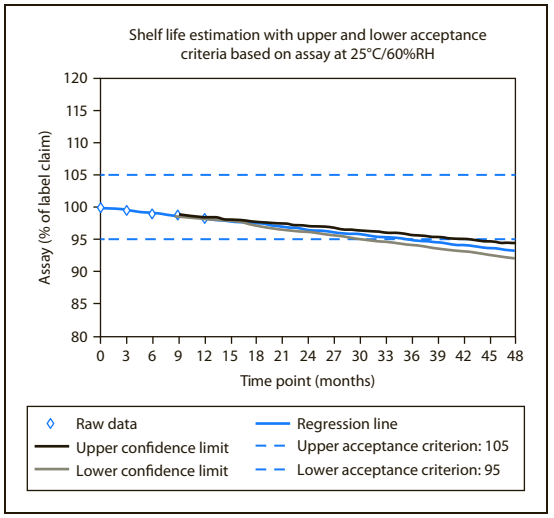

Figure 6.1 Typical two-sided shelf life estimation plot.

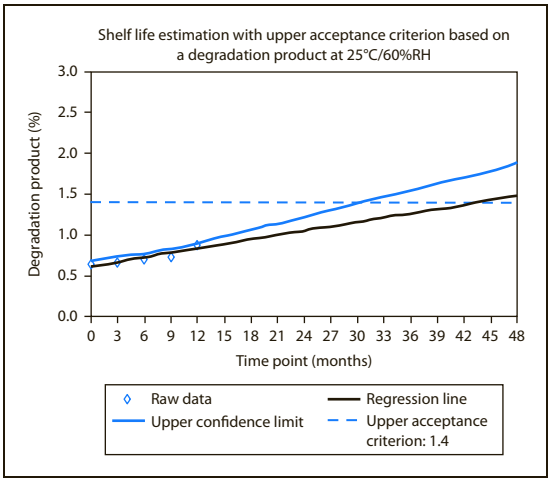

Figure 6.2 Typical one-sided shelf life estimation plot.

Pharmaceutical containers

The official standards for containers apply to articles packaged by either the pharmaceutical manufacturer or the dispensing pharmacist unless otherwise indicated in a compendial monograph. In general, repackaging of pharmaceuticals is inadvisable. However, if repackaging is necessary, the manufacturer of the product should be consulted for potential stability problems.

A pharmaceutical container has been defined as a device that holds the drug and is, or may be, in direct contact with the preparation. The immediate container is described as that which is in direct contact with the drug at all times. The liner and closure traditionally have been considered to be part of the container system. The container should not interact physically or chemically with the formulation so as to alter the strength, quality, or purity of its contents beyond permissible limits.

The choice of containers and closures can have a profound effect on the stability of many pharmaceuticals. Now that a large variety of glass, plastics, rubber closures, tubes, tube liners, etc. are available, the possibilities for interaction between the packaging components and the formulation ingredients are immense. Some of the packaging elements themselves

are subject to physical and chemical changes that may be time–temperature dependent.

Frequently, it is necessary to use a well-closed or a tight container to protect a pharmaceutical product. A *well-closed container* is used to protect the contents from extraneous solids or a loss in potency of the active ingredient under normal commercial conditions. A *tight container* protects the contents from contamination by extraneous materials, loss of contents, efflorescence, deliquescence, or evaporation and is capable of tight re-closure. When the packaging and storage of an official article in a well-closed or tight container is specified, water-permeation tests should be performed on the selected container.

In a stability program, the appearance of the container, with special emphasis on the inner walls, the migration of ingredients onto/into the plastic or into the rubber closure, the migration of plasticizer or components from the rubber closure into the formulation, the possibility of two-way moisture penetration through the container walls, the integrity of the tac-seal, and the back-off torque of the cap, must be studied.

Glass

Traditionally, glass has been the most widely used container for pharmaceutical products to ensure inertness, visibility, strength, rigidity, moisture protection, ease of re-closure, and economy of packaging. Although glass has some disadvantages, such as the leaching of alkali and insoluble flakes into the formulation, these can be offset by the choice of an appropriate glass. As the composition of glass may be varied by the amounts and types of sand and silica added and the heat treatment conditions used, the proper container for any formulation can be selected.

According to USP 35, glass containers suitable for packaging pharmacopeial preparations may be classified as either Type I, Type II, Type III, or type NP. Containers of Type I borosilicate glass are generally used for preparations that are intended for parenteral administration, although Type II treated soda-lime glass may be used where stability data demonstrate its suitability. Containers of Type III and Type NP are intended for packaging articles intended for oral or topical use.

New, unused glass containers are tested for resistance to attack by high-purity water by use of a sulfuric acid titration to determine the amount of released alkali. Both glass and plastic containers are used to protect light-sensitive formulations from degradation. The amount of transmitted light is measured using a spectrometer of suitable sensitivity and accuracy.

Glass is generally available in flint, amber, blue, emerald green, and certain light-resistant green and opal colors. The blue-, green-, and flint-colored glasses, which transmit UV and violet light rays, do not meet the official specifications for light-resistant containers.

Colored glass usually is not used for injectable preparations, since it is difficult to detect the presence of discoloration and particulate matter in the formulations. Light-sensitive drugs for parenteral use usually are sealed in flint ampoules and placed in a box. Multiple-dose vials should be stored in a dark place.

Manufacturers of prescription drug products should include sufficient information on their product labels to inform the pharmacist of the type of dispensing container needed to maintain the identity, strength, quality, and purity of the product. This brief description of the proper container, such as light-resistant, well-closed, or tight, may be omitted for those products dispensed in the manufacturer's original container.

Plastics

Plastic containers have become very popular for storing pharmaceutical products. Polyethylene, polystyrene, polyvinyl chloride, and polypropylene are used to prepare plastic containers of various densities to fit specific formulation needs.

Factors such as plastic composition, processing and cleaning procedures, contacting media, inks, adhesives, absorption, adsorption, and permeability of preservatives also affect the suitability of a plastic for pharmaceutical use. Hence, biological test procedures are used to determine the suitability of a plastic for packaging products intended for parenteral use and for polymers intended for use in implants and medical devices. Systemic injection and intracutaneous and implantation tests are employed. In addition, tests for nonvolatile residue, residue on

ignition, heavy metals, and buffering capacity were designed to determine the physical and chemical properties of plastics and their extracts.

The high-density polyethylene (HDPE) containers, which are used for packaging capsules and tablets, possess characteristic thermal properties, a distinctive IR absorption spectrum, and a density between 0.941 and 0.965 g/cm^3. In addition, these containers are tested for light transmission, water-vapor permeation, extractable substances, nonvolatile residue, and heavy metals. When a stability study has been performed to establish the expiration date for a dosage form in an acceptable HDPE container, any other HDPE container may be substituted provided that it, too, meets compendial standards and that the stability program is expanded to include the alternative container.

Materials from the plastic itself can leach into the formulation, and materials from the latter can be absorbed onto, into, or through the container wall. The barrels of some plastic syringes bind various pharmaceutical preservatives. However, changing the composition of the syringe barrel from nylon to polyethylene or polystyrene has eliminated the binding in some cases.

A major disadvantage of plastic containers is the two-way permeation or *breathing* through the container walls. Volatile oils and flavoring and perfume agents are permeable through plastics to varying degrees. Components of emulsions and creams have been reported to migrate through the walls of some plastics, causing either a deleterious change in the formulation or collapse of the container. Loss of moisture from a formulation is common. Gases, such as oxygen or carbon dioxide in the air, have been known to migrate through container walls and affect a preparation.

Solid dosage forms, such as penicillin tablets, when stored in some plastics, are affected deleteriously by moisture penetration from the atmosphere into the container.

Single unit does packaging in the form of blister packages are often used to package capsule and tablet dosage forms. A typical blister package comprises a polymeric film that is molded to have a cavity into which the dosage form is placed. The polymer film is then heat bonded to a paper backed foil liner.

As with plastic bottles, the blister package will allow a certain amount of moisture vapor permeation to occur, and this must be a consideration when selecting the type of film used for the package. The choice of packaging materials used depends on the degree to which the product needs to be protected from light, heat, and moisture. Each material has different resistance to each of these elements and will affect the shelf life and storage conditions of the packaged pharmaceutical.

Polyvinylchloride (PVC) offers the least resistance to moisture vapor permeation. Polyvinylidenechloride (PVdC) has characteristics similar to PVC but offers superior resistance to moisture vapor permeation. Aclar, which is a polychlorotrifluoroethylene (PVC-CTFE) film has the lowest water vapor permeability and thus offers the best protection from moisture.

Metals

The pharmaceutical industry was, and to a degree still is, a tin stronghold. However, as the price of tin constantly varies, more-collapsible aluminum tubes are being used.

A variety of internal linings and closure fold seals are available for both tin and aluminum tubes. Tin tubes can be coated with wax or with vinyl linings. Aluminum tubes are available with lining of epoxy or phenolic resin, wax, vinyl, or a combination of epoxy or phenolic resin with wax. As aluminum is able to withstand the high temperatures required to cure epoxy and phenolic resins adequately, tubes made from this metal presently offer the widest range of lining possibilities.

Closure fold seals may consist of unmodified vinyl resin or plasticized cellulose and resin, with or without added color.

Collapsible tubes are available in many combinations of diameters, lengths, openings, and caps. Custom-use tips for ophthalmic, nasal, mastitis, and rectal applications also are available. Only a limited number of internal liners and closure seals are available for tubes fitted with these special-use tips.

Lined tubes from different manufacturers are not necessarily interchangeable. Although some converted resin liners may be composed of the same base resin, the actual liner may have been modified to achieve better adhesion, flow properties, drying qualities, or

flexibility. These modifications may have been necessitated by the method of applying the liner, the curing procedure, or, finally, the nature of the liner itself.

Closures

The closures for the formulations also must be studied as a portion of the overall stability program. Although the closure must form an effective seal for the container, the closure must not react chemically or physically with the product. It must not absorb materials from the formulation or leach its ingredients into the contents.

The integrity of the seal between the closure and container depends on the geometry of the two, the materials used in their construction, the composition of the cap liner, and the tightness with which the cap has been applied. Torque is a measure of the circular force, measured in inch-pounds, which must be applied to open or close a container. When pharmaceutical products are set up on a stability study, the formulation must be in the proposed market package. Thus, they should be capped with essentially the same torque to be used in the manufacturing step.

Rubber is a common component of stoppers, cap liners, and parts of dropper assemblies. Sorption of the active ingredient, preservative, or other formulation ingredients into the rubber and the extraction of one or more components of the rubber into the formulation are common problems.

The application of an epoxy and polytetrafluoroethylene lining to the rubber closure reduces the amount of leached extractives but essentially has no effect on the sorption of the preservative from the solution. Polytetrafluoroethylene-coated rubber stoppers may prevent most of the sorption and leaching.

Bioavailability and bioequivalence testing

Introduction

Understanding the concepts of bioavailability and bioequivalence testing is essential in the drug development process because they create the foundation for regulatory decision making when evaluating formulation changes and lot-to-lot consistency in innovator products. They also serve as the primary components to demonstrate therapeutic equivalence between generic products and the reference innovator product.

Changes in bioavailability can be thought of in terms of changes in exposure to the drug. If these changes are substantial, then they can alter the safety and efficacy profile of the compound in question. The bioavailability of orally administered drugs can be affected by numerous factors. These include food or fed state, differences in drug metabolism, drug–drug interactions, gastrointestinal transit time, and changes in dosage form release characteristics (especially for modified release products).

Bioequivalence is an important consideration in ensuring lot-to-lot consistency, including whenever evaluating changes in a marketed product's formulation, manufacturing process, and dosage strength. Bioequivalence is also critical in regulatory authority decision making when determining whether a generic product is therapeutically equivalent to the original innovator product.

In addition, chemical equivalence, lot-to-lot uniformity of physicochemical characteristics, and stability equivalence are other factors that are important, as they too can affect product quality. Also, bioavailability and bioequivalence topics are emphasized for solid oral dosage forms. However, many of the general concepts can also be applied to other dosage forms, including biologics.

General concepts

The terms used in this section require careful definition, since, as in any area, some terms have been used in different contexts by different authors.

Bioavailability is a term that indicates measurement of both the rate of drug absorption and the total amount (extent) of drug that reaches the systemic circulation from an administered dosage form. It is specific to the parent or active drug substance as contrasted to metabolites.

Equivalence is more a general and relative term that indicates a comparison of one drug product with another. Equivalence may be defined in several ways:

- *Bioequivalence* indicates that a drug in two or more similar dosage forms reaches the systemic circulation at the same relative rate and extent (i.e.,

the plasma level profiles of the drug obtained using the two dosage forms are the same).

- *Chemical equivalence* considers that two or more dosage forms contain the same labeled quantities (within specified limits) of the drug.
- *Clinical equivalence* occurs when the same drug from two or more dosage forms gives identical *in vivo* effects as measured by a pharmacological response or by control of a symptom or disease.
- *Pharmaceutical equivalence* refers to two drug products with the same dosage form and same strength.
- *Therapeutic equivalence* implies that two brands of a drug product are expected to yield the same clinical result. The FDA specifically uses the term "therapeutic equivalence" in the evaluation of multi-source prescription drug products (generic drugs).

Area under the Concentration–Time Curve (AUC) is the integral of the concentration–time curve after administration of a single dose of drug or after achieving a steady state. The calculated area under the serum, blood, or plasma concentration–time curve is reported in amount/volume multiplied by time (e.g., μg/mL × h or g/100 mL × h) and can be considered representative of the amount of drug absorbed. Several variants of AUC exist, including $AUC_{0\text{-}t}$; $AUC_{0\text{-}\infty}$; and $AUC_{\tau,\,ss}$, corresponding to the calculated area from time zero to a truncated time point (e.g., $AUC_{0\text{-}48}$), the total area under the curve, and the area when steady state has been achieved.

Peak-height Concentration (C_{max}) is the peak of the blood level–time curve and represents the highest drug concentration achieved after drug administration.

Time of Peak Concentration (T_{max}) is the measured length of time necessary to achieve the maximum concentration (C_{max}) after drug administration.

Bioequivalence testing

The awareness of the potential for clinical differences between otherwise chemically equivalent drug products has been brought about by a multiplicity of factors that include, among others:

- better methods for clinical efficacy evaluation
- development of techniques to measure microgram or nanogram quantities of drugs in biological fluids
- improvements in the technology of dosage form formulation and physical testing
- awareness of reported clinical differences from the literature in otherwise similar products
- increased cost of classical clinical evaluation
- objective and quantitative nature of bioavailability tests
- an increase in the number of chemically equivalent products on the market because of patent expirations and the Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Act), which established the generic drug approval procedures that are in place today.

The increase in the number of drugs that are available from multiple sources frequently has placed people involved in the delivery of healthcare in the position of having to select one from among several marketed products. As with any decision, the more data available, the more comfortable one is in arriving at the final decision. The need to make these choices, in light of the potential failure to demonstrate *in vivo* equivalence between products or different batches of the same product, has increased the demand for quantitative data. Bioequivalence testing represents a bridging alternative to clinical testing for efficacy and safety in such cases and is the means by which generic drugs are approved for marketing. In addition, this is also the means by which the quality of all drug products is maintained in situations involving major changes in formulation or manufacturing process.

Requirements for bioequivalence data on drug products should be applied reasonably. The reason for bioequivalence testing should not be overlooked (i.e., it is used as a surrogate, in certain situations, for the clinical evaluation of drug products). In some instances, bioequivalence data cannot reliably be obtained if the bioanalytical methodology is not available. However, in such cases pharmacodynamic data may provide a more sensitive, objective evaluation of a product's therapeutic equivalence and may be explored as an alternative evaluation method in the absence of relevant bioanalytical methodology.

Basic pharmacokinetic evaluation of bioavailability data is not necessary to show bioequivalence of two drug products. Pharmacokinetics has its major

utility in the prediction or projection of dosage regimens and/or in providing a better understanding of observed drug reactions or interactions that result from the accumulation of drug in some specific site, tissue, or compartment of the body. The basis for the conclusion that two drug products are bioequivalent must be that the drug concentrations measured in a biological matrix, or alternatively the pharmacological response, for one drug product are essentially the same for the second drug product. The more straightforward decisions in the evaluation of bioequivalence between two drug products are those in which the two products are exactly superimposable (definitely bioequivalent). Those in which the two products differ in their bioequivalence parameters by a large amount, such as 50% or more, are most definitely not bioequivalent. Statistical evaluation of the data is necessary for all situations, particularly for data that exist between these two extremes.

Methods for determining bioequivalence

Bioequivalence usually involves human testing but sometimes may be demonstrated using an *in vitro* bioequivalence standard, especially when such an *in vitro* test has been correlated with human *in vivo* bioavailability data. In other situations, bioequivalence may be demonstrated through comparative clinical trials or pharmacodynamic studies.

The FDA has categorized (21CFR320.24) various *in vivo* and *in vitro* approaches that may be utilized to establish bioequivalence. These are, in descending order of accuracy, sensitivity and reproducibility,

1. An *in vivo* test in humans in which the active drug substance, as well as active metabolites when appropriate, is measured in plasma.
2. An *in vitro* test that has been correlated with human *in vivo* bioavailability data. This approach is most likely for oral modified release products and is described in detail in FDA Guidance.
3. An *in vivo* test in animals that has been correlated with human bioavailability data.
4. An *in vivo* test in humans, where urinary excretion of the active drug substance, as well as active metabolites when appropriate, is measured.
5. An *in vivo* test in humans in which an appropriate acute pharmacological effect is measured.
6. Well-controlled clinical trials in humans that establish the safety and efficacy of the drug product, for establishing bioavailability. For bioequivalence, comparative clinical trials may be considered. This approach is the least accurate, sensitive, and reproducible approach, and should be considered only if other approaches are not feasible.
7. A currently available *in vitro* test, acceptable to FDA, that ensures bioavailability. This approach is intended only when *in vitro* testing is deemed adequate, but no *in vitro–in vivo* correlation (IVIVC) has been established. It also can relate to considerations involving the Biopharmaceutics Classification System (BCS).

Most bioequivalence studies involve the direct measurement of the parent drug, as described in item 1 above. Bioequivalence testing in animals is not a recommended approach due to possible differences in metabolism, gastrointestinal physiology, weight, and diet.

Therapeutic equivalence evaluations

The FDA publication *Approved Drug Products with Therapeutic Equivalence Evaluations*[31] identifies drug products approved on the basis of safety and effectiveness. In addition, this list contains therapeutic equivalence evaluations for approved multi-source prescription drug products. These evaluations have been prepared to serve as public information and advice to state health agencies, physicians, and pharmacists to promote public education in the area of drug product selection and to foster containment of healthcare costs.

To help contain drug costs, virtually every state has adopted laws and/or regulations that encourage the substitution of drug products. These state laws generally require either that substitution be limited to drugs on a specific list (the positive formulary approach) or that substitution be permitted for all drugs except those prohibited by a particular list (the negative formulary approach). Because of the number of requests for FDA assistance in preparing both positive and negative formularies, it became apparent that the FDA could not serve the needs of each state on an individual basis. The agency also recognized

that providing a single list based on common criteria would be preferable to evaluating drug products on the basis of differing definitions and criteria in various state laws. The therapeutic equivalence evaluations in this publication reflect FDA's application of specific criteria to the approved multi-source prescription drug products.

FDA classifies as therapeutically equivalent those products that meet the following general criteria:

1. They are approved as safe and effective.
2. They are pharmaceutical equivalents in that they (A) contain identical amounts of the same active drug ingredient in the same dosage form and route of administration and (B) meet compendial or other applicable standards of strength, quality, purity, and identity.
3. They are bioequivalent in that (A) they do not present a known or potential bioequivalence problem, and they meet an acceptable *in vitro* standard, or (B) if they do present such a known or potential problem, they are shown to meet an appropriate bioequivalence standard.
4. They are adequately labeled.
5. They are manufactured in compliance with Current Good Manufacturing Practice regulations.

This concept of therapeutic equivalence applies only to drug products containing the same active ingredient(s) and does not encompass a comparison of different therapeutic agents used for the same condition. The FDA considers drug products to be therapeutically equivalent if they meet the criteria outlined above, even though they may differ in certain other characteristics such as shape, scoring configuration, release mechanisms, packaging, excipients, expiration date/time, and minor aspects of labeling (e.g., the presence of specific pharmacokinetic information). The FDA believes that products classified as therapeutically equivalent can be substituted with the full expectation that the substituted product will produce the same clinical effect and safety profile as the prescribed product.

As described, the concepts of bioavailability and bioequivalence testing are essential in the drug development process by creating the foundation for regulatory decision for both innovator and generic drug products.

Chromatographic methods of analysis

The term "*chromatography*" is derived from Greek, chroma meaning, "*color*," and graphein meaning "*to write*." Mikhail Tswett (1906),[32] a Russian botanist, used the technique to separate various plant pigments by passing solutions of them through glass columns packed with finely divided calcium carbonate. The separated species appeared as colored bands on the column, and based on this phenomenon, this process was called chromatography. The chromatographic technique is now widely used for the separation, identification, and determination of the chemical components in complex mixture.

Chromatography, according to USP, can be defined as a procedure by which solutes are separated by a differential migration process in a system consisting of two or more phases, one of which moves continuously in a given direction and in which the individual substances exhibit different mobilities by reason of differences in adsorption, partition, solubility, vapor pressure, molecular size, or ionic charge density. The individual substances thus obtained can be identified or determined by analytical methods.[33] Thus, the term chromatography can be applied to a group of methods for separating molecular mixtures. One of the phases is a fixed bed of large surface area, whereas the other is a fluid that moves through or over the surface of the fixed phase. The components of the mixture must be of molecular dimensions, which require that they be in solution or in the vapor state. The relative affinity of the solutes for each of the phases must be reversible to ensure that mass transfer occurs during the chromatographic separation. The fixed phase is called the *stationary phase*, and the other is termed the *mobile phase*. The stationary phase may be a porous or finely divided solid or a liquid that has been coated in a thin-layer on an inert supporting material. It is necessary that the stationary phase particles be as small and homogeneous as possible to provide a large surface area so that sorption and desorption of the solutes will occur frequently and efficiently. Depending on the type of chromatography employed, the mobile phase may be a pure liquid or a mixture of solutions (e.g., buffers), or it may be a gas (pure or a homogeneous mixture).

Modern pharmaceutical formulations are complex mixtures including, in addition to one or more medicinally active ingredients, a number of inert materials such as diluents, disintegrants, colors, and flavors. To ensure quality and stability of the final product, the pharmaceutical scientist must be able to separate these mixtures into individual components prior to quantitative analysis. The complex nature of the polymers used in the manufacture of novel drug delivery systems makes the drug separation even more complicated. Moreover, comparison of the relative efficacy of different dosage forms of the same drug entity requires the analysis of the active ingredient in biological matrices such as blood, urine, and tissue.

Among the most powerful techniques available to the analyst for the resolution of these mixtures are a group of highly efficient methods collectively called chromatography. Because this technique is involved so intimately in all aspects of pharmaceutical research and development, the pharmacist or pharmaceutical scientist should possess a working knowledge of chromatographic principles and techniques. Electrophoresis, a separation technique especially useful for resolving mixtures of biological molecules, has some similarities to chromatography.

Classification of chromatographic methods

Chromatographic techniques can be classified into six types based on the type of equilibration process. These are (1) adsorption, (2) partition, (3) ion-exchange, (4) permeation, (5) affinity, and (6) capillary electrochromatography.

Adsorption chromatography

The stationary phase is a solid on which the sample components are adsorbed. The mobile phase may be a liquid (liquid–solid chromatography) or a gas (gas–solid chromatography); the components distribute between the two phases through a combination of sorption and desorption processes. Column chromatography is a typical example of adsorption chromatography in which the solid stationary phase is packed in a tubular column, and the mobile phase is allowed to flow through the solid. Thin-layer chromatography is another example of adsorption chromatography in which the stationary phase is a plane, in the form of a solid supported on an inert plate.

Partition chromatography

The stationary phase is a liquid supported on an inert solid. Again, the mobile phase is a liquid (liquid–liquid partition chromatography) or a gas (gas–liquid chromatography). Paper chromatography is a type of partition chromatography in which the stationary phase is a layer of water adsorbed on a sheet of paper. In the normal mode of operations of liquid–liquid partition, a polar stationary phase (e.g., water or methanol) is used with a nonpolar mobile phase (e.g., hexane). This favors retention of polar compounds and elution of nonpolar compounds and is called normal-phase chromatography. If a nonpolar stationary phase is used along with a polar mobile phase, then nonpolar solutes are retained favoring elution of polar solutes. This is called reversed-phase chromatography.

Ion-exchange chromatography

This technique uses an ion-exchange resin as the stationary phase. Ion-exchange resin is a polymeric matrix with the surface of which ionic functional groups, such as carboxylic acids or quaternary amines, have been chemically bonded. The mechanism of separation is based on ion-exchange equilibrium. As the mobile phase passes over this surface, ionic solutes are retained by forming electrostatic chemical bonds with the functional groups. The mobile phases used in this type are always liquid. When choosing a chromatographic format for the analysis of an ionic compound, ion-exchange is generally considered after attempts at developing a reversed-phase method have proven unsuccessful. However, ion-exchange chromatography is the method of choice for the analysis of inorganic ions, and it is often preferable to reversed-phase methods for the analysis of small organic ions.

Permeation chromatography

In this technique, the stationary phase is a polymeric substance containing numerous pores of molecular dimensions. The mobile phase contains analytes as solvated molecules that are separated according to their size by their ability to penetrate a sieve-like structure (the stationary phase). Larger molecules that

will not fit into the pores remain in the mobile phase and are not retained. This method is most suited to the separation of mixtures in which the solutes vary considerably in molecular size. The mobile phase may be either liquid or gaseous. Size-exclusion chromatography is used extensively for the preparative separations of macromolecules of biological origin as well as for the purification of synthetic-organic polymers.

Affinity chromatography

This technique utilizes highly specific interactions between one kind of solute molecule and a second molecule covalently attached (*immobilized*) to the stationary phase. The immobilized molecule can be an *antibody* to a particular protein. When a crude mixture containing a large number of proteins is passed through the column, only the protein that reacts with the antibody is bound to the column. After washing all the other solutes off the column, the desired protein is dislodged from the antibody by changing the pH or ionic strength.

Capillary electro-chromatography (CEC)

Capillary electro-chromatography (CEC) can be defined as a liquid chromatographic method, in which the mobile phase is electro-osmotically driven through the chromatographic bed. The mobile phase in CEC has proven to be superior over other chromatographic methods in terms of its efficiency in separating ionic compounds and biomolecules.

The classifications given above for the various types of chromatographic processes can be deceptive in their simplicity. Except in isolated cases, pure adsorption or partition chromatography rarely occurs. In practice, separations frequently result from combination of adsorption and partitioning effects. The ultimate success of a chromatographic separation depends on the ability of analysts to recognize the limitations of the methods and adjust their experiments accordingly. The individual types of chromatographic techniques mentioned above are shown in Fig. 6.3. The types of chromatography useful in qualitative and quantitative analysis that are employed in the USP assays and tests are Column, Gas, Paper, Thin-Layer, and High-Pressure or High-Performance Liquid Chromatography (HPLC). Paper and thin-layer chromatography are ordinarily more useful for purposes of identification because

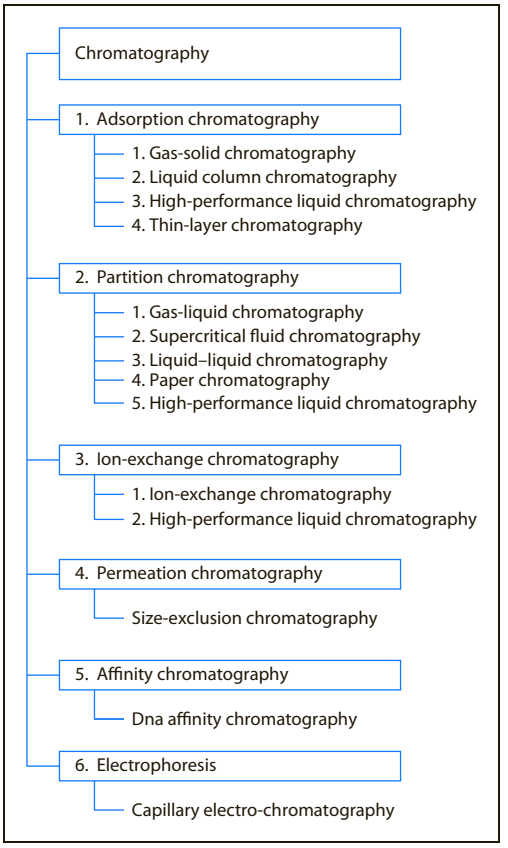

Figure 6.3 Classification of chromatographic techniques.

of their convenience and simplicity. Column chromatography offers a wide choice of stationary phases and is useful for the separation of individual compounds, in quantity, from mixtures. Both GC and HPLC require elaborate apparatus and usually provide sophisticated methods to identify and quantify very small amounts of the material. A distinction needs to be made between *analytical* and *preparative-scale chromatography*. Analytical processes are used to identify and quantify tiny amounts of unknown materials. Preparative-scale chromatographic systems generally consist of a large cylindrical column within which the stationary material is packed. The mobile phase is invariably a liquid, and the stationary phase is either a solid, or a liquid supported by an adsorbent solid. Since the column is packed with stationary phase, liquid mobile phase must be forced through the column at a steady *pressure* for achieving the separation of the solutes of interest.

Spectroscopic methods of analysis

Introduction

Spectroscopic methods of analysis have the advantage over chromatographic methods in that they give direct information concerning the structure of a molecule. Thus, they are used to characterize molecules and, with sufficient information, conclusively identify both structurally and conformationally. Spectroscopic methods of analysis rely on the absorption or emission of electromagnetic radiation, as a result of its interaction with matter. These methods include UV, visible, near-infrared (NIR), infrared (IR), florescence, and Raman techniques together with nuclear magnetic resonance (NMR) spectroscopy. Figure 6.4 shows their relative positions in the electromagnetic spectrum, and Table 6.2 provides a comparison of the characteristics of the different spectroscopic methods of analysis.

Theory

Maxwell first expressed the concept of the electromagnetic field in 1860. His equations theorized the existence of waves that travel through electromagnetic fields and whose properties are identical to those of light. The oscillation of an electron gives rise to electromagnetic radiation. As is illustrated in Fig. 6.4, at each point in the direction of the beam, the electric field and magnetic field, represented by two vectors (E and H, respectively), are perpendicular to each other. The wavelength (λ) is defined as the distance between successive maxima or minima and is expressed in nanometers (nm, 10^{-9} meters), although it was formerly measured in Angstroms (Å, where 1 Å = 0.1 nm). It is nm which is the usual unit used in UV, and sometimes NIR spectroscopy. The reciprocal of wavelength ($1/\nu$) is referred to as the wavenumber (ν), expressed in reciprocal centimeters (cm^{-1}). The wavenumber is employed particularly in describing the position of peak maxima for IR spectra, and sometimes for NIR spectra. The frequency in cycles per second (cps or Hz) is denoted by ν. The frequency is related to λ by $\nu = c/\lambda$, where c is the velocity of light in vacuum. The time required for the completion of one cycle is designated by τ, which is related to ν by $\tau = 1/\nu$.

Planck, in 1900, formulated a concept of quantum restriction. He stated that oscillating atoms of a hot body can only have energies that are integral multiples of $h\nu$, where h is Planck's constant (6.6256×10^{-27} erg s; $6.62606957 \times 10^{-34}$ J s; $4.135667516 \times 10^{-15}$ eV s). In other words, the energy of an oscillator

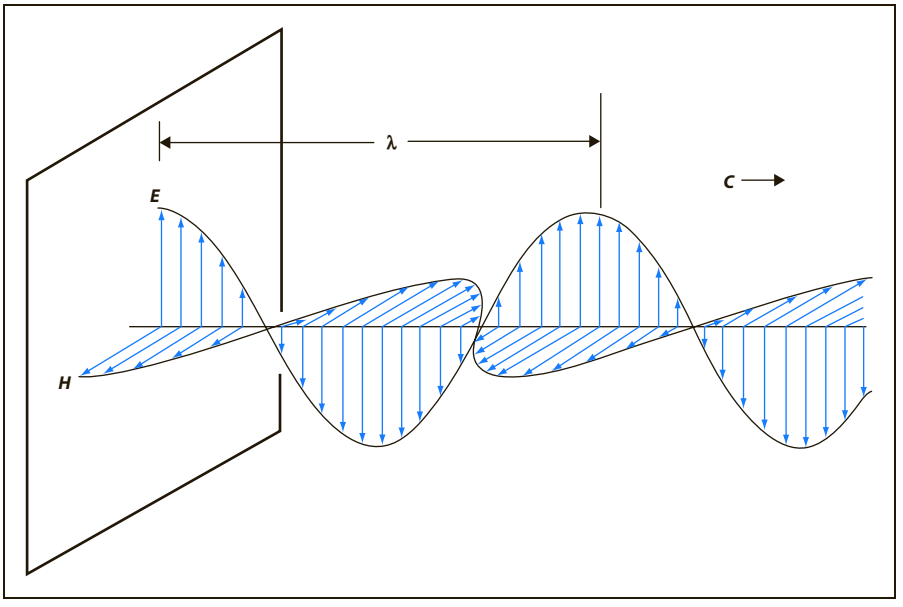

Figure 6.4 The electromagnetic spectrum.

Table 6.2 Comparative characteristics of spectroscopic methods of analysis

Technique	Wavelength (nm)	Source	Detector	Sample	Information type	Application
Absorption Spectroscopy						
Ultraviolet/Far UV	200 to 380 nm	Hydrogen or deuterium lamp	Photomultiplier tube (photodiode array, photon diode) and semiconductors (Charge transfer devices)	Vapor/solution	Little structural information but the presence of unsaturated sites in the molecule	Qualitative and quantitative analysis, confirmation analysis, multi-component analysis, derivative spectroscopy
Visible	380 to 780 nm	Tungsten lamp or deuterium arc lamp	Photomultiplier tube and semiconductors	Vapor/solution	Presence of unsaturated sites in the molecule	Quantitative analysis, confirmation analysis (purity control)
Infrared	2.5 to 40 μm	Nernst or globar unit	Thermocouple or bolometer	Gas, liquid or solid (NaCl, KBr, and CsBr disks)	R–H vibrational mode	Characterization of molecules
Fourier transform infrared (FTIR)	2.5 to 40 μm	Zirconium oxide or rare earth oxides (Nernst source), silicon carbide	Mercury cadmium telluride (MCT), deuterated triglycerine sulfate (DTGS) crystal or lithium tantalite ($LiTaO_3$)	Same as IR	Structural analysis	Qualitative powers of FTIR coupled with separation technique as GC-FTIR and LC-FTIR
Diffuse Reflectance (Specular or diffuse or attenuated total reflection)	1 to 10 μm	Same as IR	Same as IR	Sample is diluted with KBr powder	Structural analysis	IR spectra of solid samples, i.e., drugs, pharmaceuticals, food products, soap powder, coal, clay, paper, painted surfaces, polymer foam, catalysts
Infrared Microscopy	Same as IR	Same as IR	Same as IR	Same as IR	Same as IR	Flaws and variations in bulk properties of matrices
Pattern Recognition Analysis	UV and IR regions					Identification and differentiation of plastic materials used in pharmaceutical packing
Hierarchical Cluster Analysis	UV and IR regions					

(continued overleaf)

Table 6.2 *(continued)*

Technique	Wavelength (nm)	Source	Detector	Sample	Information type	Application
Emission Spectrometry	AC-, DC, and AC spark					Qualitative detection of all metals and nonmetallic elements
Flame Photometry	No light source				Qualitative and quantitative analysis	Group IA and IIA metals (Quality control measurement of alkaline or alkaline earth metals)
Plasma Emission	No light source/hollow cathodelamp					Elemental analysis
Fluorescence Spectroscopy	Visible or UV range	Xenon arc lamp				Polycyclic aromatic hydrocarbons (PAH) analysis in water, measurement of aflatoxins
Raman Spectroscopy	4000 to 25 cm^{-1}	Helium/neon laser	Photomultiplier detector		Vibrational and rotational energy modification	Qualitative/quantitative analysis of inorganic, organic, and biological systems

is discontinuous, and any change in the energy can occur only by a jump between two energy states. Planck showed that the energy in a photon of light is related to wave frequency by the expression $E = h\nu = hc/\lambda$. In 1903, Einstein conducted his experiments on the photoelectric effect of light. He concluded that electrons are emitted from the surface of a specific metal upon its illumination with light of a relatively low wavelength, such as blue light.

Red light, irrespective of its intensity, fails to eject an electron from a similar metal. These findings by Michelson and Morley, Planck, Einstein, and others could not be explained by Maxwell's assigned wave properties. Considering these facts, a reliance on the dual nature of light, behaving both like a wave and a particle, seemed to be indispensable for resolving many physicochemical phenomena.

Molecular interactions and electromagnetic radiation

The presence of radiation of a particular frequency is necessary, but is not always sufficient, to induce a change in the energy level of a molecule. Quantum restrictions specify certain conditions for the interaction of radiation with a molecule. On many occasions, energy is absorbed only if the radiation frequency corresponds to the components of the molecular frequency. This is referred to as resonance absorption.

The position of maximum absorption (λ_{MAX}) for a molecule in a particular region of the spectrum is a function of the total structure of the molecule with a transition energy corresponding to a given wavelength. The intensity of the absorption maximum (ε_{MAX}) is a function of the probability of electromagnetic radiation–molecule interaction and polarity of the excited state. At ground state (i.e., room temperature) a molecule is in its lowest energy state. The transition between E_1 and E_2, two energy states or levels of a molecule, occurs by the interaction of electromagnetic radiation with a molecule. The difference between E_1 and E_2 (ΔE) is related to the frequency with a relationship, $\Delta E = h\nu$ ergs.

Very high energies ($> 10^8$ cm^{-1}) disturb and cause changes in the nucleus of the atom, regardless of its

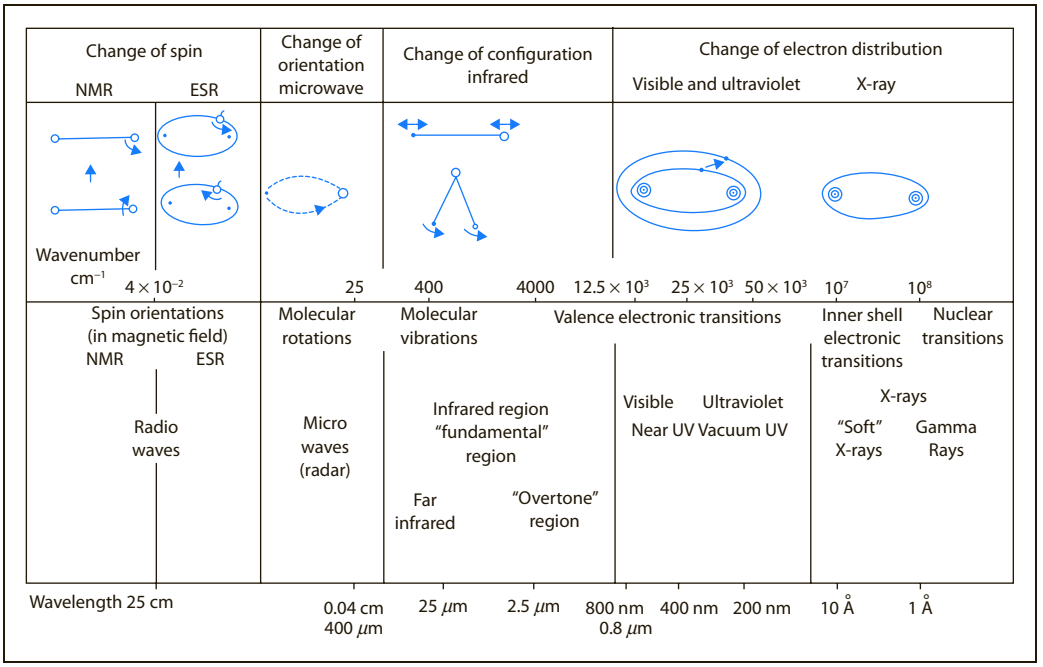

Figure 6.5 A plane-polarized electromagnetic radiation: *E*, electric vector; *H*, magnetic vector; λ, wavelength; c, direction of propagation.

environment. However, lower energy causes a change in the electronic distribution around the nucleus.

The whole range of electromagnetic radiations is divided into a number of regions (Fig. 6.5). Interaction between a molecule and various kinds of electromagnetic radiation gives rise to a change in the electronic energy and/or kinetic energy of the molecule. In most cases, the energy absorbed is converted quickly to vibrational, rotational, and translational energy. However, in specific cases, emission occurs either immediately as in fluorescence, or after a short time as in phosphorescence. These specific changes in the energy of a molecule result in the generation of a characteristic spectrum that can be used for both structural elucidation and quantitative determination.

Mass spectroscopic methods of analysis

Introduction

A mass spectrometer works by generating charged molecules or molecular fragments either in a high vacuum or immediately before the sample enters the high-vacuum region. Instruments typically maintain vacuums of about 10^{-6} mmHg (1.33×10^{-4} Pa), since ionised molecules have to be generated in the gas phase to enable them to be manipulated using magnetic or electrostatic fields. In classic mass spectrometry (MS) only one method could produce the charged gaseous molecules, but now quite a number of alternatives are available. Once the molecules are charged and in the gas phase, they can be manipulated by the application of either electric or magnetic fields to enable the determination of their relative molecular mass and the relative molecular mass of any fragments produced by the molecules breaking up. A number of useful introductory texts that describe mass spectrometers and mass spectral interpretation are available.[34–40]

Identification of drug metabolites

Metabolism is an important component in the drug discovery and development process, and LC-MS has an important role in identifying drug metabolites.[41] The pathways of Phase I and phase 2 drug metabolism are well known, and it is possible to derive useful

information even from a single quadrupole instrument by using extracted ion chromatograms to search for predicted metabolites. For example, formation of a monoglucuronide of a drug results in a shift of 176 amu from the molecular ion of the parent. However, the process of searching for metabolites is easier if tandem MS is available. The preferred mode of metabolite profiling in the preliminary analysis of metabolites is to use product-ion scanning. The predicted ion for a metabolite is selected by the first quadrupole and subjected to fragmentation in the collision cell, and the fragments are analysed by the third quadrupole. This enables acquisition of clean metabolite spectra that are free from any interfering solvent background. If a quantitative analysis is required, selected-reaction monitoring may be carried out, in which a critical transition is monitored. For example, the transition produced by loss of a glucuronide moiety from a glucuronide metabolite might be monitored if it gives a very specific response for that particular metabolite. Constant neutral-loss scanning is especially useful for searching for a particular class of metabolite, since it can readily detect metabolites resulting from both Phase I and phase 2 metabolism. For example, glucuronide metabolites for which the loss of the glucuronide moiety (−177 amu) is a major fragmentation pathway might be monitored. If the masses of the metabolites fall in a range (e.g., between 400 and 700 amu), the first quadrupole is set to scan between 400 and 700 amu and the second quadrupole to scan in the range 400−177 amu to 700−177 amu. In this way, any metabolites that are, for example, methylated or undergo additional hydroxylation followed by glucuronidation are picked out, as well as simple glucuronides.

Ion-trap instruments can also be used to good effect in drug-metabolism studies and have approximately ten times the sensitivity of triple-sector quadrupole instruments when used to examine full-scan spectra. This is advantageous in the first phase of metabolite identification when the metabolites are unknown. Another advantage of trap instruments is that fragmentation of selected ions can be carried out several times with all the ions, apart from the molecular ion of the metabolite of interest, being ejected from the trap before the next fragmentation. This process produces clean spectra for the metabolite.

Some applications of mass spectrometry in quantitative analysis

Mass spectrometric detectors are able to carry out precise and accurate quantification of analytes. However, it is generally necessary to use an internal standard in analyses, since the instrumentation is more subject to sensitivity fluctuations than simpler detectors, such as the UV−visible detectors used in HPLC analyses. The selection of an internal standard has to be made carefully so that its mass spectrometric behavior is reproducible and closely similar to that of the analyte. The internal standards labelled with stable isotope (described below) are ideal, since they mimic the analyte very closely, but often a close structural analog of the analyte will suffice.

The most common application of MS to quantitative analysis of biomedical samples is in the quantitative determination of drugs and their metabolites in biological fluids and tissues. The advantage of MS in this area is that its selectivity means that it is less subject to interference by other compounds extracted from the biological matrix along with the compound of interest. The greatest accuracy in such analyses is afforded by using as internal standards analogs of the compound being measured that are labelled with stable isotopes. An isotopomeric internal standard of a drug co-elutes with it from a chromatographic column (sometimes deuterated compounds elute very slightly earlier than the unlabelled compound) and should have an almost identical response factor. Figure 6.6 shows the negative ion chemical ionization (NICI) mass spectra of the trimethylsilyl oxime derivative of prednisolone and its tetradeuterated analogue. The deuterated analogue of prednisolone can be used as an internal standard in the determination of prednisolone in a biological matrix. On the basis of the mass spectra shown the ions at *m/z* 457 and 472 are monitored for prednisolone and those at *m/z* 461 and 476 for the tetradeuterated internal standard.

Since isotopomeric internal standards co-elute with the analyte, they aid in the recovery of the analyte from the chromatographic system (carrier effect). Figure 6.7 shows a selected-ion chromatogram of prednisolone methyl oxime/trimethylsilyl (MO/TMS) derivative[42] (monitored as the sum of the ions *m/z* 457 and 472, Fig. 6.6), which was extracted from aqueous humor after addition of 10 ng of tetradeuterated

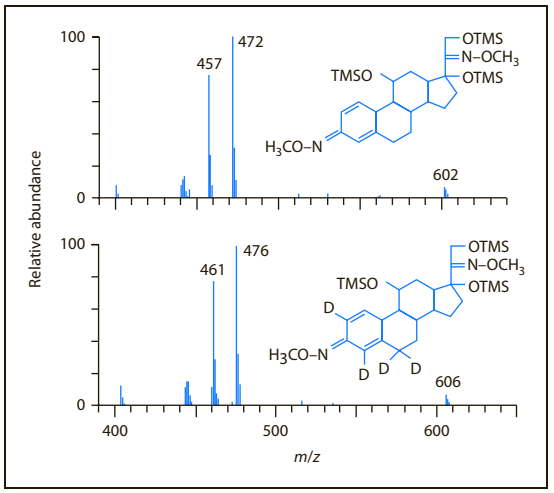

Figure 6.6 NICI spectra of trimethylsilyl prednisolone oxime and its tetradeuterated isotopomer.

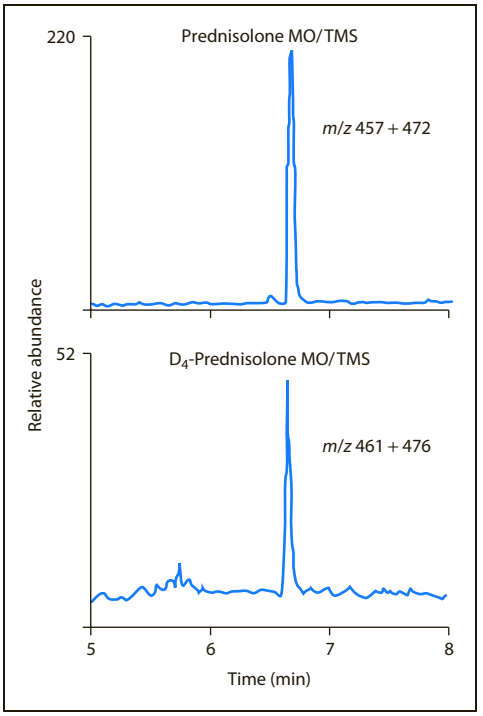

Figure 6.7 Prednisolone extracted from aqueous humor in comparison with D_4-prednisolone (10 ng) added as an internal standard (both as their trimethylsilyl oximes).

prednisolone (the MO/TMS derivative was monitored as the sum of the ions *m/z* 461 and 476, Fig. 6.6); the analysis was carried out using GC-MS. Similar types of approaches can be taken in LC-MS analysis.

Dissolution

Dissolution is the process by which a solid enters into solution. The earliest reference to dissolution is the 1897 article by Noyes and Whitney, titled as "The rate of solution of solid substances in their own solution."[43] The authors suggested that the rate of dissolution of solid substances is determined by the rate of diffusion of a very thin layer of saturated solution that forms instantaneously around the solid particle. They developed the mathematical relationship that correlates the dissolution rate to the solubility gradient of the solid. Their equation is still the basic formula upon which most of the modern mathematical treatments of the dissolution phenomenon revolve.

Interestingly, the work of Noyes and Whitney, together with the studies that followed in the early part of the twentieth century, was primarily based on the physicochemical aspects of dissolution applied to chemical substances. The most prominent part of these investigations that deserve recognition are those of Nernst and Brunner, in 1904,[44] for their application of Fick's law of diffusion to the Noyes–Whitney equation, and those of Hixson and Crowell, in 1931,[45] for their development of the famous "Cube Root Law" of dissolution.[46] The Hixson–Crowell equation is

$$Q_0^{1/3} - Q_t^{1/3} = K_{HC}^t$$

where Q_t is the amount of drug released in time t, Q_0 is the initial amount of drug in the dosage form/product, and K_{HC} is the rate constant for Hixson–Crowell cube root equation, which describes the surface area–volume relationship. This equation applies to products, such as powders and tablets, where the dissolution occurs in the planes that are parallel to the surface of the dosage form.

Two more alternative explanations were available, as reviewed by William Higuchi in 1961,[47] by the 1950s. The interfacial barrier model considered that interfacial transport, rather than diffusion

through the film, is the limiting step, due to a high activation energy level for the former, first proposed by Wilderman in 1909. Another model was Danckwerts' model, which appeared in 1951. According to this, constantly renewed macroscopic packets of solvent reach the solid surface and absorb molecules of solute, delivering them to the solution.

By the middle of the twentieth century, emphasis started to shift to the examination of the effects of dissolution behavior of drugs on the biological activity of pharmaceutical dosage forms. One of the earliest studies, with this purpose in mind, was conducted by J Edwards in 1951, on aspirin tablets. He reported, "because of its poor solubility, the analgesic action of aspirin tablets would be controlled by its dissolution rate within the stomach and the intestine."[48] No *in vivo* studies, however, were conducted by Edwards to support his postulate.

About eight years later, Shenoy and colleagues proved the validity of Edwards's suggestion of the *in vitro/in vivo* correlation by demonstrating a direct relationship between the bioavailability of amfetamine from sustained-release tablets and its *in vitro* dissolution rate. Other studies, especially those reported by Nelson, Levy, and others,[49–54] confirmed, beyond doubt, the significant effect of the dissolution behavior of drugs on their pharmacological activities. Nelson, in 1957,[54] was the first to explicitly relate the blood levels of orally administered theophylline salts to their *in vitro* dissolution rates. Due to the importance of these findings, dissolution testing began to emerge as a dominant topic within both the pharmaceutical academia and the drug industry.

During this 20-year period from 1950 to 1970, a number of studies were conducted, especially in the United States, that confirmed the significance of the dissolution–bioavailability relationship in pharmaceutical product development. As a result, the basket-stirred-flask test (USP apparatus 1) was adopted as an official dissolution test in six monographs of the USP/NF, in 1970. Also, due to the sustained interest in the subjects of dissolution and gastrointestinal absorption, an explosion in the number of monographs of the dissolution requirements in subsequent USP/NF editions was noted. Notable developments during this evolution are the adoption of the paddle method (USP apparatus 2) in 1978, the publication of a General Chapter on Drug Release in USP21 (1985), the presence of 23 monographs for modified-release dosage forms in USP22/NF18 (1990), the adoption of the reciprocating cylinder (USP apparatus 3) for extended-release products in 1991, and the adoption of the flow-through cell in (USP apparatus 4) for extended-release products in 1995.

In the late 1960s, dissolution testing became a mandatory requirement for several dosage forms. The role of dissolution in the absorption of drug products, however, is still far from being understood completely. Although considerable efforts were made to establish *in vitro/in vivo* correlations between release of drug from the formulation and drug absorption, the limited knowledge of the complex composition and hydrodynamics of the gastrointestinal fluids remains a real barrier. In spite of the reported success of several *in vitro/in vivo* correlation studies, dissolution cannot be relied upon as a predictor of therapeutic efficiency. Rather, it is a qualitative tool that can provide valuable information about the biological availability of a drug, as well as batch-to-batch consistency. Another area of difficulty is the accuracy and precision of the testing procedure, which is dependent, to a large extent, on the strict observance of so many subtle parameters and detailed operational controls.

In spite of these shortcomings, dissolution is considered, today, as one of the most important quality control procedures performed on pharmaceutical dosage forms, and dissolution studies have become an essential part of drug applications to regulatory bodies worldwide. Whether or not it has been correlated with biological effectiveness, the standard dissolution test is a simple and inexpensive indicator of a product's physical consistency. If one batch differs from the other in its dissolution characteristics, or if the dissolution profiles of the production batches show a consistent trend upwards or downwards, it sounds a sure warning that some factor in the raw material, formulation, or process is out of control.[30] Additionally, dissolution data seem to be a useful tool in the early stages of drug development and molecular manipulation. In the early stages of research, steps may be taken to optimize characteristics that influence subsequent data concerning biological availability. Based on simple dissolution testing, selection of a proper salt for a new drug can be done at an early drug development stage.

Definition of dissolution and theoretical concepts for the release of the drug from dosage forms

Dissolution is defined as the process by which solid substances enter in solvent to yield a solution. Stated simply, dissolution is the process by which a solid substance dissolves. Fundamentally, it is controlled by the affinity between the solid substance and the solvent.' The physical characteristics of the dosage form, the wettability of the dosage unit, the penetration ability of the dissolution medium, the swelling process, the disintegration, and the deaggregation of the dosage forms are a few of the factors that influence the dissolution characteristics of drugs. Wagner proposed a scheme, depicted in Fig. 6.8, for the processes involved in the dissolution of solid dosage forms.[55]

This scheme was later modified to incorporate other factors that precede the dissolution process of solid dosage forms. Carstensen[56] proposed a scheme incorporating the following sequence:

1. Initial mechanical lag
2. Wetting of the dosage form
3. Penetration of the dissolution medium into the dosage form
4. Disintegration
5. Deaggregation of the dosage form and dislodgement of the granules
6. Dissolution and occlusion of some particles of the drug

Carstensen explained that the wetting of the solid dosage form surface controls the liquid access to the solid surface and, many times, is the limiting factor in the dissolution process. The speed of wetting directly depends on the surface tension at the interface (interfacial tension) and upon the contact angle between the solid surface and the liquid. Generally, a contact angle of more than 90° indicates poor wettability. Incorporation of a surfactant, either in the formulation or in the dissolution medium, lowers the contact angle and enhances dissolution. Also, the presence of air in the dissolution medium causes the air bubbles to be entrapped in the tablet pores and act as a barrier at the interface. For capsules, the gelatin shell is extremely hydrophilic, and, therefore, no problems in wettability exist for the dosage itself, although it may exist for the powders inside.

After the solid dosage form disintegrates into granules or aggregates, penetration characteristics play a prime role in the deaggregation process. Hydrophobic lubricants, such as talc and magnesium stearate, commonly employed in tablet and capsule formulations, slow the penetration rate and, hence, the deaggregation process. A large pore size facilitates penetration, but, if it is too large, it may inhibit penetration by decreasing the internal strain caused by the swelling of the disintegrant.

After deaggregation and dislodgment occur, the drug particles become exposed to the dissolution medium and dissolution proceeds. Figure 6.9[32] graphically presents the model proposed by Carstensen.

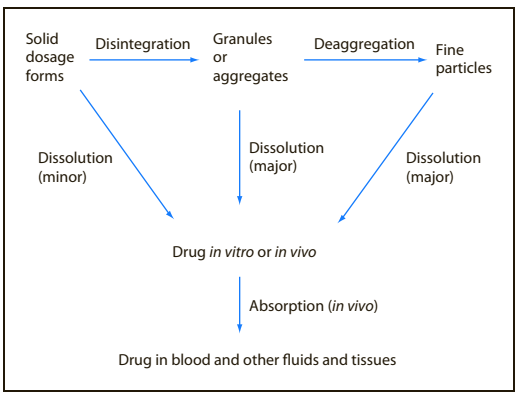

Figure 6.8 Schematic illustration of dissolution process of solid dosage forms.

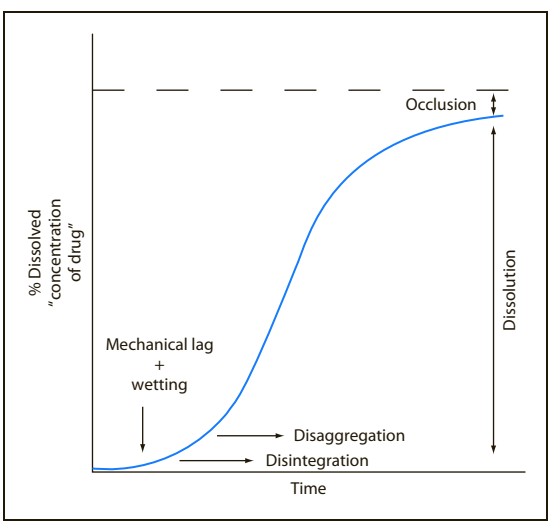

Figure 6.9 The S-shaped dissolution curve of solid dosage forms.

It is apparent from Fig. 6.8 that the rate of dissolution of the drug can become a rate-limiting step before it appears in the blood. However, when the dosage form is placed into the gastrointestinal tract in solid form, there are two possibilities for the rate-limiting step. The solid must first dissolve, and the drug in solution must then pass through the gastrointestinal membrane. Freely water-soluble drugs tend to dissolve rapidly, making the passive diffusion of the drug or the active transport of the drug rate-limiting step for absorption through the gastrointestinal membrane. Conversely, the rate of absorption of poorly water-soluble drugs will be limited by the rate of dissolution of the undissolved drug or disintegration of dosage form.

The rate of dissolution of drug substance is determined by the rate at which solvent–solute forces of attraction overcome the cohesive forces present in the solid. This process is rate-limiting, when the release of solute into solution is slow and the transport into the bulk solution is fast. In this case, the dissolution is said to be interfacially controlled. Dissolution may also be diffusion controlled, where the solvent–solute interaction is fast, compared to transport of solute into the bulk solution. In a diffusion-controlled process, a stationary layer of solute adjacent to the solid–liquid interface is postulated and is commonly referred to as the diffusion layer. The saturation concentration of solute develops at the interface and decreases with distance across the diffusion layer.

Appendix A: Example specifications

Table A.1 ABC1234 injection specifications

Attribute	Method	Acceptance criteria
Appearance	Visual	Clear, colorless solution and essentially free of particles or foreign matter
Identification	Reversed-phase HPLC Method ABC-2012-0001	Conforms to Reference Standard (RRT 1.00 ± 0.05)
Assay	Reversed-phase HPLC Method ABC-2012-0001	90.0–110.0% of label claim
Impurities	Reversed-phase HPLC Method ABC-2012-0001	**Specified Identifed Impurities** ABC0001 (RRT ˜ 0.37): ≤ 0.30% area; ABC0002 (RRT ˜ 1.15): ≤ 1.00% area; ABC0003 (RRT ˜ 1.58): ≤ 3.00% area **Specified Unidentifed Impurities** RRT ˜ 1.08: ≤ 0.20% area **Unspecified Unidentified Impurities** Any other individual Impurity≤ 0.10% area **Total Impurities** ≤ 4.00% area
Enantiomeric purity	Chiral HPLC Method ABC-2012-0002	≤ 1.00% area
pH	USP <791>	5.5 ± 0.3
Particulate matter	USP <788>	**Light Obscuration Particle Count** particles per container ≥10 µm: ≤ 6000 particles per container ≥25 µm: ≤ 600 **Microscopic Particle Count**[a] particles per container ≥10 µm: ≤ 3000, particles per container ≥25 µm: ≤ 300
Sterility	USP <71>	No growth
Endotoxin	USP <85>	< 3.5 EU/mg of ABC1234

[a] Microscopic particle count will be performed only if the light obscuration particle count exceeds the acceptance criteria.

Table A.2 ABC1234 injection specifications

Attribute	Method	Acceptance criteria
	Lyophilized Cake	
Appearance	Visual	White to off-white cake or powder, essentially free of foreign matter
Identification	Reversed-phase HPLC Method ABC-2012-0003	Conforms to Reference Standard (RRT 1.00 ± 0.05)
Assay	Reversed-phase HPLC Method ABC-2012-0003	90.0–110.0% of label claim (5.0 mg ABC1234/vial)
Impurities	Reversed-phase HPLC Method ABC-2012-0003	**Specified Identifed Impurities** ABC0001 (RRT ~ 0.37): ≤ 0.30% area; ABC0002 (RRT ~ 1.15): ≤ 1.00% area; ABC0003 (RRT ~ 1.58): ≤ 2.00% area **Specified Unidentifed Impurities** RRT ~ 1.08: ≤ 0.20% area **Unspecified Unidentified Impurities** Any other individual impurity ≤ 0.10% area **Total Impurities** ≤ 3.00% area
Enantiomeric purity	Chiral HPLC Method ABC-2012-0004	≤ 1.00% area
Moisture content	USP <921>	Record result
Content uniformity	USP <905> Reversed-phase HPLC Method ABC-2012-0005	Conforms to USP and Ph. Eur. requirements
Sterility	USP <71>	No growth
Endotoxin	USP <85>	< 3.5 EU/mg of ABC1234
Reconstitution time	Visual	≤ 120 seconds
	Reconstituted Solution	
Appearance	Visual	Clear, colorless solution, essentially free of particles and foreign matter
pH	USP <791>	5.0 ± 0.3
Particulate matter	USP <788>	**Light Obscuration Particle Count** particles per container ≥10 µm: ≤ 6000 particles per container; ≥25 µm: ≤ 600 **Microscopic Particle Count**[a] particles per container ≥10 µm: ≤ 3000; particles per container ≥25 µm: ≤ 300

[a] Microscopic particle count will be performed only if the light obscuration particle count exceeds the acceptance criteria.

Table A.3 ABC5678 tablet (10- and 100-mg) specifications

Attribute	Method	Acceptance criteria
Appearance	Visual	White to off-white round convex tablets
Identification	Reversed-phase HPLC Method ABC-2012-0006	Conforms to Reference Standard (RRT 1.00 ± 0.05)
Assay	Reversed-phase HPLC Method ABC-2012-0006	90.0–110.0% of label claim
Impurities	Reversed-phase HPLC Method ABC-2012-0006	**Specified Identifed Impurities** ABC0001 (RRT ~ 0.37): ≤ 0.30% area; ABC0002 (RRT ~ 1.15): ≤ 1.00% area; ABC0003 (RRT ~ 1.58): ≤ 1.50% area **Specified Unidentifed Impurities** RRT ~ 1.08: ≤ 0.20% area **Unspecified Unidentifed Impurities** Any other individual impurity ≤ 0.10% area **Total Impurities** ≤ 3.00% area
Enantiomeric purity	Chiral HPLC Method ABC-2012-0007	≤ 1.00% area
Contentuniformity	USP <905> Reversed-phase HPLC Method ABC-2012-0008	Conforms to USP and Ph. Eur. requirements
Dissolution	USP <711> Reversed-phase HPLC Method ABC-2012-0009	Record result
Moisture content	USP <901>	Record result
Tablet breaking force	USP <1217>	Record result
X-ray powder diffraction	USP <941>	Consistent with a reference pattern
Microbial enumeration tests	USP <61> or Ph. Eur. 2.6.12	Total Aerobic Microbial Count ≤ 10^3 CFU/g Total Yeast and Molds Count ≤ 10^2 CFU/g
Microbial specified Microoganisms Test	USP <62> or Ph. Eur. 2.6.13	Absence of *E. coli*

Appendix B: 21 CFR food and drugs

PART 211 Current good manufacturing practice for finished pharmaceuticals

Subpart A: General provisions

211.1 The regulations in this part contain the minimum current good manufacturing practice for preparation of drug products for administration to humans or animals.

211.3 (Definitions) The scope of the regulations are explained for human prescription and OTC drug products including drugs used to produce medicated animal feed. Reference is made to Part 210.3 of the chapter that gives definitions for all significant terms used in the regulations.

Subpart B: Organization and personnel

211.22 (Responsibilities of Quality (QC) unit) The QC unit has total responsibility for ensuring that

adequate systems and procedures exist and are followed to ensure product quality.

211.25 (Personnel qualifications) Personnel, either supervisory or operational, must be qualified by training and experience to perform their assigned tasks.

211.28 (Personnel responsibilities) The obligations of personnel engaged in the manufacture of drug products concerning their personal hygiene, clothing, and medical status are defined.

211.34 (Consultants) The qualifications (education, training, and experience, or any combination thereof) of consultants must be sufficient for the project to which they are assigned.

Subpart C: Buildings and facilities

Buildings and facilities are considered acceptable only if they are suitable for their intended purpose and can be cleaned and otherwise maintained. Design and construction features for lighting, pest control, and maintenance are described below.

211.42 (Design and construction features)
211.44 (Lighting)
211.46 (Ventilation, air filtration, air heating and cooling)
211.48 (Plumbing)
211.50 (Sewage and refuse)
211.52 (Washing and toilet facilities)
211.56 (Sanitation)
211.58 (Maintenance)

Subpart D equipment

Equipment must be designed, constructed, of adequate size, suitably located, and able to be maintained and cleaned to be considered suitable for its intended use. Regarding the use of automatic equipment, data processors, and computers, there is a need for input/output verification and for proper calibration of recorders, counters, and other electrical or mechanical devices.

211.63 (Equipment design, size, and location)
211.65 (Equipment construction)
211.67 (Equipment cleaning and maintenance)
211.68 (Automatic, mechanical, and electronic equipment)

211.72 (Filters) Filters to be used for liquid filtration shall not release fibers into products.

Subpart E: Control of components and drug product containers and closures

211.80 (General requirements) Written procedures must be available that describe the receipt, identification, storage, handling, sampling, testing, and approval or rejection of components (raw materials) and drug products.

211.82 (Receipt and storage of untested components, drug product containers, and closures)

211.84 (Testing and approval or rejection of components, drug product containers, and closures)

211.86 (Use of approved components, drug product containers, and closures) Materials shall be rotated so that the oldest approved stock is used first.

211.87 (Retesting of approved components, drug product containers, and closures) Materials shall be retested or reexamined as necessary after storage for long periods or after exposure to air, heat or other conditions that might adversely affect the component, drug product container, closure.

211.89 (Rejected components, drug product containers, and closures) These items shall be identified and controlled to prevent their use in manufacturing.

211.94 (Drug product containers and closures) Containers and closures (product contact materials) must protect the product and must be nonreactive with or additive to the product, suitable for their intended use, and controlled using written procedures.

Subpart F: Production and process controls

211.100 (Written procedures and deviations) Written standard operating procedures (SOPs) for each production process and control procedure are necessary. Any deviation from an SOP must be investigated, recorded, and approved prior to final product acceptance.

211.101 (Charge-in of components) The procedures used to formulate a batch shall be written and followed.

211.103 (Calculation of yield) Actual yields and theoretical yields shall be determined. All products are to be formulated to provide not less than 100% of the required amount of active ingredient. The identity and quantity of each component incorporated into a batch must be recorded.

211.105 (Equipment identification) Equipment shall be properly identified.

211.110 (Sampling and testing of in-process materials and drug products) Significant in-process steps are to be identified and appropriate sampling, testing, and approvals obtained before proceeding further in the production cycle. Rejected material must be controlled.

211.111 (Time limitations on production) If required, time limitations will be placed on in-process steps.

211.113 (Control of microbiological contamination) Appropriate procedures are to be prepared for the control and prevention of microbiological contamination. The sterilization process must be validated.

211.115 (Reprocessing) Reprocessing of product is allowed providing there are written procedures covering the methods and QC unit review to be used.

Subpart G: Packaging and labeling control

211.122 (Materials examination and usage criteria) Labeling and packaging materials are to be received, identified, stored, sampled, and tested following detailed written procedures.

211.125 (Labeling issuance) Strict control shall be exercised over labeling for use in drug product labeling operations.

211.130 (Packaging and labeling operations) There shall be written procedures designed to ensure that correct labels, labeling, and packaging materials are used for drug products. Special controls must be exercised over labeling to ensure that only the correct labels are issued to packaging for a specific product and that the quantities used are reconciled with the quantity issued.

211.132 (Tamper-resistant packaging requirements for over-the-counter (OTC) human drug products) Provides details of tamper-resistant packaging.

211.134 (Drug product inspection) Packaged and labeled products shall be inspected for correct labels.

211.137 (Expiration dating) As supported by appropriate stability studies, products on the market shall bear an expiration date.

Subpart H: Holding and distribution

211.142 (Warehousing procedures) Describes the requirements for warehousing holding product under appropriate conditions of light, temperature, and humidity.

211.150 (Distribution procedures) Written procedures describing product distribution shall be prepared.

Subpart I: Laboratory controls

211.160 (General requirements) The general requirements for laboratory control mechanisms are described.

211.165 (Testing and release for distribution) There shall be written procedures in the form of specifications, standards, sampling plans, and test procedures that are used in a laboratory for controlling components and finished drug products. Acceptance criteria for sampling and approval shall be adequate to support release of product for distribution.

211.166 (Stability testing) There shall be a written testing program designed to assess the stability characteristics of drug products. The results of this testing shall be used in assigning appropriate storage conditions and expiration dates.

211.167 (Special testing requirements) There are special testing requirements for sterile and/or pyrogen-free ophthalmic ointment and controlled-release dosage form products.

211.170 (Reserve samples) Reserve sample quantity and retention times are described.

211.173 (Laboratory animals) Animals used in any testing shall be maintained and controlled in a manner suitable for use.

211.176 (Penicillin contamination) Drug products cannot be marketed if, when tested by a prescribed procedure, found to contain any detectable levels of penicillin.

Subpart J: Records and reports

211.180 (General requirements) Describes record retention time and availability for inspection.

211.182 (Equipment cleaning and use log) A written record of major equipment cleaning, maintenance, and use shall be included in major equipment logs.

211.184 (Component, drug product container, closure, and labeling records) Deals with the issues of the receipt, testing, and storage of components, drug product containers, and closures. Details the various records and documents that should be generated during the manufacture of drug products and that are to be available for review.

211.186 (Master production and control records) A master production record must be prepared for each drug product, describing all aspects of its manufacture, packaging, and control. Individual batch records are derived from this approved master.

211.188 (Batch production and control records) Batch production and control records with information about the production and control of each batch are prepared.

211.192 (Production record review) All drug product batch records shall be reviewed and approved by the QC unit (QA/QC) before the batch is released.

211.194 (Laboratory records) Complete records of any laboratory testing shall be maintained to include raw data, test procedures and results, initials or signatures of personnel performing the test or reviewing the results of tests, periodic equipment calibration, and stability test results.

211.196 (Distribution records) Distribution records include warehouse shipping logs, invoices, bills of lading, and all documents associated with distribution. These records should provide all the information necessary to trace lot distribution to facilitate product retrieval if necessary.

211.198 (Complaint files) Written records of complaints received from consumers and professionals are to be maintained along with the report of investigations and responses.

Subpart K: Returned and salvaged drug products

211.204 (Returned drug products) Records are to be maintained of drug products returned from distribution channels and the reason for their return. These data can be used as part of the total lot accountability, should the need arise, to trace its distribution and/or for its recall.

211.208 (Drug product salvaging) Drug products that have been stored improperly are not to be salvaged.

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7

Pharmaceutics

Modern-Day drug discovery and development

Medical and pharmaceutical research provides a basis for the development of new therapeutic approaches to human and animal disease. This process of drug discovery research can be basic (seeking an understanding of biological phenomena that are unknown) or applied (using principles that are known to produce a desired new product or effect). In either case, drug discovery research results from an unmet clinical need, a recognized deficit in treatment options. Drug discovery is the process by which drugs are discovered or designed. In the past most drugs were discovered either by identification of the active ingredient from traditional remedies or by serendipitous discovery. Today we know how disease and infection are controlled at the molecular and physiological level. Drug discovery involves the identification of candidates, synthesis, characterization, screening, and assays for therapeutic efficacy. Drug discovery is still a lengthy, expensive, difficult, and inefficient process with a low rate of new therapeutic discovery. The outcome of a successful drug discovery program is the generation of a therapeutic entity where none previously existed or the replacement of established therapies in favor of a newer modality that is safer and more efficacious.[1] The main function of the pharmaceutical industry is to create products (i.e., drugs that have an impact on healthcare). Drug development is the process of bringing a new drug to the market once a lead compound has been identified through drug discovery. Drug development includes preclinical research (microorganisms/animal) and clinical trials (human). Products of this type can be foreseen to

some extent through knowledge and study and thus are amenable to planned research and development (R&D). For example, if the cause of a disease has been identified as an infection by a microorganism, a search can be undertaken for an agent that will prevent or cure the infection. However, in some instances, the etiology of a disease is unknown despite intensive investigation. In this situation, the pathway to a satisfactory cure or method of prevention cannot be foreseen or forecast. In such cases, products may only be developed after application of careful investigations, from a revolutionary new approach, or perhaps from a serendipitous finding.

Although much of the drug discovery research in the United States is carried out by major pharmaceutical manufacturers and biotechnology companies, this research is dependent on a vast and growing background of scientific knowledge generated by diverse organizations. Universities, private institutes, governmental laboratories, and industrial research all play significant roles in developing new technologies and knowledge that provide the basis for discovery and the ultimate generation of a new product. This new knowledge may involve development of a new technology, improved scientific methodology and instrumentation, or increased understanding of the basic molecular or cell biology underlying a disease.

The major objective of research in the pharmaceutical industry is to produce safe drugs that prevent, cure, or ameliorate disease. Interim research goals that lead to this major objective are to

- Understand the molecular basis of biological mechanisms in health and disease.
- Develop new biological testing procedures relevant to human and veterinary medicine.
- Develop a quantitative understanding of the interaction of drugs with key biological systems, leading to the more rational design of drugs.
- Understand the absorption, transport, and mode of action of drugs.
- Develop drugs of low toxicity, reproducible delivery, and high specificity for a given pathological state or target organ.

The above points illustrate how drug discovery research is used to develop new products that fulfill clinical needs.

Metrology and pharmaceutical calculations

One of the first technical operations that the student of pharmacy must learn is the manipulation of balances, weights, and measures of volume. This entails a study of the various systems of weights and measures, their relationships, and a mastery of the mathematics involved to understand the testing, manufacturing, and compounding of pharmaceutical preparations:

- Weights and measures – An accumulation of facts concerning the various systems, with tables of conversion factors and practical equivalents. The relationships among the various systems of weights and measures are clarified.
- Weighing and measuring – A discussion of the various types of balances, particularly prescription balances and methods of using, testing, and protecting them; also of various devices and methods for measuring large or small volumes of fluids.
- Density and specific gravity – A consideration of the mass/volume ratio of a substance (density), and the ratio of the weight (mass) of one substance to the weight (mass) of another substance taken as the standard (specific gravity).
- Pharmaceutical calculations – A review of basic mathematical principles and their use in solving pharmaceutical problems.

Weights and measures

Weight is a measure of the gravitational force acting on a body; weight is directly proportional to the body's mass. The latter, being a constant based on inertia, never varies, whereas weight varies slightly with latitude, altitude, temperature, and pressure. The effect of these factors is usually not considered unless very precise weighing and large quantities are involved.

Measure is the determination of the volume or extent of a body. Temperature and pressure have a pronounced effect, especially on gases or liquids. These factors, therefore, are considered when making precise measurements.

All standard weights and measures in the US are derived from or based on the United States National

Prototype Standards of the Meter and the Kilogram. The standards are made of platinum-iridium, and are in the custody of the National Institute of Standards and Technology (NIST) in Washington, DC.

History

A brief outline of the origin of the many systems of weights and measures may help clarify the essential distinctions between them. The sense of the weight of a body cannot be conveyed intelligibly to the mind unless a means of comparison is chosen. As weight is the measure of the gravitational force of a body, this force is expressed in terms of standards of resistance, which exactly balance the body and keep it in equilibrium when used with a mechanical device constructed for this specific purpose. Such standards are termed *weights* and the mechanical devices are called *balances* or *scales*.

The standards that have been chosen by various nations are arbitrary, and instances are common where different standards are in use at the same time in the same country. Many of the ancient standards clearly are referable to variable parts of the human body, such as nail, foot, span, pace, cubit (length of the forearm), and fathom or faethm (stretch of the arms). In the history of metrology three periods may be traced:

- The *Ancient* period, during which the old classical standards originated, terminated with the decline of the Roman Empire. The unit of distance used by all nations for maritime measurements, the *nautical* or *meridian* mile (1/60 of a degree of the earth's equatorial circumference) is exactly equal to 1000 Egyptian fathoms or 4000 Egyptian cubits. These Egyptian measurements, which have persisted for more than 4000 years, were based on astronomical or meridian measurements that were recorded imperishably in the great Pyramid at Ghizeh, whose perimeter is exactly 500 of these fathoms, or 1/2 nautical mile.
- The *Medieval* period extended to the sixteenth century. During this period the old standards were lost, but their names were preserved, and European nations adopted various independent standards.
- The *Modern* period extends from the sixteenth century to the present. Since the seventeenth century, the efforts of most enlightened nations have been directed toward scientific accuracy and simplicity, and during the twentieth century toward international uniformity.

Historical metrology, also referred to as *documentary metrology*, is concerned with the study of monuments and records of ancient periods. *Inductive metrology* is concerned with the accumulation of data concerning the measurement of large numbers of objects that have been referred to as standards but which have no exact measure except by statutory regulation.

The English systems

In Great Britain, in 1266, the 51st Act of the reign of Henry III declared:

> that by the consent of the whole realm of England the measure of the King was made – that is to say, that an English silver penny called the sterling, round and without clipping, shall weigh *thirty-two grains of wheat*, well dried and gathered out of the middle of the ear; and twenty pence (pennyweights) do make an ounce and twelve ounces a pound, and eight pounds do make a gallon of wine, and eight wine gallons do make a bushel, which is the eighth of a quarter.

The 16-ounce pound (*avoirdupois pound*), undoubtedly of Roman origin, was introduced at the time of the first civilization of the British island. However, according to Gray, the word "haberdepois" was first used in English laws in 1303. A statute of Edward I (AD 1304) states:

> that every *pound* of money or of *medicines* is of *twenty shillings weight*, but the pound of all other things is *twenty-five shillings weight*. The *ounce of medicines* consists of *twenty pence*, and the *pound* contains *twelve* ounces [the troy pound], but in other things the pound contains *fifteen* ounces, in both cases the ounce weighing twenty pence.

These laws unfold the theory of the ancient weights and measures of Great Britain, and reveal the standards (i.e., a natural object, grains of wheat). A difference existed then between the troy and the

avoirdupois pound, but the weights now in use are 1/16 heavier than those of Edward I, due to the change subsequently made in the value of the coin by the sovereign. In addition, the true pennyweight standard was lost, and, in the next revision of the weights and measures, the present troy and avoirdupois standards were adopted.

The *troy weight* is of still earlier origin. The great fairs of the eighth and ninth centuries were held at several French cities, including Troyes, the gathering place of traders from all countries. Coins were frequently mutilated, so they were sold by weight, and the standard weight of Troyes for selling coin was adopted for precious metals and medicines in all parts of Europe. The troy ounce and the avoirdupois ounce were originally intended to have the same weight, but after the revision it was found that the avoirdupois ounce was lighter by 42½ gr (grains) than the troy ounce. The subsequent adoption of troy weight by the London College of Physicians in 1618, on the recommendation of Sir Theodore Turquet de la Mayerne who compiled their first pharmacopeia, has entailed upon all apothecaries who are governed by British customs to this day the very great inconvenience of buying and selling medicines by one system of weights (the *avoirdupois*) and compounding them by another (the *apothecary* or *troy*).

In the next century efforts were made toward reforming the standards, and in 1736 the Royal Society began the work that ended in the preparation, by Mr. Bird under the direction of the House of Commons, of the standard *yard* and standard *pound* troy in 1760. Copies of these were prepared and no intentional deviation has been made since.

The growing popularity of the French metric system – and the desirability of securing a standard that could be recovered easily in case of loss or destruction, and that should be commensurable with a simple unit – prompted steps in England to secure these advantages in 1816. The labors of English scientists led to the adoption of the *imperial* measures and standards, which were legalized on January 1, 1826; imperial standards are now in use in Great Britain, thus introducing another element of confusion into an already complicated subject. In this system the *yard* is equivalent to 36 inches, and its length was determined by comparison with a pendulum beating seconds of mean time, in a vacuum, at a temperature of 62°F at the level of the sea in the latitude of London, a length that was found to be 39.1393 inches. The *pound troy* (containing 5760 gr) was determined by comparison with a given measure of distilled water under specified conditions. Thus, a cubic inch of distilled water was weighed with brass weights in air at 62°F, the barometer at 30 inches, and it weighed 252.458 gr. The standard for measures of capacity in Great Britain (either dry or liquid) is the *imperial gallon*, which contains 10 lb avoir (each 7000 gr) of distilled water weighed in air at 62°F, the barometer standing at 30 inches. The *bushel* contains eight such gallons.

George Washington, in his first annual message to Congress, in January 1790, recommended the establishment of uniformity in currency, weights, and measures. Action was taken with reference to the currency and recommendations were made by Thomas Jefferson, then the Secretary of State, for the adoption of either the currently used English systems or a decimal system. However, nothing was accomplished until 1819–1820, when efforts again were made in the United States to secure uniformity in the standards that were in use by the several states. Finally, after a lengthy investigation, on June 14, 1836, the Secretary of the Treasury was directed by Congress to furnish each state in the Union with a complete set of the revised standards, and thus the *troy pound* (5760 gr), the *avoirdupois pound* (7000 gr), and the *yard* (36 inches) are all identical with the British standards. However, the *US gallon* is quite different; the old wine gallon of 231 $inch^3$ – containing 58 372.2 gr of distilled water at its maximum density, weighed in air at 62°F, the barometer standing at 30 inches – was retained. The bushel contained 77.274 lb of water under the same conditions, thus making the dry quart about 16 percent greater in volume than the liquid quart.

In 1864 the use of the metric measures was legalized in Great Britain, but was not made compulsory, and in 1866 the United States followed the same course. By the US law of July 28, 1866, all lengths, areas, and cubic measures are derived from the international meter equivalent to 39.37 inches. Since 1893 the US Office of Standard Weights and Measures has been authorized to derive the yard from the meter: one yard equals 3600/3937 m, and the customary weights are referred to the kilogram by an Executive Order approved April 5, 1893. Capacities were to be based

on the equivalent; dm^3 equals one liter, the decimeter being equal to 3.937 inches. The gallon still remains at 231 $inch^3$ and the bushel contains 2150.42 $inch^3$. This makes the liquid quart equal to 0.946 liter and the dry quart equal to 1.1013 liter, whereas the imperial quart is 1.1359 liter. The customary weights are derived from the international kilogram, based on the value that one avoir lb equals 453.5924277 g and that 5760/7000 avoir lb equals one troy lb.

Avoirdupois weight is used in general in the United States for commercial purposes, including the buying and selling of drugs on a large scale and occasionally on prescription orders.

The metric system

The idea of adopting a scientific standard for the basis of metrology that could be reverified accurately was suggested by a number of individuals after the Renaissance. Jean Picard, the seventeenth-century French astronomer, proposed that the length of a pendulum beating one second of time at sea level, at latitude 45° should be taken as a unit.

In 1783, the Scottish inventor James Watt first suggested the application of decimal notation, and the commensurability of weight, length, and volume. The French National Assembly in 1790 appointed a committee to decide the preferability of the pendulum standard or a terrestrial measure of some kind as a basis for the new system. The committee reported in 1791 in favor of the latter, and commissions were appointed to measure an arc of meridian and to perfect the details of the commensurability of the units and of nomenclature. However, certain inaccuracies were inherent in the early standards, so they do not bear the intended exact relationships to each other. The present accepted standards are defined in publications of the National Institute of Standards and Technology (NIST).

In its original conception, the meter was the fundamental unit of the metric system, and all units of length and capacity were to be derived directly from the meter, which was intended to be equal to one ten-millionth of the earth's quadrant. Furthermore, it originally was planned that the unit of mass, the kilogram, should be identical with the mass of a cubic decimeter of water at its maximum density. At present, however, the units of length and mass are defined independently of these conceptions.

For all practical purposes, calibration of length standards in industry and scientific laboratories is accomplished by comparison with the material standard of length: the distance between two engraved lines on a platinum-iridium bar, the *International Prototype Meter*, which is kept at the International Bureau of Weights and Measures.

The *kilogram* is defined independently as the mass of a definite platinum-iridium standard, the *International Prototype Kilogram*, which also is kept at the International Bureau of Weights and Measures. The *liter* is defined as the volume of a kilogram of water, at standard atmospheric pressure, and at the temperature of its maximum density, approximately 4°C. The *meter* is thus the fundamental unit on which are based all metric standards and measurements of length and area and of volumes derived from linear measurements.

Of basic scientific interest is that on October 14, 1960, the 11th General Conference on Weights and Measures, meeting in Paris, adopted a new international definition for the standard of length: the meter is now defined as the length equal to 1,650763.73 wavelengths of the orange-red light of the krypton-86 isotope. This standard will be used in actual measurements only when extreme accuracy is needed.

The kilogram is the fundamental unit on which all metric standards of mass are based. The liter is a secondary or derived unit of capacity or volume. The liter is larger by about 27 ppm (parts per million) than the cube of the tenth of the meter (the cubic decimeter): 1 liter = 1.000027 dm^3.

The relative length of the yard and meter are based on the relation: 1 m = 39.37 inch, contained in the Act of Congress of 1866. From this relation it follows that 1 inch = 25.40005 mm (nearly). In recent years engineering and industrial interests the world over have urged the adoption of the simpler relation, 1 inch = 25.4 mm exactly, which differs from the preceding value by only 5 ppm. This simpler relation has not as yet been adopted officially by either Great Britain or the United States but is in wide industrial use.

In the United States, the abbreviation "cc" (for cubic centimeter) still persists in general use and is taken as synonymous for the more correct milliliter. The *US Pharmacopeia* (USP) IX and *National Formulary* (NF) IV adopted the term *milliliter* with its

abbreviated form *mil*, but it proved so unpopular in practice that the following pharmacopeial convention directed the return to the older term cubic centimeter (cc). However, in 1955, USP XV and NF X once again adopted the term *milliliter* with the abbreviation mL.

National jealousies and the natural antipathy to changing established customs interfered greatly with the adoption of the metric system during the early part of the nineteenth century. At present the metric system is in use in every major country of the world. In the United States and Great Britain it is legalized for reference to and definition of other standards, and it is in exclusive use by nearly all scientists and by increasing segments of industry and the public. In the United States the metric system was legalized in 1866, but not made compulsory; in the same year the international prototype meter and kilogram were adopted as fundamental standards. The US silver coinage was based upon the metric system, the half dollar being exactly 12.5 g and the quarter and the dime being of the proportionate weights.

As corporations became more international, the need for a universal standard increased. Since 1875 there has been established and maintained an International Bureau of Weights and Measures, with headquarters in Paris. This Bureau is managed by an international committee that enjoys universal representation. One objective of the committee is to make and provide prototypes of the meter and kilogram for the subscribing nations; approximately 40 such copies have been prepared.

The US prototype standards of both the meter and the kilogram mass, constructed of a platinum-iridium alloy, were brought from Paris in 1890 and are now in the custody of the NIST in Washington, DC. They have been reproduced and distributed by the US government to the various states having bureaus needing such replicas. The original US prototype meter was taken back to Paris in 1957 for reverification and was found to have altered only 3 parts in 100,000,000 after 67 years of use. Thus, there was no demonstrable change within the limits of experimental error. With the adoption of the krypton-86 wavelength of light definition for the meter the different countries have the means to check their prototype meter bars without returning them to Paris at periodic intervals for comparison with the international meter bar.

Statistics

The laws of physics in connection with mathematical models and tools are quite capable to deterministically describe natural phenomena. But the more complex the situation to be described gets, i.e., the more influences need to be considered if we wanted to describe them accurately, the more we find our results to be erroneous. And in a scale where quantum effects also play a role, we have to deal with true uncertainty.

Statistics gives us a means to deal with probabilities or errors in measurements. With the help of statistics, we can (among others) describe data, calculate estimates of its distribution, and decide whether to reject a hypothesis in a rational and reproducible manner.

Data

Data may come in discrete steps, as for instance, the number of patients that benefit from a certain therapy, or they may be continuous, meaning that the values can have infinitely many manifestations, even in a finite interval. An example for continuous data are, for instance, the masses of tablets.

In reality, however, all our measuring devices have a limited measuring accuracy, so in principle all experimental data come in discrete quantities. This is important when statistical methods demand continuous data as a prerequisite, like the Mann–Whitney U test. We have to deal carefully with values that occur multiple times – statisticians call them "ties." (Ties are not supposed to occur with continuous data because there will always be a difference, however small it may be. But in gathering real data, ties become real, too, because of the limited precision of the measurement.)

Data visualization

In statistics we want to explore data and make inferences from it. An important first step is to visualise the data. The human brain has developed extraordinary capabilities for pattern recognition, and thus we can grasp important statistical parameters like location and spread of the data, or spot correlations, clusters, outliers, and so on, with a single glance.

Stem-and-leaf plot

A simple means to display data is the stem-and-leaf plot. It puts the data in order and provides visual

information on the location, spread, and form of the data. It retains a least two significant digits of each data point.

A stem-and-leaf plot is constructed as follows:[2]

1. Split each score or value into two sets of digits. The first or leading set of digits is the stem, and the second, or trailing, set is the leaf.
2. Draw a vertical line, and list all possible stem digits left to the line from lowest to highest.
3. For each data point write the leaf values on the line labeled by the appropriate stem number.

If appropriate, you can list each stem digit twice and put leaves starting with digits 0 to 4 on the first line, and leaves starting with digits 5 to 9 on the second.

Example 1

A stem-and-leaf plot

Consider the heights of the students of my statistics class: Their heights in centimetres are as follows: 195, 191, 198, 185, 158, 170, 160, 158, 172, 165, 185, 169, 187, 180, 178, 172, 180, 173, 168, 168, 172, 174, 160, 184, and 171.

Table 7.1 Stem-and-leaf plot of students' heights

15	88
16	005889
17	01222348
18	004557
19	158

The corresponding stem-and-leaf plot is presented in Table 7.1.

Samples and populations

Many experiments have as an objective the definition or comparison of two or more groups of data. For example, one may wish to compare the efficacy of two antihypertensive agents or a new antipsychotic drug versus a placebo. Or it may be desired to estimate the average drug content and variability of a batch of tablets. In virtually all such experiments, it is not realistic to observe all possible experimental units. In fact, sometimes the entire population of conceivable observations cannot be identified completely. The potential experimental material for a clinical study comparing an antipsychotic drug to a placebo would include not only patients but also persons with the disease who are not yet diagnosed. All of these people are the population or universe. Clearly, one would not perform an experiment that included the entire population for many reasons:

- All of these people could not be identified.
- The time or money to conduct such a huge experiment is not available.
- To include so many people in such an experiment could be dangerous or unethical.

It is not necessary to run such a large experiment to arrive at a fair conclusion regarding the efficacy of the drug. In fact, in most cases, the test consists of a relatively small *sample* taken from a relatively large *population*.

Another more concrete example is the process of sampling in quality control. It may be of interest to estimate the proportion of defective tablets or the average drug content and uniformity of tablets in a production batch. Certainly in the latter case every tablet in the batch would not be examined because the test is destructive, i.e., the tablet is destroyed during the analysis for drug content. Rather, a sample of 20 tablets would be chosen to estimate the average drug content of the more than 1 million tablets in the batch.

Thus, in typical experiments in the pharmaceutical sciences, a small sample from the population is examined in order to make inferences about the large population.

Summary numbers

In the next step we try to reduce the amount of data. We can try to specify a distribution by a mathematical model (e.g., normal distribution) and a finite set of parameters of that distribution. A sentence like, "The data follow a normal distribution with mean μ and variance σ^2." contains more information than a

thousand or more data points. This is because any normal distribution is completely determined by its mean and its variance (or its standard deviation, the square root of the variance).

Molecular structure, properties and states of matter

Introduction

Pharmaceuticals are made up of molecules, the properties of which are determined by their shape and electronic structure (i.e., the nature of their bonds). These, in turn, are determined by the constituent atoms and how those atoms are held together (bonded). A striking example of this is the element carbon. This can exist in a variety of forms – including nanotubes and buckyballs – but the two forms that illustrate the difference in bonding most strongly are graphite and diamond. Both are entirely composed of carbon atoms, but one is a hard crystalline material, colorless in its pure form (diamond), the other a black greasy material used in pencils and as a lubricant.

Atoms are built from neutrons, protons, and electrons; the former are much more massive than the electrons. The properties of these subatomic units are given in Table 7.2. The fundamental ideas for atomic structure and bonding were developed in the early part of the twentieth century.

States of matter

In everyday life we usually consider three states of matter: the solid state (solids), the liquid state (liquids), and the gaseous state (gases). For example, water can be differentiated into the three states: ice, liquid water, and water vapor, and at a given pressure (usually normal or atmospheric pressure, 1.013 bar) it is the temperature that decides in which state water is present; at normal pressure ice melts at 0°C and boils at 100°C. What we are observing at these temperatures are phase transitions from the solid state to the liquid state (melting) and from the liquid state to the gaseous state (boiling). If we lower the temperature of water vapor below 100°C, we observe condensation (gas to liquid transition) and if we further lower the temperature below 0°C, we observe freezing of the liquid water to ice.

In this section we will describe the different states of matter (including a few "exotic states," which nevertheless do play a role in some pharmaceutical applications) and highlight their most important characteristics. We will also discuss how we can describe the different states of matter in phase diagrams and identify a few experimental techniques that can be used to determine the characteristics of a given state of matter. Because most drugs and dosage forms used in the pharmaceutical field are solid at room temperature, we will discuss the solid state in a little more detail than the other states of matter.

Solids, liquids and gases – a question of intermolecular forces

When we think about states of matter, we usually think of them in terms of solids, liquids, and gases. These distinctions are based on the interactions between the molecules (or in some cases atoms or ions) of the matter in question. Since in the pharmaceutical field we are most often dealing with molecules, the discussions below will mainly consider molecules as the components forming the various states of matter, and the reader should keep in mind that in many cases the word "molecule" could be exchanged for the words "atom" or "ion."

Table 7.2 Masses and charges for the neutron, proton and electron

Subatomic particle	Mass/kg	Relative mass	Charge/C	Relative charge
Proton	1.673×10^{-27}	1837	1.602×10^{-19}	1
Neutron	1.675×10^{-27}	1839	0	0
Electron	9.109×10^{-31}	1	-1.602×10^{-19}	−1

In the solid state of a drug, the drug molecules are held together by comparatively strong interactions, which do not allow the molecules to change their position but only to vibrate around a fixed position. These intermolecular interactions result in some important properties of solids. A given mass of a solid at a given temperature and pressure has a defined volume and keeps its shape, if no external forces (such as in milling, agglomeration or tableting operations) are acting on the solid material. Similarly, a given mass of a liquid has a defined volume at a given temperature and pressure (like solids, liquids are practically incompressible), but in contrast to a solid, its shape can vary and will take on the shape of the container it is placed in. The reasons for this are again the interactions between the molecules in the liquid state. These are still considerably strong, but the kinetic energy of the molecules is now sufficiently high to allow the molecules to change their positions (not only to vibrate around a fixed position) and to move relative to each other by diffusion or convection. This is also the reason why the density of a liquid is usually lower than that of a solid (with the most important liquid in the pharmaceutical field being the exception: water has its highest density at normal pressure at 4°C, i.e., in the liquid state). A gas, on the other hand, does not have a defined shape or volume (in fact, gas molecules will fully occupy each volume available to them) and thus has a very low density, depending on the volume it occupies. This is due to the fact that intermolecular interactions in real gases are very weak and, in fact, are considered zero for an ideal gas. Since interactions between the molecules (or between atoms or ions) are very strong or strong in solids and liquids, these two states of matter are also summarized as condensed matter. In contrast, since the molecules in the liquid and gas state are able to change their positions, these two states of matter are summarized as fluid matter.

Changes between the states of matter

Upon the heating (at constant pressure), for example, of a solid drug material (usually in a crystalline form, see below), the solid transforms into a liquid (melt) and further into a gas (if it is not chemically degraded in the heating process). Heat (Q, a form of energy, unit: joules, J) is transferred into the material during the heating process. This leads to an increase in the enthalpy ΔH [J] of the material.

$$Q = \Delta H \tag{7.1}$$

It follows that a gas has a higher enthalpy than a liquid and a liquid has a higher enthalpy than a solid for a given material. At the same time, the number of ways in which the molecules can be arranged with respect to each other also increases. This is known as the entropy S [$\mathrm{J\,K^{-1}}$] of the system and is often described as the "disorder" of the system. It follows that upon a state change due to heating, both the enthalpy and the entropy of the material increase. Since every system has a tendency to exist in the lowest enthalpy and the highest entropy form, it depends on the temperature T of a given system (here considered solely as the material in question) in which form it is present. This can be summarized in form of the equation:

$$\Delta G = \Delta H - T\Delta S \tag{7.2}$$

where ΔG [J] is the free energy of the system.

If a liquid is heated, the temperature of the liquid will increase. How much the temperature increases as a function of the added heat energy depends on the heat capacity of the liquid. The heat capacity, C, can be defined as the amount of heat energy, Q, required to change the temperature, T, of a given material by a given temperate interval ΔT (measured in kelvin, K):

$$C = Q/\Delta T \tag{7.3}$$

In this form C is an extensive variable, i.e., its value will depend on the mass of the material. To convert the heat capacity into an intensive variable, i.e., a variable whose value is independent of the mass of the material (measured in kg) or its amount (measured in mol), the heat capacity is usually expressed as either specific heat capacity, C_{sp} [$\mathrm{J\,K^{-1}\,kg^{-1}}$], or molar heat capacity, C_{mol} [$\mathrm{J\,K^{-1}\,mol^{-1}}$].

In any case, the result of heating the liquid for a given period of time is that the temperature of the liquid increases. However, when the liquid starts to boil, i.e., the state of the material changes from the liquid to the gaseous (vapor) state, we observe that the temperature of the material stays constant during this state transition. This temperature is the boiling point (T_b in Fig. 7.1). Similarly, when a solid melts, the temperature of the material stays constant during this

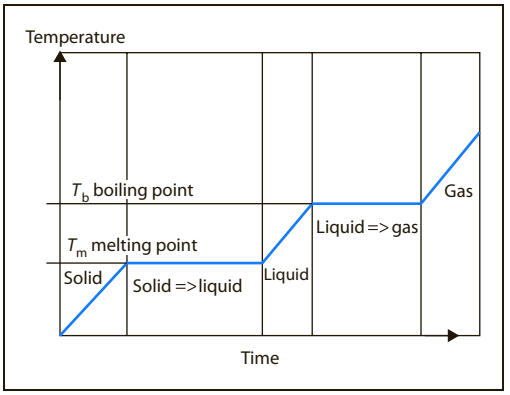


Figure 7.1 Heating curve of a material undergoing a state transition from solid to liquid and from liquid to gas. Note that the temperature stays constant during the state transitions.

state transition (melting point, T_m in Fig. 7.1). This is because when a substance boils, the liquid and vapor state are in equilibrium, and when a substance melts, the solid and liquid state are in equilibrium. Any heat that is applied to the system will be used to bring about the state transition until the liquid (or solid) has completely gone into the vapor state (or liquid state). Only then does the temperature rise further. The energy used for boiling the liquid is known as latent heat of vaporization (or boiling) and in the case of condensation, the energy released is known as latent heat of condensation. The amount of energy used in the vaporization process is identical to the heat of condensation released in the condensation process, since these processes are reversible.

During a phase transition the heat capacity of the material is infinitely high (all heat energy is used to bring about the state change), and such transitions are termed first-order phase transitions. The same holds true for the state transition from a solid to a liquid (latent heat of melting) or from a liquid to a solid (latent heat of freezing). In melting and boiling processes, the change is endothermic (the system absorbs energy), whereas in freezing and condensation processes, the change is exothermic (the system releases energy). At the melting and boiling point, the change in Gibbs free energy (ΔG) is zero. However, as discussed above, the enthalpy and the entropy of the material are increasing (i.e., ΔH and ΔS have positive values). Taking into account the relationship between the free energy and the enthalpy and entropy of the systems (see equation 7.2, $\Delta G = \Delta H - T\Delta S$, note the minus sign between ΔH and ΔS), we can conclude that a phase transition occurs when the free energy of the gas (or liquid) is lower than that of the liquid (or solid) at a given temperature for the material in question. At a given pressure, the temperature that denotes the boiling or melting point is the temperature at which ΔG for this process is zero, i.e., at exactly the boiling or melting point (for a given pressure), the two states can coexist.

So far we have considered the temperature as being decisive for a given material in what state of matter it is present. However, to fully describe a given state of matter, we require a second intensive variable, pressure, p. If we plot temperature on the x-axis and pressure on the y-axis of a coordinate system, and determine the state of a given material at any temperature–pressure combination, we obtain the phase diagram of the material in question. Let us again consider water.

Figure 7.2 shows the (partial) phase diagram of water as a function of pressure and temperature. We can differentiate three areas, those of solid water (ice), liquid water (water), and water vapor. To fully describe the state of water in each of these areas, we need to specify the temperature and pressure at which the material is present. For example, water exists in the liquid state at both temperature–pressure combinations indicated in the diagram by the symbol ▲ and, in fact, at an infinite possibility of other temperature–pressure combinations in the region of liquid water. The same holds true for the areas of solid water and water vapor. The different areas of the phase diagram are separated by boundary lines, known as the phase boundaries. At combinations of pressure and temperature which lie on these phase boundaries, two states of water exist in equilibrium. The curves a, b, and c in Fig. 7.2 are known as the sublimation (or re-sublimation) curve (solid and gas in equilibrium), the melting (or freezing) curve (solid and liquid in equilibrium), and the boiling (or condensation) curve (liquid and gas in equilibrium). Note the orientation of the melting curve b in Fig. 7.2: its slope is negative; that is, at constant temperature ice can melt if the pressure is increased (this is the principle of ice-skating). Most other compounds behave oppositely; they can solidify under pressure, so their melting curves will have a positive slope. This

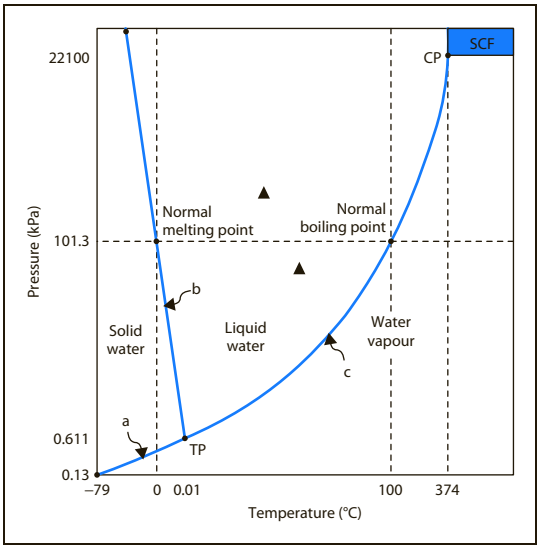


Figure 7.2 Partial phase diagram of water. The curves a, b, and c are the sublimation (or re-sublimation) curve (solid and gas in equilibrium), the melting (or freezing) curve (solid and liquid in equilibrium), and the boiling (or condensation) curve (liquid and gas in equilibrium), respectively. TP: triple point, CP: Critical point, SCF: region in which water exists as supercritical fluid. ▲ shows two different pressure and temperature combinations at which water exists in the fluid state. Note that the temperature and pressure axes are not linear.

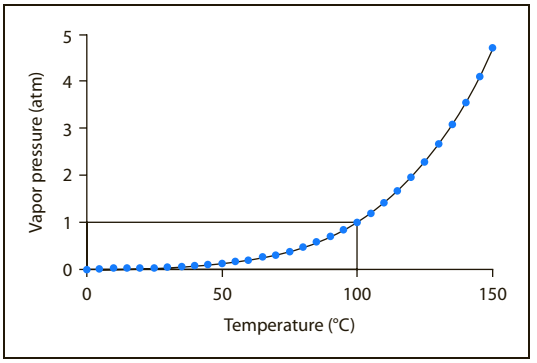


Figure 7.3 Temperature dependence of the vapor pressure of water.

is termed the anomality of water and also explains the observation that ice has a lower density than liquid water.

To determine, for instance, the position of the boiling curve in the phase diagram of water, we have to determine the vapor pressure of water at various temperatures. If we place a liquid in a vacuum at a temperature T, some of the molecules of the liquid will leave the liquid phase and will go into the free space above the liquid until an equilibrium is reached, in which the same number of molecules from the free space above the liquid will go into the liquid as are leaving the liquid (this is a dynamic equilibrium). As long as there is still liquid water left (note: it is not important how much water is left), the resulting pressure is known as the vapor pressure of the liquid, and will constitute a point on the boiling curve at the temperature T. Figure 7.3 shows the temperature dependence of the vapor pressure of water. In a closed system the vapor pressure increases with increasing temperature. This is true not only for water but for all substances, since an increase in temperature increases the likelihood for molecules to leave the condensed phase, as the increased kinetic energy of the molecules counteracts the attractive forces holding the molecules together in the condensed phase. Different liquids have different vapor pressures at given temperatures. A liquid will boil at a temperature at which its vapor pressure equals the pressure exerted onto the liquid by the surrounding pressure of the environment. Taking again the example of water, at 100°C the vapor pressure of water is 101.3 kPa, so under normal (sea level) condition of atmospheric pressure, water will boil. At 20°C, however, the vapor pressure of water is only 2.3 kPa, so it will not boil under these conditions. An interesting consequence of this is that water, for example, on a high mountain (where the atmospheric pressure is lower than at sea level) will boil at a lower temperature than 100°C.

At this point it let us make a quick stop and consider the question why drying (for example, of wet granules, to take a pharmaceutical example) occurs even if the temperature is far below 100°C at normal atmospheric conditions (i.e., below the boiling point of water). To understand this, we have to differentiate between the processes of boiling and evaporation. We have seen that, in a closed system, molecules from the liquid will leave the liquid phase until the equilibrium vapor pressure for the given temperature is reached. However, in an open system (for example, wet granules in a laboratory) some molecules from the surface of the liquid will have a sufficiently high kinetic energy to leave the liquid and are then transported away. This

process takes place at any temperature also below the boiling point of the liquid, and its rate depends on factors such as

- The surface area between the liquid and the air (evaporation is a surface phenomenon)
- The temperature of the liquid (the number of molecules with a sufficiently high kinetic energy to leave the liquid phase increases with increasing temperature)
- The air above the liquid (if there is an air stream, transport of the molecules away from the liquid is facilitated)
- The humidity of the air above the liquid (evaporation of water molecules from a liquid will be faster if the air is dryer), as well as other factors.

It should be noted that evaporation takes place from the surface of a liquid, whereas boiling takes place also in the liquid (that is the reason why water vapor bubbles are formed in boiling water).

We have seen how we can determine the boiling curve for a liquid to construct the phase diagram of a substance. Similarly, we can determine the sublimation curve, although experimentally this is more difficult due to the much lower vapor pressure of solids. The melting curve can be determined by thermo-analytical methods. This is usually done by determining the cooling curve of a material at various pressures as a function of time.

As we have already discussed for the boiling of a liquid, during the phase transition from the liquid to the solid, the temperature does not decrease. If we are heating a liquid in a closed container, the vapor pressure will also increase. However, since the space above the liquid is limited, further heating will increase the number of molecules in the space above the liquid, and thus the density of the gas phase will increase. At a certain, material-dependent temperature, the density of the gas phase will be equal to the density of the liquid, so that there will no longer be a phase boundary between the liquid and gas phase, and both are now indistinguishable (this is called a supercritical fluid). The temperature (critical temperature) and pressure (critical pressure) combination at which a supercritical fluid is formed is known as the critical point (CP in Fig. 7.2). At temperatures above the critical temperature a liquid can no longer exist or be formed by increasing the pressure, and thus the critical point marks the end of the boiling curve. The region in the phase diagram at temperatures and pressures higher than that of the critical temperature is known as the supercritical fluid region (SCF). For water, the critical point is at approximately 374°C and 22.1 MPa, and for CO_2 the critical point is at approx. 31.1°C and 7.38 kPa. Supercritical fluids have gained pharmaceutical importance since this state of matter combines properties of gases, such as low viscosity and high diffusivity, with properties of liquids, such as a high capacity to dissolve other substances.

From Fig. 7.2 we can see another critical point in the phase diagram, known as the triple point (TP in Fig. 7.2). At this combination of temperature and pressure, all three states of water coexist in a dynamic equilibrium. For water the triple point is at 0.01°C and 0.61 kPa. The triple point also marks the lowest temperature at which a liquid can exist, so the temperature range for liquids to exist is between the triple point and the critical point of the material. Similarly, sublimation and re-sublimation can only occur at temperatures below the triple point (see sublimation curve in Fig. 7.2). Since sublimation (in the same way as boiling) occurs when the vapor pressure of the solid material equals that of the gas phase, sublimation should only occur under atmospheric conditions if the pressure at the triple point of the system is above 101.3 kPa (1 atm). For example, solid CO_2 (dry ice) sublimates at atmospheric pressure at −78.5°C since its triple point is at −56.4°C and 517 kPa. For the same reason, in the pharmaceutically relevant process of freeze drying (which at least in the primary drying phase is based on the sublimation of water), an aqueous solution or dispersion is initially frozen (below the temperature of the triple point of water) and is then subjected to a reduced pressure (below the pressure of the triple point of water). In the earlier mentioned real-life example, however, we also observe that wet clothes on a washing line (i.e., at atmospheric pressure) at or below freezing temperature (so the water in the clothes is frozen to ice) eventually will be dry. We thus observe sublimation also for substances for which the triple point has a pressure below 1 atm. The reason for this is that in an open system like that on a washing line, the partial pressure (see below) of the solid does not attain the vapor pressure of the material at the triple point. The situation is similar to

the one discussed above for liquids in an open and closed system (evaporation versus boiling).

Phases

In the examples discussed above, we have talked about states of matter, and we have considered the solid, liquid, and gaseous state. In the phase diagrams we have seen that these states of matter constitute different phases of a material. It is, however, possible and, in fact, very likely that a solid material can in its own right exist in different phases. We can define a phase as a volume element of a system, separated from other volume elements of the system by a phase boundary. The physical properties within the phase do not show abrupt changes, which means that the phase is physically homogeneous. If two phases coexist, such as at the phase boundaries in the phase diagram, the physical properties between the phases, however, are different. For example, at normal pressure and 0°C, the density of ice is approximately 920 kg/m^3; and that of liquid water is approximately 999.8 kg/m^3. Note that water makes an exception from most other materials, in that its higher density is as a liquid rather than as a solid at the equilibrium of liquid water and ice.

Let us again consider the phase diagram of water, but now have a look at a larger temperature and pressure range (Fig. 7.4). We can see that different forms of ice can exist (termed ice I to ice VII). These all constitute a solid state of water but are all different in the molecular arrangement of the water molecules. They therefore have different physical properties, and these change abruptly at the phase boundary. These different solid forms of water thus constitute different water phases. While these different ice phases may not be relevant in pharmaceutical applications, they nevertheless show that molecules in the solid state can be arranged in different ways and thus give rise to the existence of different solid phases. At any given temperature and pressure, only one such solid form can be thermodynamically stable, but other forms may exist as metastable forms for considerable times at conditions where another form is the stable form. This will become important when we are considering crystalline solids in more detail later in this section.

The phase diagram of water in Fig. 7.4 also shows that for a given chemical compound, more than one triple point can exist. In fact, in Fig. 7.4 we can see six

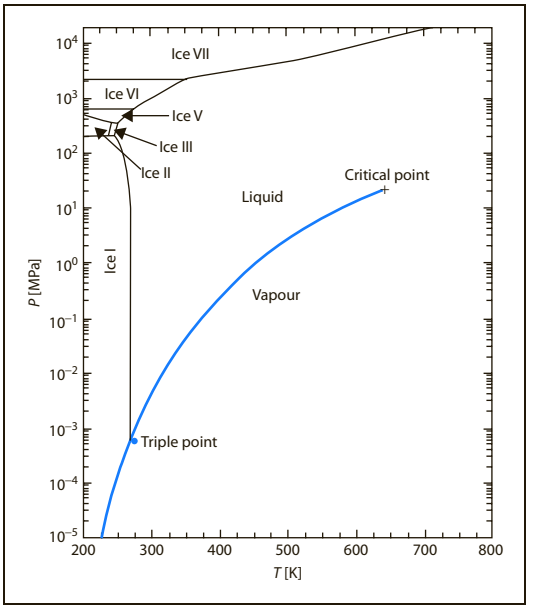


Figure 7.4 Phase diagram of water, showing several solid forms of ice (Ice I – VII). Note that the temperature is given in kelvin [K], and the pressure axis is in shown in logarithmic form.

other temperature–pressure combinations at which three phases coexist in equilibrium. However, unlike the triple point between ice I, water, and water vapor, these are conditions in which either two solid phases and liquid water or three solid phases coexist.

Earlier, we have stated that to fully describe a system in one of the areas of the phase diagram, we have to specify both its pressure and temperature. Pressure and temperature are known as the degrees of freedom of the system. The number of degrees of freedom can be defined as the least number of intensive variables (i.e., of variables that do not depend on the amount of material or its mass) of the system that are independent of other variables of the system and that can be changed without changing the number of phases that are coexisting. For any sample within an area of the phase diagram (e.g., in the area of liquid water or in the area of ice III, etc.), we can freely change pressure and temperature (until we reach a phase boundary) without changing the number of phases present (one phase).

If two phases coexist (such as for systems on the phase boundaries), the situation is different. If we change the pressure of the system, we cannot

freely change the temperature but have to change the temperature to a specific value, if we don't want to change the number of phases. In the case of two phases coexisting, the system thus only has one degree of freedom. This is important, for example, in moist heat sterilization, such as sterilization in an autoclave. To have both liquid water and water vapor present in the sterilization process (this is most effective in killing microorganisms) at 106 kPa, the temperature has to be 121°C (if no air is present in the autoclave). If we raise the temperature to 134°C, we have to increase the pressure to 312 kPa to maintain the coexistence of liquid water and water vapor.

Finally, if we are at a triple point in the phase diagram, i.e., three phases are coexisting, we cannot change either pressure or temperature without getting a change in the number of phases, which means that here the system has zero degrees of freedom.

From these considerations, Gibbs' phase rule can be formulated as follows:

$$F = 3 - P \tag{7.4}$$

where F is the number of degrees of freedom and P is the number of phases coexisting (one, two, or three).

So far, we have only considered phase diagrams of a single chemical component (e.g., H_2O). It is, however, also possible to have a single phase system which consists of more than one component. Let us now consider, for example, a salt solution. Here we have a single phase system (the salt molecules are dissolved as sodium and chloride ions in water, and the system is homogeneous). However, in this case, we can vary not only pressure and temperature without getting a phase change but also the salt concentration until we get a saturated solution of the salt in water. In this case, we have three independent variables that can be changed without changing the number of phases coexisting. Of course, as with pressure and temperature changes, this can only be done within limits, i.e., until we reach a boundary line in the phase diagram. If we, for example, increase the salt concentration above the saturation solubility of NaCl at the given pressure and temperature, the excess salt will form a second, solid phase, coexisting with the salt solution phase.

In the example of a salt solution, we have to consider two chemical entities, H_2O and the salt (e.g., NaCl). These chemical entities must be independent of each other. So even though NaCl is dissociating into Na^+ and Cl^- ions, in the current discussion these do not constitute two chemical entities because the Na^+ concentration is not independent of the Cl^- concentration. The same holds true, for example, for H_3O^+ and OH^- ions from the auto-protolysis of water. The independent chemical entities of a system are called components and are defined as the least number of chemically independent entities required to describe the composition of the system. A little tongue-in-cheek, we might say that the **p**hase is **p**hysically defined, whereas the **c**omponent is **c**hemically defined (however, note that chemically a Na^+ ion is very different to a Cl^- ion). For multicomponent systems we can formulate Gibbs' phase law as follows:

$$F = C - P + 2 \tag{7.5}$$

where C represents the number of components.

For the examples of a salt solution, F = 2 – 1 + 2 =3. We can see pressure, temperature, and salt concentration here as the degrees of freedom of the system. In most cases, phase diagrams of two component systems are given at a constant pressure, usually normal atmospheric pressure (i.e., one degree of freedom is used up). In this case we can express Gibbs' phase law for a two component system as $F^* = 3 - P$, with F^* being the remaining degrees of freedom of the system. An example of such a phase diagram will be discussed with Eutectics.

Crystalline solids

The solid state of matter is perhaps the most important state in pharmaceutics since the starting material for most formulations and the majority of orally administered dosage forms are in a solid form (most often as tablets or as powders, pellets, or granules in hard gelatine capsules).

Crystals are defined by a high degree of order, with a three-dimensional periodicity in position for atoms or ions and, additionally, with configurational periodicity for molecules that form the crystal. Most solid forms of drugs are used in the crystalline state, and most pharmaceutically relevant crystals are formed by organic molecules. Not all solids, however, are crystalline as some are amorphous.

The reason for the high degree of order of crystals lies in the strong interactions between the atoms, ions, or molecules that form the crystal. As we have seen

earlier, in the case of diamond, carbon atoms form a periodic three dimensional tetrahedral network of covalently bonded sp^3 hybridized carbon atoms. Diamond is thus an example of a crystal formed by atoms through covalent bonds. Most inorganic materials form ionic crystals. A pharmaceutically relevant example is NaCl. Here the crystal is formed by sodium and chloride ions, held together by ionic interactions. In the case of NaCl, each sodium ion is surrounded by six chloride ions, and each chloride ion by six sodium ions. The number of ions (or atoms or molecules) that each ion has as its nearest neighbors is called the coordination number. The coordination number for NaCl is, therefore, six. For ionic crystals, the coordination number depends on the relative size of the cation and the anion. If the size difference is very large, the most often found coordination number is four, and if the size differences are small, a coordination number of eight is found. Higher coordination numbers are found in metal crystals (eight or twelve), and the coordination number of diamond is four.

If atoms or ions are held together by covalent or ionic interactions, the resulting crystals have very high melting points and are often hard and brittle. In metals, the crystalline structure is formed by cations, where the electrons are delocalized. This is the reason for both the high coordination numbers of metal crystals as well as the ductile behavior of many metals.

Most drugs are organic molecules. The crystals formed by these substances are held together by dipole–dipole interactions, hydrogen bonds, or London forces. Since these are at least an order of magnitude weaker than ionic or covalent interactions, the melting points of molecular crystals are lower than those of the aforementioned crystalline structures. For example, the melting points of paracetamol (molecular crystal), NaCl (ionic crystal), copper (metal crystal), and diamond (covalent crystal) are 169°C, 801°C, 1084°C, and 3550°C, respectively.

We have already seen that different types of crystals can have different coordination numbers. In fact, since crystals are periodically organized, we can define a specific unit cell characteristic for each crystal. A unit cell is defined as the smallest unit of a crystal, which, if repeated, could generate the whole crystal. For this we imagine the atoms, ions, or in the case of drug crystals, molecules, as points in a lattice, disregarding their actual shape. Within the crystal structure we now look for the smallest unit which, when endlessly repeated, forms the crystal structure. Since there may be different ways to do this, the unit cell of a given crystal is the one with the shortest dimensions, and that includes angles that deviate the least from a right angle. The unit cell is a geometric construction and does not take into account the size and shape of the crystal forming atoms, ions, or molecules, nor the type and strength of interactions between them. For this reason, it is possible to summarize the types of unit cells into only seven crystal systems, which can be understood as unique unit cell shapes and which can be differentiated with respect to the relative lengths on their axes a, b, and c and the angles α, β, and γ between the axes. These seven crystal systems are called cubic, tetragonal, orthorhombic, monoclinic, triclinic, rhombohedral (or trigonal), and hexagonal (Fig. 7.5).

While there are only seven crystal systems, there are 14 Bravais lattices. This is because additional points can be present in a unit cell, other than the points at the corners of the unit cell, without changing the essential symmetry elements of the crystal system. If there is an additional point in the centre of the unit cell, these lattices are called body (or volume) centered (for example, body centered (cubic I in Fig. 7.5)). If there are additional points in the centre of each side (face) of the unit cell, they are called face-centered (for example, face centered (cubic F in Fig. 7.5), and if an additional point is present at the centre of two opposite faces of the unit cell, they are called base-centered (for example, base-centered (monoclinic C in Fig. 7.5). Bravais lattices without extra points are called simple or primitive, for example cubic P in Fig. 7.5. The 14 Bravais lattices are shown in Fig. 7.5.

Every crystalline material belongs to one of these Bravais lattice types but differs in their lattice parameters, and for each unit cell we can define three axes, with a length characteristic for the individual crystal, and three angles, also characteristic for this crystal. For example, NaCl crystals belong to the crystal system: cubic, Bravais lattice type: face-centered. The only lattice parameter we need is the length of one axis, a = 5.6402 Å, since for a cubic crystal the axes $a = b = c$, and the angles $\alpha = \beta = \gamma = 90°$. Paracetamol (polymorphic form I) belongs to the crystal system: monoclinic, Bravais lattice type: primitive,

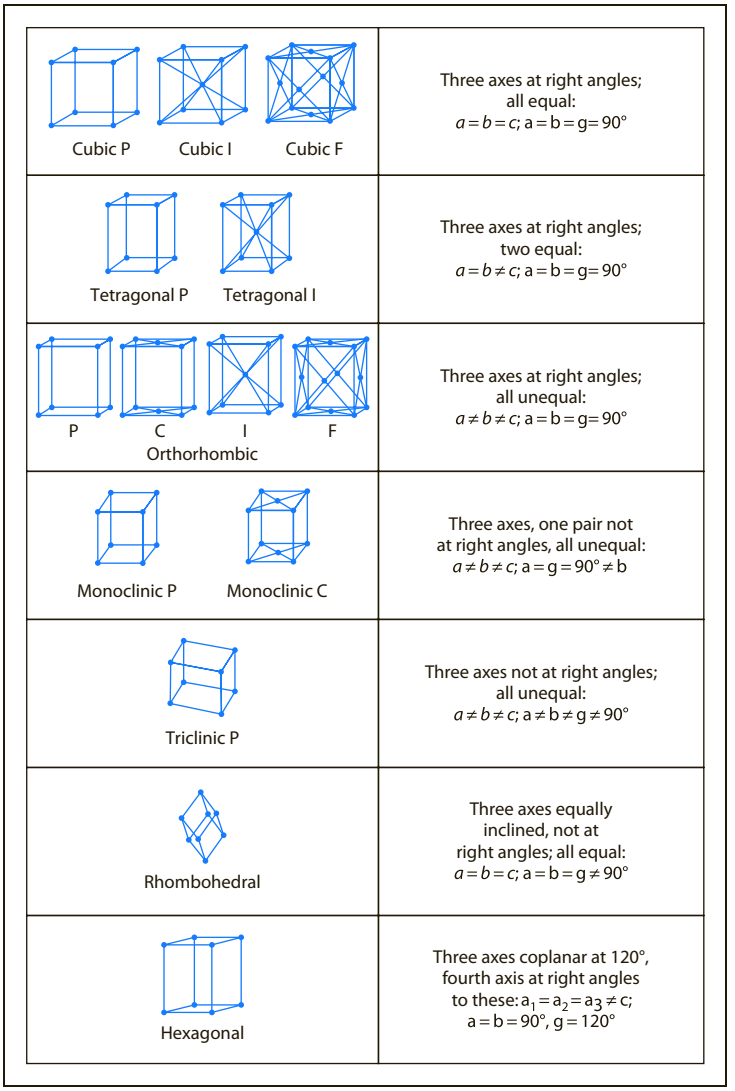


Figure 7.5 The 14 Bravais lattices.

a = 11.74 Å, b = 9.396 Å, c = 7.117 Å and β = 97.47° ($\alpha = \gamma = 90°$, for a monoclinic unit cell).

In the above discussion, we have considered the crystalline structure as infinitely periodic. In reality most crystals, however, will show defect structures, i.e., structures in which there are packing mistakes of some kind, so the crystalline structure of a real crystal will not be perfect. Depending on the number of these defects in a crystalline material, properties of the crystalline substance may vary, for example, its behavior in a milling process. Point defects occur at a single lattice point (Fig. 7.6). For example, a single lattice point may be vacant (vacancy) or occupied by a different atom, ion, or molecule from the ones that form the crystal (substitutional point defect; this would constitute a chemical impurity). It is also possible that there may be additional lattice points (interstitial point defects), either from the same or a different atom, ion, or molecule.

The dislocation is an example of a line defect, and the grain boundary is an example of a planar defect (Fig. 7.7). A grain boundary marks an interface between different crystalline regions, called crystallites. Such a material is termed polycrystalline and

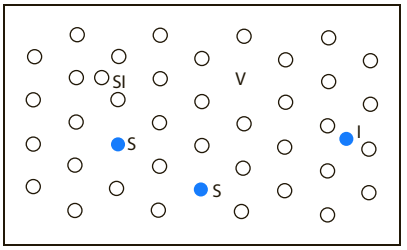


Figure 7.6 Point defects in a crystal lattice. V: vacancy, S: substitutional point defect (different atom, ion, or molecule from the ones that form the crystal), I: interstitial point defect (different atom, ion, or molecule from the ones that form the crystal), SI: self-interstitial point defect (same atom, ion, or molecule as the ones that form the crystal).

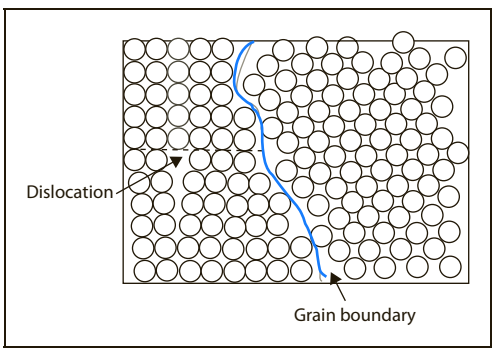


Figure 7.7 Dislocation (a line defect) and grain boundary (a planar defect).

is the reality for most crystalline materials, including drug substances.

Polymorphism

An important property of many chemical entities, including most drug molecules, is that they are able to crystallize in several different crystalline forms, termed polymorphic forms. These different crystalline forms consist of the same molecules, but these are arranged in different ways. If the crystal former is an element (as we have seen in the case of carbon), different polymorphic forms are termed allotropes. For molecular crystals, the crystal is held to together by secondary forces, as outlined above. Since these interactions are fairly weak (compared to ionic, metal, or covalent crystals), and because the molecules may adopt different molecular configurations in the crystalline structures, it is not surprising that most pharmaceutical drugs show polymorphism, and are often able to crystallize in more than two, and in some case even more than ten, different crystalline forms. These different polymorphs are also termed polymorphic modifications of the substance in question. It is important to note that different modifications of a drug may not necessarily form crystals with a different type of Bravais lattice. Although this is, of course, possible, it is also possible that two polymorphic forms of a drug both have, for example, a monoclinic unit cell. In this case, however, the lattice parameters of the two polymorphic forms will be different. Also, for some polymorphic forms, for example, of drug substances, the molecules present in the lattices of the different modifications will adopt different molecular conformations (termed conformational polymorphism), while other polymorphic pairs will contain the drug molecules with the same conformation (termed packing polymorphism).

Polymorphism is important in the pharmaceutical field, since the physical properties of different polymorphic forms are often considerably different, which can have consequences for important quality-relevant attributes of a drug substance or dosage form. Differences may be encountered in, for example, dissolution rate, solubility, flow properties, behavior under mechanical stress (for example during milling, tableting, agglomeration), hygroscopicity, etc. These differences may be sufficiently large so that different polymorphic forms may have different bioavailabilities. It is thus possible, or even common, that for a given drug regulatory approval is only given to a specific polymorphic form of the drug.

While often different polymorphic forms of a drug form macroscopically different crystals, such as needle-like versus plate-like crystals (the macroscopic appearance of a crystal is also known as the habit of the crystal), it is important to note that different polymorphic forms may not necessarily look different macroscopically, and thus it may be difficult to differentiate these by visual inspection or in the light or electron microscope alone. It is also possible that if one and the same polymorphic form of a crystal is crystallized, for example, from different solvents or from either a solution or the melt, it may adopt different crystal habits. So while the habit is important, most notably for further processing of the drug powder, it is also important to have techniques available to unambiguously identify the crystalline

structure of a drug and its polymorphic form. This will be discussed in the section on Methods to Characterize Solids, where some techniques to identify and characterize polymorphs (or indeed solid state forms in general) will be mentioned.

If a drug can crystallize in different polymorphic forms, it should be noted that at any given condition of pressure and temperature, only one polymorphic form can be the thermodynamically stable form. All other polymorphic forms that may form under these conditions will be only metastable. Metastable here means that these polymorphs can form but eventually will convert to the stable form over time if the environmental conditions are not changed. The metastable forms, on the other hand, are not unstable (in contrast to amorphous forms which will be discussed in the next section), since (sometimes considerable) activation energy is required to bring about a phase transition from the metastable to the stable polymorphic form. For some metastable polymorphs, therefore, the polymorphic transition may be very slow and may take much longer than the shelf life of the drug product containing a metastable polymorphic form. In general, if not precluded by a too low solubility of the stable form, most drugs will be manufactured in solid dosage forms in the stable polymorphic form. However the drug ranitidine-HCl, which can exist in two polymorphic forms, is manufactured using both polymorphs, i.e., the metastable polymorph is "practically" stable enough to allow safe manufacturing.[3]

It is often found that not the most stable, but a less stable (often the least stable) polymorphic form of a substance crystallizes first, for example, upon cooling of a melt. This is known as Ostwald's rule. While not universally applicable (not being a law, but rather a rule), it nevertheless highlights the importance in drug development to carefully check which polymorphic form of a drug one is indeed dealing with.

Let us consider a given set of two polymorphs of a substance. Because the solid state forms are different, their phase diagrams will also be different, and the overall phase diagram of this polymorphic substance will be the superimposed phase diagram of the two forms. This is illustrated in Fig. 7.8. We can differentiate two possible scenarios, shown in Figs. 7.8a and b. For the monotropic system (Fig. 7.8a), the sublimation curve of form I is below the sublimation curve of form II. Since the stable polymorph is the one with the lower vapor pressure, in the case of a monotropic pair of polymorphs, one form (here form I) is always the stable form until either of the forms melts. Note that after melting there is no difference between the melts of the substance, irrespective of the polymorphic solid form. Should initially form II have been generated by cooling from a melt (according to Ostwald's rule this is not unlikely to happen in a practical scenario), then if conversion occurs to the stable form I, this conversion will be irreversible. The situation is different for enantiotropic systems (Fig. 7.8b). Here form II has a lower vapor pressure than form I at low temperature (so it is the stable polymorph at these temperature conditions), but at higher temperatures there is a crossover in the sublimation curves of the two polymorphs before either of

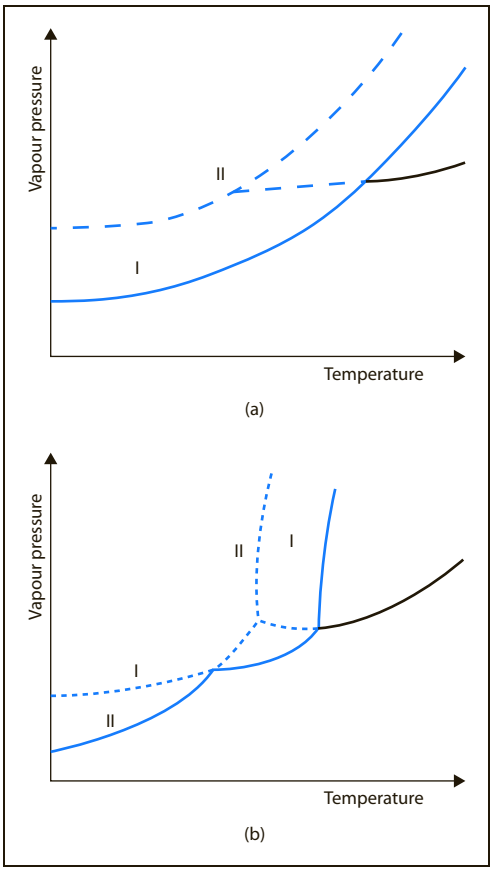


Figure 7.8 Phase diagrams of (a) a monotropic and (b) an enantiotropic polymorphic system. The solid lines represent stable states.

these forms melts. After the crossover, form I now has the lower vapor pressure and is the stable form. This means if we have form II present at low temperature, this is the stable form, but upon heating at a certain temperature, polymorphic conversion will take place and form I is the stable form. If we now cool down form I again, conversion back to form II will occur. In other words, the process is reversible.

Amorphous solids

In the previous section we have seen that a crystalline solid is characterized by its long-range positional order. Amorphous solids lack the long-range order seen in crystals, although short-range order over several molecular dimensions may exist. The molecular arrangement is thought to represent that of a frozen liquid with the rheological properties of a solid.

Heating of a crystalline material leads to a gradual increase in the thermodynamic properties such as enthalpy and entropy until the melting point, T_m, is reached (Fig. 7.9). As we have seen, a significant increase in thermodynamic properties marks the first order transition (melting) from the solid to the liquid state. Above the melting temperature, the material exists as a molten liquid. This is a reversible process, so upon cooling, crystallization of the melt occurs whereby the molecules rearrange themselves in their crystal lattice. However, if the liquid is cooled sufficiently fast below its melting temperature, crystallization may be prevented so that a super-cooled liquid is formed, and the slope of the equilibrium liquid line (Fig. 7.9) may be followed, resulting in a gradual decrease of the thermodynamic properties below T_m.

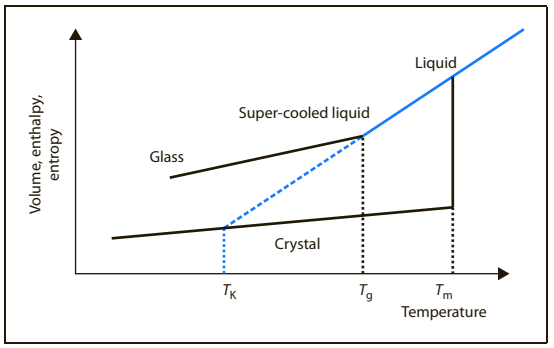


Figure 7.9 Thermodynamic relationship of crystalline and amorphous solids as a function of temperature. Shown are the melting temperature (T_M), the glass transition temperature (T_G), and the Kauzmann temperature (T_K).

At temperatures above the glass transition temperature (T_g, Fig. 7.9) the material is said to be in the super-cooled liquid state (sometimes also called the rubbery state), the viscosity of which is typically between 10^{-3} and 10^{12} Pa s. In the super-cooled liquid state, the molecules are able to follow any further decrease of temperature to attain equilibrium conditions. However, cooling of the super-cooled liquid increases the viscosity of the system, and upon further cooling the molecules are not able to reach equilibrium any longer. At this temperature, the T_g, the molecules are "kinetically frozen in" and the super-cooled liquid solidifies into a glass. (Note that in a glass the molecules still show some mobility.) The T_g represents the temperature at which the system falls out of equilibrium. Amorphous solids are therefore non-equilibrium solids and the glass transition is a second order phase transition. Unlike melting or boiling, the heat capacity is not infinitively high at the phase transition, but jumps from one value to another. The non-equilibrium state of a glassy amorphous system has special implications: the fundamentals of thermodynamics only apply to systems in equilibrium, and therefore, the behavior of the glassy state cannot be predicted from regular thermodynamics.

Due to the high viscosity of the resulting glass (viscosity is usually greater than 10^{12} Pa s), it appears as a solid. The T_g represents a characteristic thermal event for an amorphous systems, but it should be noted that the T_g is a kinetic property of the material, and its exact position depends, for example, on the cooling rate of the super-cooled liquid, i.e., on its thermal history.

In principle, the amorphous state can be produced in two ways:

1. From a liquid state, either by rapidly cooling the molten liquid or by fast evaporation of a solvent from a solution, hence "freezing in" the molecular arrangement of the liquid (vitrification), or
2. By gradually inducing and increasing defects in the crystal lattice until the amorphous state is generated (amorphization).

The vitrification process (**1**) is also termed the thermodynamic pathway to form amorphous materials, and

the amorphization process (2) has been named the kinetic pathway. A schematic representation of the conversion from crystalline to amorphous is depicted in Fig. 7.10.

If the amorphous state is produced via the thermodynamic pathway, the crystalline material has to be transferred to a liquid state, either by melting or by dissolution in an appropriate solvent. If the kinetic pathway is followed, the crystalline lattice is continuously disrupted by mechanical processing like milling, inducing crystal defects. As long as the crystal defects remain small in number, the material still exhibits crystalline properties. However, if a critical number of defects are introduced, the crystal cannot retain its structure and converts to the amorphous state. The main difference between these two approaches is that while the thermodynamic pathway abruptly destroys the long-range order of the crystal, the kinetic pathway gradually increases the number of crystal defects, thereby creating non-equilibrium crystalline states. Such materials, still crystalline but with increasing number of defects, are termed defective crystals.

While the thermodynamic pathway is commonly employed in order to deliberately generate the amorphous state, the kinetic pathway is usually associated with the unintentional amorphization of a crystalline material, for example when the actual objective of a milling process is to reduce the particle size of the crystalline material, not to change its solid state form.

It should be noted that not every preparation technique to convert a crystalline drug into its amorphous counterpart is suitable for every drug, e. g. thermolabile drugs cannot be converted to the amorphous form by using heat based methods; drugs that are insoluble in a range of organic solvents cannot easily

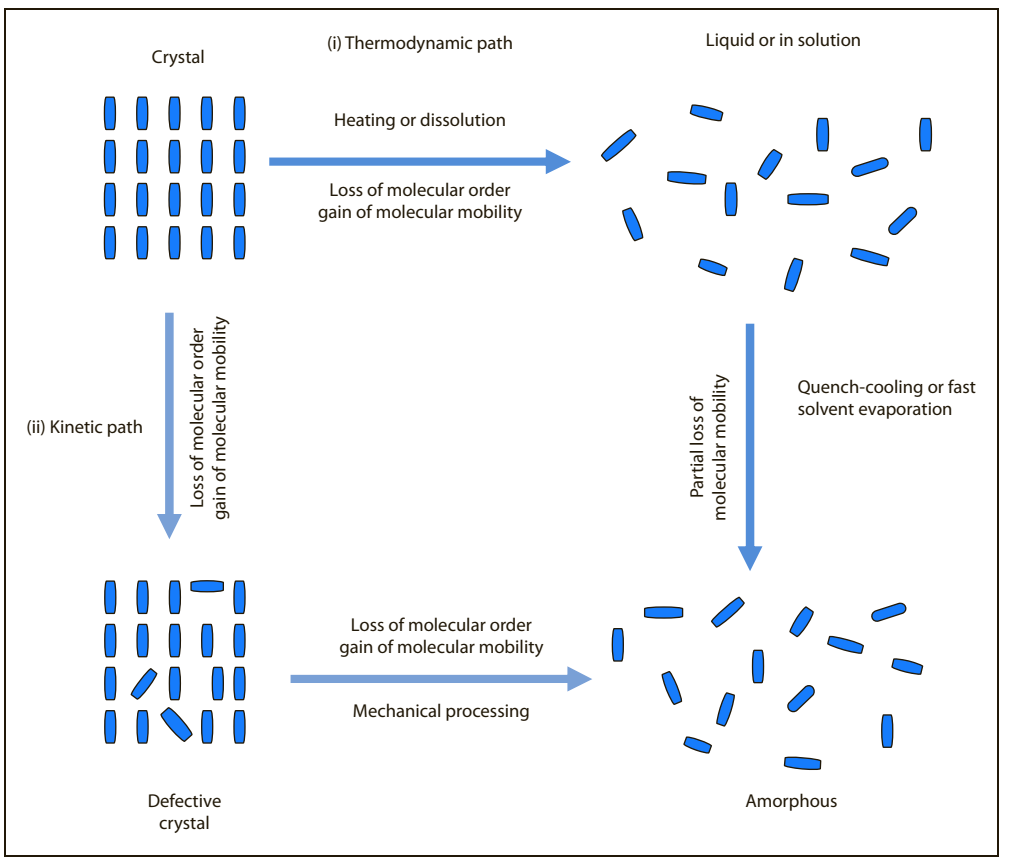


Figure 7.10 Schematic representation of the crystalline to amorphous conversion via the thermodynamic and kinetic pathways.

be spray-dried to amorphize the substance, and some methods (milling) may not completely convert certain drugs into the amorphous state. We have now seen a variety of methods that can be used to generate the amorphous state of a drug. The question arises whether the amorphous state generated is the same in all cases.

Let us take a closer look at the T_g, an important feature in the amorphous state. Above the T_g the system is still in an equilibrium state; below the T_g the system has fallen out of equilibrium. Let us imagine that the T_g did not exist: in Fig. 7.9 we see that the decrease of the temperature would eventually lead to the super-cooled liquid line intersecting with the crystal line. This would cause the super-cooled liquid eventually to have a lower entropy than the crystal upon further cooling. This, however, is not considered possible. The theoretical temperature at which the super-cooled liquid would attain the same properties as the crystal is known as the Kauzmann temperature, T_K (see Fig. 7.9). The kinetic nature of the glass transition is evident from its dependence on the heating and cooling rates, which means that the T_g does not exist at a defined temperature. Slow cooling rates lead to a prolonged super-cooled liquid state and result in a T_g with a lower temperature, as displayed by T_gII in Fig. 7.11. As the super-cooled liquid is cooled at a slower rate, the system is able to adjust to the temperature dependent increase in viscosity, resulting in a lower temperature for the glass transition. Glasses created by slower cooling rates also show lower values of enthalpy and entropy than glasses that are created by faster cooling rates.

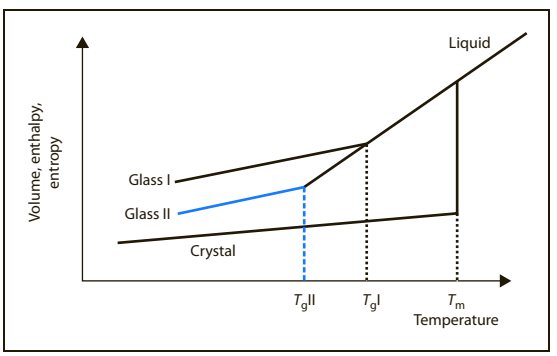


Figure 7.11 Thermodynamic relationship of glasses created by different cooling rates. Glass I has been cooled fast, and glass II has been cooled slowly.

The explanation for this is that due to the lower onset of the T_g, the super-cooled liquid state is maintained at lower temperatures, therefore decreasing the value of enthalpy and entropy further.

For practical purposes, this means that for a given material an amorphous system which is prepared by one method is not identical to the amorphous system prepared by another method. Even if the method is the same but parameters are varied, the resulting amorphous states will not be identical. So, unlike the "crystalline state," which has defined properties, there is no "amorphous state". Depending on the preparation method, sample history, geometry and mass, and the experimental heating and cooling rates, the amorphous states can differ considerably in properties, especially in physical stability (recrystallization to the crystalline state).

From Fig. 7.9 we can see that the amorphous state has higher thermodynamic properties, like enthalpy and entropy, compared to the crystal. What Fig. 7.9 does not show, however, is that the properties of the amorphous state are time-dependent. As time passes, we observe that the amorphous state decreases in properties such as enthalpy even though the temperature is kept constant. This phenomenon is called relaxation, and it has its origin in the instability of the amorphous state. The molecules may be frozen in, but they still have some molecular mobility left. This is sufficient for the molecules to relax over time and rearrange themselves in a more thermodynamically favorable way. By doing this, they decrease their enthalpy, and this is also considered an important factor in the stability of amorphous systems. This relaxation can be visualized in a differential scanning calorimetry (DSC) thermogram, in which the relaxation appears as an endothermic peak on top of the glass transition event.

In recent years the amorphous state of drugs has gained increasing interest in pharmaceutics due to its favorable solubility properties, compared to its crystalline counterpart.[4] Many new drugs show insufficient solubility for oral dosage form development. Because of its higher energy, the solubility of amorphous forms is often orders of magnitude higher than for crystals and, thus, this solid form is attractive in dosage form development. However, issues when dealing with the amorphous state, such as physical and chemical instabilities, remain. Also, to date, the

prediction of physical and chemical stability of drugs in the amorphous state still proves challenging, since, for example, the application of stress tests is not straightforward for amorphous systems (they don't behave in an Arrhenius fashion).

Solids with more than one component

In the previous sections we have discussed crystalline and amorphous solids on the basis of single component systems, i.e., we were considering a single chemical entity (e.g., the drug molecules). In this section we will expand the discussion on solids by introducing a second component.

Solvates and co-crystals

Not only can most drugs crystallize in different polymorphic forms, but they can also incorporate other molecules to form crystalline structures. For example, during a crystallization process from a solvent, solvent molecules may be incorporated into the crystalline structure. This occurs if the solvent molecules can interact with the drug molecules through hydrogen bonding or other weak interactions. In this case a new crystalline structure of the drug and the solvent molecules may be formed. These crystalline structures are termed solvates. In the specific case of water as the additional molecule to be incorporated into the crystalline structure, the solvate is called a hydrate. Hydrates can also form from crystalline or amorphous non-hydrate drug substances by addition of water molecules from the air or during a dissolution process in water. Thus, hydrate formation of a drug (if the drug can indeed form hydrates, which is compound specific) may even occur during the oral administration of the drug. This is of pharmaceutical significance, for in most cases the resulting hydrate will have lower water solubility than the respective non-hydrate, which may even result in a lower bioavailability. For example, partial hydrate formation has been made responsible for erratic bioavailability of carbamazepine and theophylline after administration of the drug in a non-hydrate form.[5,6]

Since the water molecules (or other solvent molecules) are incorporated into the crystalline lattice in a regular structure, the molar ratio of drug to solvent molecules will take on fixed ratios (stoichiometric hydrates). However, this molar ratio does not have to be 1:1 (monohydrates), and, for example, hemihydrates (the molar ratio of drug to water molecules in a hemihydrate is 2:1) or dihydrates (the molar ratio of drug to water molecules is 1:2) are not uncommon. Some drugs can form different hydrates (for example, mono- and dihydrates), and even within one group of hydrates, polymorphism may occur, further increasing the possibilities of a given material to crystallize in many different forms, with different physicochemical properties.

Not all hydrates, however, have a fixed stoichiometric ratio between the drug and the water molecules. If the water molecules can be incorporated into channels that may be present in a non-hydrate crystalline structure, many different ratios of water to drug molecules are possible, depending, for example, on the relative humidity of the air surrounding the hydrate. These types of hydrates are called channel hydrates.

If a stoichiometric hydrate loses its water (for example, by heating), the water in most cases will leave the crystal at a defined temperature. If we are measuring the weight loss of a hydrate as a function of temperature (these types of measurements are called thermogravimetric measurements), typical weight loss curves, as shown in Fig. 7.12, are obtained for stoichiometric hydrates. In case of a dihydrate, for example, water may be leaving the crystal initially to form a monohydrate that is then losing the remaining water at a higher temperature, so two steps in the weight loss curve may be observed (Fig. 7.12b). For a given mass of material, if the molecular weights of the drug and the solvate molecule ($18\,g\,mol^{-1}$ in case of water) are known, the stoichiometric ratio of drug to solvate molecules can be determined by these measurements. In some cases the water only leaves the crystal upon melting of the material. In contrast, for channel hydrates the water molecules are leaving the crystalline structure often before melting and over a broader temperature range. If the water in a stoichiometric hydrate leaves the crystal before melting this may result in a collapse of the crystalline structure altogether, leading to the formation of an amorphous material. In the case of channel hydrates, the result of water leaving the crystal may be a non-hydrate with almost the same crystalline structure as the hydrate (same crystal lattice type and similar, but not identical, lattice parameters), sometimes called a vacant

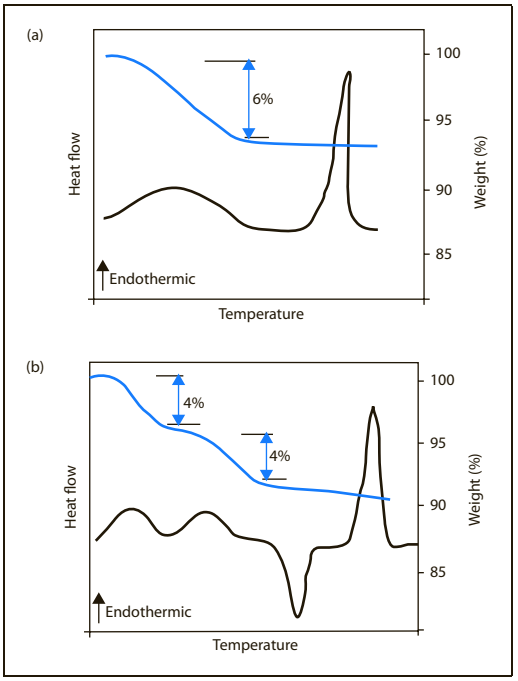


Figure 7.12 Thermogravimetric weight loss curves (—) and corresponding DSC curves (—) of (a) a hypothetical monohydrate and (b) a hypothetical dihydrate. Note that the water loss also appears as an endothermic event in the DSC thermogram. Other thermal events in the DSC curves (e.g., a polymorphic conversion, or melting) are not accompanied by a weight loss in the thermogravimetric curves.

hydrate, before further polymorphic conversion to the stable non-hydrate form occurs.

Of recently increasing pharmaceutical interest are co-crystals.[7] Unlike salts, in which the drug (as an anion or cation, depending on the nature of the drug) is bound by ionic interaction to the counterion, in a co-crystal the drug and the co-crystal former (see below) are interacting via weaker interactions, in most cases by hydrogen bonding, as is the case for solvates. However, in contrast to solvates, both components of the co-crystal are solid at room temperature. If the hydrogen bond between the two molecules is formed by similar molecular moieties (for example, two carboxylic acid groups), this is known as a supramolecular homosynthon, whereas a hydrogen bond between two different moieties of the two components (for example, a phenol group and an amide group) is known as a supramolecular heterosynthon. Generally, the formation of a heterosynthon leads to a higher likelihood of formation of a stable co-crystal. Typical co-crystal formers used in the pharmaceutical field include maleic acid, tartaric acid, nicotinamide, saccharin, and many others. Since co-crystals have other properties, including solubility, hygroscopicity, and pharmaceutical processability, they offer interesting possibilities in drug development. Co-crystals (for example, the carbamzepine–nicotinamide co-crystal and the carbamazepine–saccharin co-crystals) can also show polymorphism.[8]

Eutectics

Above we have considered solid state materials containing two components but forming a single phase. Eutectics are an important example of a solid mixture of crystals (in contrast to co-crystals, which are "mixed crystals", rather than a "crystalline mixture"). Eutectics thus contain two phases. However, in eutectic mixtures the two phases (two materials) are intimately mixed and thus often show different properties from simple physical mixtures of the two components.

Let us consider two crystalline materials, A and B, with meeting points T_{m_A} and T_{m_B}, that are miscible in the molten state, i.e., they form a single liquid phase. This is shown in form of a phase diagram in Fig. 7.13. If we have a mixture of the two materials at the mixing ratio R1, at a temperature where both materials are molten (so we are in the liquid area of the phase diagram), and we now reduce the temperature of this melt, at the intersection with the melting curve,

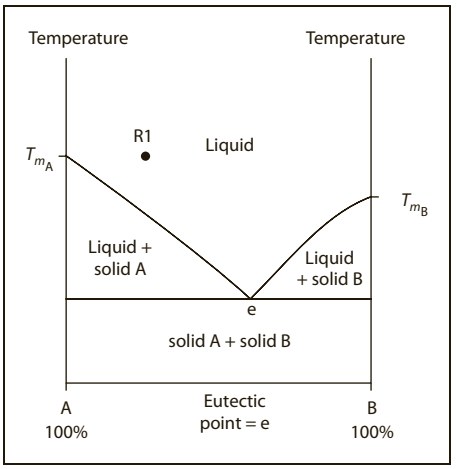


Figure 7.13 Phase diagram of two materials, A and B.

we will observe crystallization of compound A. As A will crystallize, but not B, this means that the composition of the remaining melt will change and it will become more B-rich. We thus follow the melting curve upon further lowering of the temperature until we reach the lowest point of the melting curve of A. If we lower the temperature further, now B will also crystallize. Similarly, if we have a B-rich mixture, B will crystallize when the temperature is lowered to the melting curve of B. This, in turn, will lead to the remaining melt having relatively more A than the original melt, and we follow the melting curve of B until we reach its lowest point, which is the same as for an A-rich system. The ratio of A and B at this point is called the eutectic mixture for these two compounds, and the temperature in the phase diagram is known as the eutectic temperature (e), the lowest temperature at which both compounds crystallize together. In other words, at the eutectic point both crystalline A and B and the melt are in equilibrium. For the eutectic mixture of sodium chloride and water, this occurs at a salt concentration of 22.4% and a eutectic temperature of -22°C.

For a given two compound system, the ratio of the compounds at the eutectic mixture can be estimated from the theoretical melting curves of the two compounds, using a simplified form of the Schröder–Van Laar equation:

$$\ln x = \frac{\Delta H_0}{R}\left(\frac{1}{T_0} - \frac{1}{T}\right) \tag{7.6}$$

where x is the mole fraction of one compound in the mixture, ΔH_0 and T_0 are the corresponding heat of fusion [$\mathrm{J\,mol^{-1}}$] and melting temperature [K] of the pure compound, respectively, T is the melting point of the binary mixture at x, and R is the gas constant [$8.314\,\mathrm{J\,K^{-1}\,mol^{-1}}$]. However, it should be noted that for this approach to be valid, a number of assumptions are made: there is no solid solution formation between the two compounds (see below), the melt has to be an ideal mixture, and the heat capacities of the pure compounds in the melt and as a solid should be fairly similar.

In the phase diagram shown above, we did not consider the possible formation of a solid solution between the two compounds. If this occurs, then there will be partial miscibility between the compounds in the solid state, and rather than pure compound A and pure compound B crystallizing together at the eutectic point, we will have the crystallization of an A-rich and a B-rich phase of the two corresponding solid solutions. This plays a major role in the formation of metal alloys.

Amorphous mixtures

We have discussed above that the amorphous form of a solid is thermodynamically unstable and tends to crystallize back to the stable crystalline form or a metastable polymorphic form. In order to make use of the advantages, including a higher dissolution rate and solubility that amorphous solids offer, especially for poorly water soluble drugs, it is therefore often necessary to stabilize the amorphous form. One way of achieving this is to use two components (for example, a drug and an excipient) in the formation of a solid amorphous material. In most cases this will be an amorphous, hydrophilic polymer. If an amorphous polymer (such as, for example, polyvinypyrrolidone (PVP), PVP-vinylacetate copolymer (PVPVA), hydroxypropylmethylcellulose (HPMC), HPMC-acetatesuccinate (HPMCAS), and various polymethacrylates) is melted together with the drug to form a single phase melt, this can be cooled down rapidly to form a single phase amorphous material, known as a glass solution (do not confuse the amorphous glass solution with the crystalline solid solution, mentioned above). In this solid form the drug and the polymer are molecularly mixed with each other. For this to be successful, it is required that the two compounds show mutual solubility, for example, have similar solubility parameters. It is often advantageous for the physical stability of glass solutions if some interactions between the drug and polymer occur (usually hydrogen bonding), since this will lower the molecular mobility (especially of the low molecular weight drug) and thus will slow down the processes of nucleation and crystal growth, which lead to the crystallization of the amorphous material. The polymers used for the formation of glass solutions often have a high glass transition temperature (T_g) so that the resulting glass transition temperature of the glass solution will be higher than the T_g of the pure amorphous drug, further stabilizing the drug against crystallization. If the glass transition temperatures of the two pure amorphous components are known, the resulting glass transition

temperature of the glass solution in various mixing ratios of the two compounds can be estimated based on the Gordon–Taylor equation:

$$T_{g12} = \frac{w_1 T_{g1} + K w_2 T_{g2}}{w_1 + K w_2} \tag{7.7}$$

where T_{g12} is the glass transition temperature [K] of the mixture; T_{g1} and T_{g2} are the glass transition temperatures [K] of the single amorphous compounds (e.g., the drug and the polymer); w_1 and w_2 are the weight fractions of each compound in the mixture; and K is a constant, depending on the glass transition temperatures and amorphous densities of the single compounds:

$$K = \frac{T_{g1}\rho_1}{T_{g2}\rho_2} \tag{7.8}$$

where ρ_1 and ρ_2 are the densities of the single amorphous components. It should be noted, though, that this equation assumes volume additivity, i.e., the absence of specific molecular interactions and, as such, can often only be used as an estimate for the actual glass transition temperature of the glass solution.

In most cases the T_g of the glass solution is predicted by using the T_g of the drug and polymer. However, in real situations a third component can be present: moisture. It is known that moisture can accelerate crystallization from the amorphous state, and this effect can be explained by the plasticizing effect of water. The T_g of water is approximately 139 K, which is significantly lower than the T_g of commonly used pharmaceutical materials. In the same way that a high T_g polymer is added for stability, a low T_g compound can lower the T_g of the system. If the Gordon–Taylor equation is extended to a third component, it is obvious that even small amounts of a low T_g compound can have a significant effect on the T_g and, hence, on stability. Therefore, moisture should be excluded during manufacturing and storage of amorphous systems.

If the two components (for example, the drug and the polymer) are not miscible on a molecular level, the formation of a solid suspension may occur upon cooling of a melt of the two components. These systems will show two glass transition temperatures, one for the drug (or possibly a drug rich phase, if there is partial miscibility) and one for the polymer (or the polymer rich phase).

Methods to characterize solids

We have seen that a pharmaceutical solid can be present during development or in a final dosage form in various polymorphic forms. It can also be present in form of hydrates or other solvates. Salt formation is possible, as is the formation of a co-crystal. Solvates, salts and co-crystals in their own right can show polymorphism. The drug may also be partly or fully amorphous, either on its own or in form of a glass solution or amorphous suspension. All of these solid state forms will differ in many of their physical properties, and this can be relevant for the drug and dosage form if, for example, solubility, dissolution rate, and chemical and physical stability are affected. It is thus obvious that we require a thorough identification and, in many cases quantification, of the various solid state forms of a drug that we may encounter in preformulation, formulation, during storage and upon administration of the dosage form. It is also obvious that this task is more complex for solids than, for example, if the drug is present in liquid form or in a solution, for in these cases all differences of the solid state forms disappear.

The list of analytical techniques that are useful to investigate solid state properties is almost endless, and it is convenient to differentiate the techniques available to the pharmaceutical scientist according to the different levels at which they probe the solid material. Most spectroscopic techniques, such as Raman and infrared (IR) spectroscopy, but also solid state nuclear magnetic resonance (NMR), near IR spectroscopy and others are probing predominately molecular properties. If a drug, for example, can crystallize in different polymorphic forms, these forms still contain the same molecules, and as such, the resulting spectra should be identical. Indeed, that is (almost) the case. However, the fingerprint regions of the resulting spectra will also be influenced by the neighboring molecules, for example, by the unit cell of the crystalline forms. Because these are different between different polymorphic forms, the resulting spectra, for example, for IR and Raman measurements, will also (subtly) be different. If the polymorphic pair shows configurational differences between the molecules, the differences in the resulting spectra will be larger than if the configuration of the drug molecules is the same in both polymorphs. It is often necessary to use multivariate data analytical tools, such as principal components

analysis or partial least squares analysis, to identify the different solid state forms using IR or Raman spectroscopy. It is advisable, in any case, to use such techniques if a quantification of different solid state forms that are present at the same time is desired. Generally, differences in the spectra between a non-solvate and a solvate form are larger than between two polymorphic forms, and differences between the spectra of a crystalline and an amorphous form may be even larger, with the spectra in IR and Raman measurements being less well defined (peak broadening and peak merging) for amorphous forms, compared to their crystalline counterparts. Figure 7.14 shows example IR spectra (Fig. 7.14a) and Raman spectra (Fig. 7.14b) of different solid state forms of the drug indomethacin.

The next level of analytical techniques, and in many ways the "gold standard" techniques to characterize and quantify different solid state forms of a drug, are the techniques that probe an assembly of molecules. These techniques have been termed "particulate level techniques," and include X-ray diffraction (mostly used in the forms of X-ray powder diffraction, XRPD), and various thermal analytical techniques (of which DSC plays the largest role in pharmaceutical analysis). These will be described

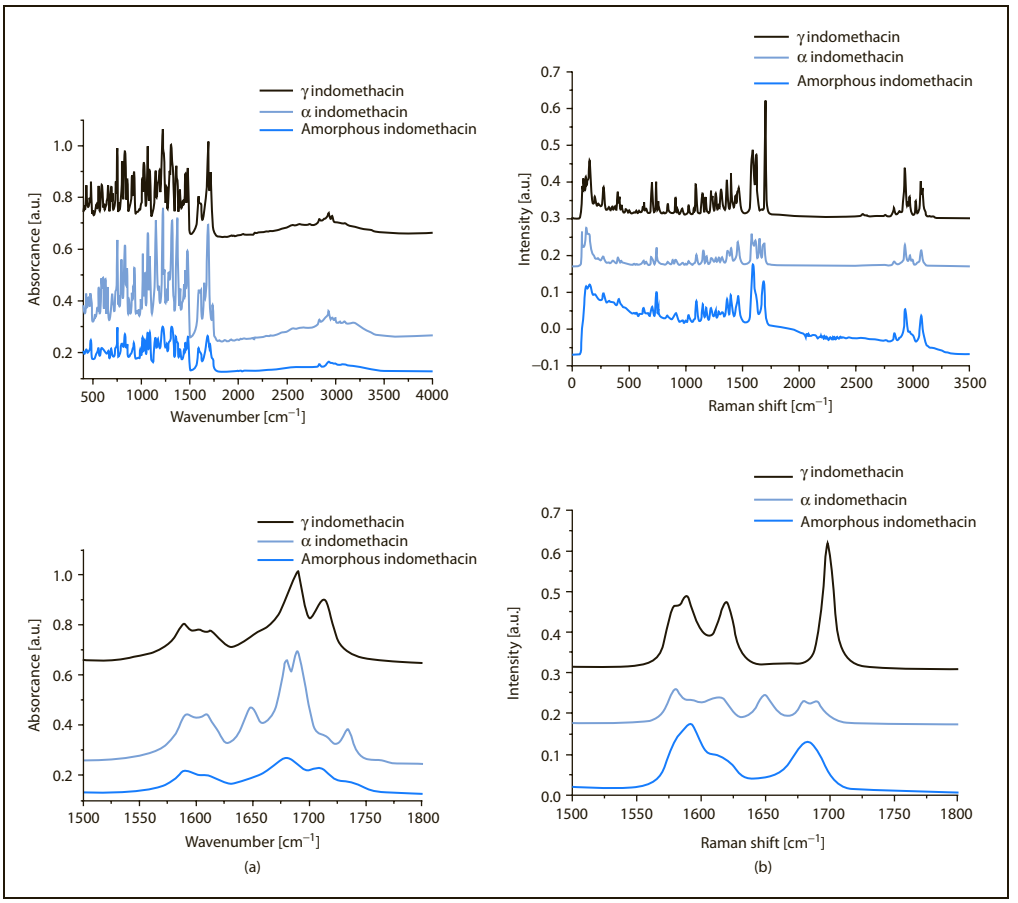


Figure 7.14 (a) Infrared spectra of amorphous indomethacin, and the α- and γ-polymorphic crystalline forms of indomethacin. The lower figure shows the wavenumber region of 1500–1800 cm^{-1} (C=O stretch), where differences between the different solid state forms can be clearly visualised. Individual traces are offset for clarity. (b) Raman spectra of amorphous indomethacin, and the α- and γ- polymorphic crystalline forms of indomethacin. The lower figure shows the wavenumber region of 1500–1800 cm^{-1} (C=O stretch), where differences between the different solid state forms can be clearly visualised. Individual traces are offset for clarity.

briefly below. It should be noted, however, that also terahertz spectroscopy, probing the phonon modes of solids, is a particulate level technique, as are the various microscopic and electron microscopic techniques.

X-ray powder diffraction is one of the most important analytical techniques used in solid-state analysis. An X-ray powder pattern is the result of scattering of an incident monochromatic X-ray beam by the lattice of the crystalline material.The resulting diffractogram is based on constructive and destructive interference of the diffracted X-ray beams. This phenomenon is described by Bragg's law:

$$n\lambda = 2d \sin \theta \tag{7.9}$$

where n is the order of reflection (an integer); λ is wavelength of the incident beam [Å]; d is distance between the planes in the crystal [Å]; and θ is angle of beam diffraction.

Constructive interference takes place when the scattered X-rays are in phase, i.e., the phase difference that the scattered X-rays reflected from two neighboring planes of the crystal lattice is an integer (Fig. 7.15). Each crystalline material will exhibit a diffractogram, which is unique to the specific compound and its solid state form, and individual peaks may be attributed to the crystalline structure. As amorphous solids do not possess an ordered lattice, no diffraction occurs and no diffraction pattern is obtained. Rather, a diffuse "amorphous halo," showing one or several broad maxima, is observed. XRPD is particularly useful to detect small amounts of crystallinity in an amorphous sample, for the residual crystallinity results in small diffraction peaks on an amorphous halo. However, the technique is of limited use for the detection of low levels of amorphous content since the halo will be obscured by the stronger crystalline diffraction peaks.

XRPD is one of the most commonly used techniques in the pharmaceutical industry for solid-state analysis because it may be used for the identification and quantification of polymorphs, solvates, hydrates and amorphous forms, based on their unique diffraction patterns. It does not require large sample sizes, and unlike thermal methods, it is a non-destructive technique. This is potentially advantageous in the early stages of pharmaceutical development, and despite its limitations in detecting low levels of amorphous material, XRPD has been used both qualitatively and quantitatively in the characterization of partially crystalline systems. Quantification of the crystalline content can be achieved by measuring the area or the height of the main peaks in the diffractogram and of the amorphous content by measuring the amorphous scattering in the diffractogram. However, quantitative analysis using XRPD has to be carried out carefully, for physical characteristics such as sample height, surface character and shape, and the presence of microcrystallinity may influence the outcome of the measurements. Figure 7.16 shows example diffractograms of different solid state forms of the drug indomethacin.

DSC is used in the study of both crystalline and amorphous materials. Two types of DSC instruments are available: power-compensated DSC and heat-flux

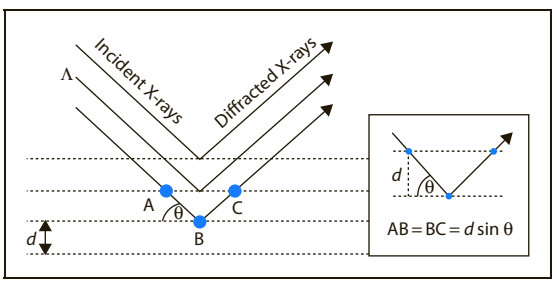


Figure 7.15 Diffraction of X-ray beams by planes of a crystal lattice. A, B, and C are points in the crystal planes; d is the distance between two planes.

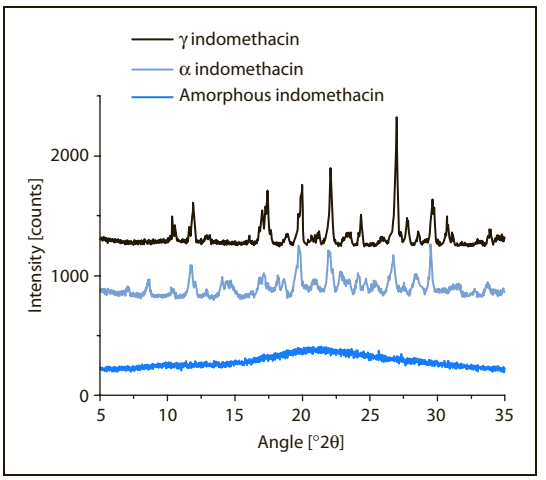


Figure 7.16 X-ray powder diffraction patterns of amorphous indomethacin, and the α- and γ-polymorphic crystalline forms of indomethacin. Individual traces are offset for clarity.

DSC. In power-compensated DSC a reference and a sample pans are placed on two individual furnaces, and the temperature difference between them is maintained at zero by varying the heat that is required to keep both pans at the same temperature. The parameter recorded is the difference in energy input which is required to maintain the samples at the same temperature, for example, during a melting process. In heat-flux DSC one heating element is used for sample and reference. Heat is applied to both via an electrically heated thermoelectric disc, and the temperature difference between sample and reference is monitored. The obtained signal is converted to heat flow [mW] via the following relationship:

$$\Delta Q = \frac{T_s - T_r}{R_\gamma} \tag{7.10}$$

where Q is heat energy [J]; R_γ is the thermal resistance [$K\,J^{-1}$]; T_s is the sample temperature [K]; and T_r is the reference temperature [K].

In DSC, thermal events connected to the sample are presented in a thermogram, in which endothermic and exothermic energy deviations from the reference pan are recorded as a function of time or temperature. Endothermic events include processes such as evaporation, melting, and some solid–solid transitions. In contrast, the recrystallization of an amorphous form and other solid–solid transitions are exothermic. It is possible to use DSC not only to determine the temperature of these events but also to calculate the heat of the respective reaction.

As we have seen above, any change in the enthalpy of a system at constant pressure can be described by the change in heat. Hence, the area under a DSC peak is directly proportional to the heat absorbed or released by the thermal event if the sample mass is known.

The determination of the heat capacity, C_p, for the amorphous state is of particular interest, for the glassy and the super-cooled liquid state exhibit different values for their respective C_ps, and the heat capacity will change in a stepwise fashion at the glass transition temperature. The extent of the difference in heat capacity (ΔC_p) is an important characteristic for amorphous materials. The enthalpy of a system increases as its temperature is increased. The heat capacity can be obtained as the slope of a plot of enthalpy versus temperature at constant pressure:

$$C_p = \left(\frac{\delta h}{\delta T}\right)_p \tag{7.11}$$

The advantages of DSC for analytical purposes lie in the requirement of only small sample sizes (typically 2 to 6 mg), the broad temperature range, and in the speed of the experiments (heating rates of 5 to 20 $K\,min^{-1}$ are typically employed). DSC can be used to analyze both crystalline and amorphous materials, and unlike XRPD, it is possible to directly detect the amorphous content through the presence of a T_g.

The thermal behavior of a solid sample may be analyzed, for example, in terms of

- Melting point and melting enthalpy of polymorphic crystalline materials
- Conversion temperature of two enantiotropic polymorphic forms
- Enthalpy and temperature of the loss of solvate molecules from solvates
- Heat capacity difference and temperature of the glass transition of amorphous material
- Enthalpy and temperature of any crystallization events of amorphous material
- Temperature of decomposition
- Extent of interactions in mixtures (e.g., with excipients).

Quantification, for example, of amorphous content in a sample is also possible. However, despite the many advantages that make DSC one of the most widely used techniques, it has to be considered that the analyzed sample is subjected to thermal treatment, which destroys or at least changes the sample and may induce thermal artifacts. Therefore, care has to be taken in the interpretation of thermograms to avoid misleading conclusions. Moreover, DSC thermograms are often difficult to interpret if multiple overlapping thermal processes are involved. Every DSC thermogram is a compromise between sensitivity and resolution as both are dependent on the heating rate, but in opposite ways. To increase the sensitivity, the scan rate may be increased; however, this may lead to decreased resolution, for the scan rate may be too rapid to separate close thermal events.

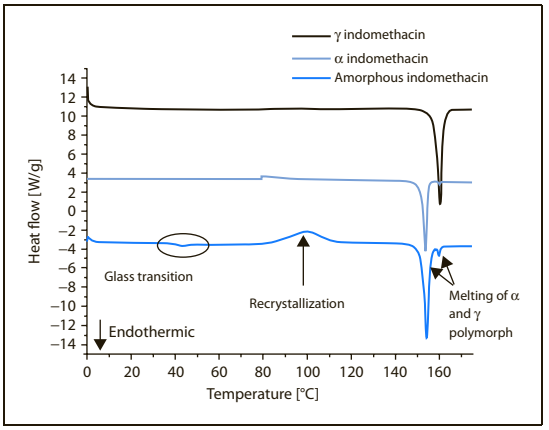


Figure 7.17 DSC thermograms of amorphous indomethacin, and the α- and γ- polymorphic crystalline forms of indomethacin. The thermogram of the amorphous form shows a glass transition and recrystallization event, in addition to the melting. Individual traces are offset for clarity.

Figure 7.17 shows example DSC thermograms of different solid state forms of the drug indomethacin.

Modulated temperature DSC (MTDSC) is an alternative to conventional DSC.[9] In MTDSC a sine wave modulation is applied to a linear temperature program. The obtained heat flow signal is analyzed by applying a discrete Fourier Transform algorithm, which results in the deconvolution of the measured heat flow signal into reversing and non-reversing components. The non-reversing signal comprises the kinetically controlled events that are dependent on the absolute temperature alone, and the reversing signal is a function of the samples' heat capacity and rate of temperature change. The heat flow signal of a sample will be a combination of these two components. The total heat flow signal may, therefore, be expressed as

$$\frac{dQ}{dt} = C_p/dT + f(t,T) \qquad (7.12)$$

where dQ/dt is the heat change over time (heat flow) [J s^{-1} or W]; C_p is the "thermodynamic" heat capacity [J K^{-1}]; T is the temperature [K]; and $f(t,T)$ is the kinetic response.

Conventional DSC records the reversing and non-reversing heat flow simultaneously and is not able to resolve them. MTDSC is able to separate the heat capacity (reversing) and kinetic (non-reversing) components, due to their different responses to the underlying and modulated heating rates. Processes that occur at defined temperatures, such as crystallization, evaporation, relaxation, and decomposition will appear in the non-reversing heat flow signal. As the reversing component is related to the samples' heat capacity, for example, the glass transition event is visible in the reversing signal. This enables the separation of the glass transition event from any endothermic relaxation.

Liquid crystals

We have seen that crystalline solids are defined by long range order in three dimensions. In contrast, liquids lack long-range order (as do amorphous solids). When some solid materials are heated, they do not directly show a phase transition to the liquid state but instead enter into a different state of matter, between the solid and the liquid state. This state of matter is called the liquid crystalline state. Liquid crystals (also called mesophases) show structural properties which are intermediate between those of crystalline solids and liquids. It should be noted, however, that liquid crystals are not simply a mixture of solids and liquids but, indeed, a separate state of matter. Also, it is important to note that not every organic material is able to exist in a liquid crystalline state. We will discuss a few structural considerations of molecules that can exist in the liquid crystalline state below. These molecules are termed mesogens and usually are anisotropic organic molecules, mostly of rod-like shape.

In a thermogram we observe a first order phase transition, when we, for example, cool a melt that at a certain temperature transforms into a liquid crystal. Similarly the transition from a solid to a liquid crystal is a first order transition. Being situated between the solid and the liquid state of matter, liquid crystals also are a condensed state of matter.

There are two principal types of liquid crystals: thermotropic liquid crystals (TLC) and lyotropic liquid crystals (LLC). TLCs are formed by heating a crystalline solid. In contrast, LLCs are formed by the addition of a liquid (in most pharmaceutical cases, water), to a usually solid mesogen. If we are applying Gibbs' phase law, we can say that the minimum number of components in a TLC is one and in a LLC is two, if a single phase liquid crystal is formed.

The number of degrees of freedom to describe a TLC is two (temperature and pressure) and for a LLC is three (temperature, pressure, and the concentration of the mesogen).

Lyotropic liquid crystals

LLCs can be understood as associations of differently shaped micelles. Micelles are colloidal assemblies of amphiphilic molecules, e.g., surfactant molecules and phospholipids, i.e., molecules that have a polar head group and a lipophilic, non-polar tail group. We can differentiate the following types of LLC, shown in Fig. 7.18.

Lamellar phase (Fig. 7.18a): This is pharmaceutically perhaps the most important liquid crystalline phase and consists of a layered packing of indefinitely extended disc-like micelles, leading to a bilayer structure as repetition unit. As such, the lamellar phase has a one-dimensional, long-range, positional order (from layer to layer) but only long-range orientational order within the layers. It is also possible that a lamellar liquid crystalline phase may be dispersed in excess water (so that we get a two phase system). The resulting lamellar liquid crystalline particles form concentric bilayers and are termed liposomes. Phospholipids are pharmaceutically relevant examples of lamellar liquid crystal forming molecules.

Hexagonal phase (Fig. 7.18b): This type of LLC consists of hexagonally packed rod-like micelles. As such, the hexagonal phase has a two-dimensional, long-range, positional order (normal to the symmetry axis of the rods) but only long-range, orientational

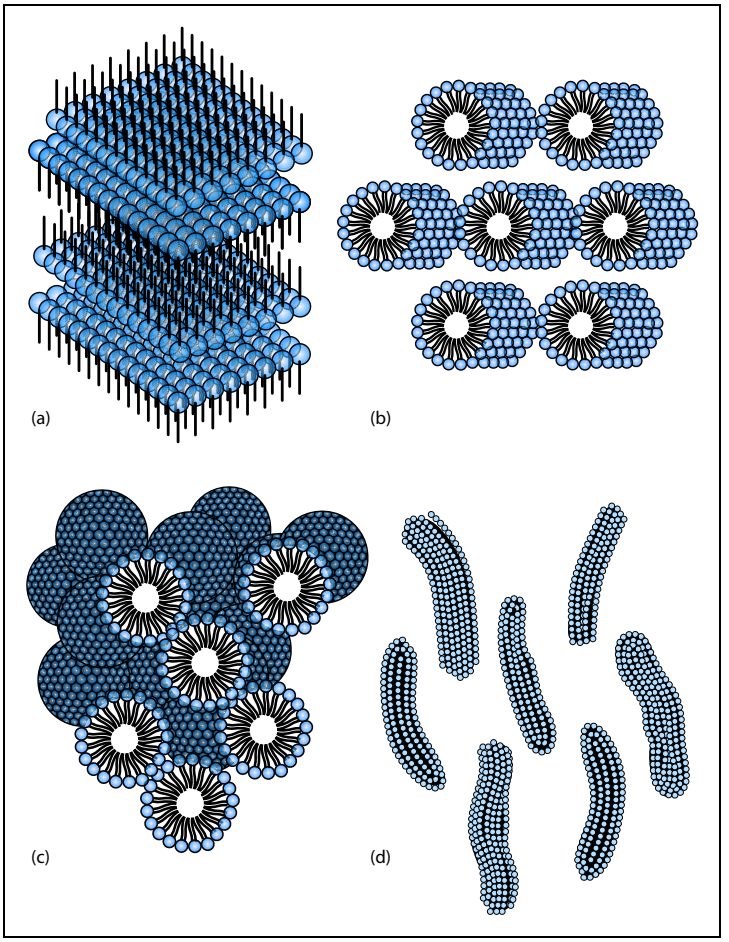


Figure 7.18 Schematic representation of several types of lyotropic liquid crystals: (a) lamellar phase, (b) hexagonal phase, (c) cubic phase, and (d) lyotropic nematic phase.

order within the rods. Depending on the nature of the solvent (polar or non-polar), hexagonal phases can exist in a normal and in a reversed form. In the normal form the polar head groups of the mesogens are pointing outwards, and in the reversed form inwards into the rod-like micelles that are forming the hexagonal phase. As we have just discussed for the lamellar phase, also the hexagonal phase of some amphiphilic molecules may be dispersed into colloidal particles, known as hexosomes.

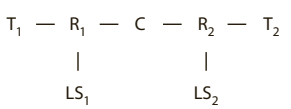
Cubic phase (Fig. 7.18c): This type of LLC consists, in the simplest case, of a cubic packing of spherical micelles. As such, the cubic phase has a three-dimensional, long-range, positional order, like a crystalline solid. In contrast to a solid crystal, however, the mesogens in the micelles forming the cubic phase show rotational–diffusional motion and not merely vibrations, as in the case of crystals. Micellar cubic phases can also exist in a normal and in a reverse form, depending on the nature of the solvent. Moreover, bicontinuous cubic phases exist, which cannot simply be interpreted as assemblies of spherical micelles, and some bicontinuous cubic phases may also be dispersed into particles called cubosomes.

Lyotropic nematic phase (Fig. 7.18d): This LLC is composed of rod-like micelles and shows a long-range orientational order with respect to the symmetry axis of the micelle. There is no long-range positional order in this type of LLC.

As we could expect from the increasing degree of order, the viscosity of the liquid crystals increases as we go from lyotropic nematic to lamellar, hexagonal, and cubic liquid crystals. Many surfactant and phospholipid mesogens may also show liquid crystalline polymorphism, i.e., they are able to self-assemble into different LLCs, depending on the concentration of the mesogens and temperature.

Thermotropic liquid crystals

The typical structure of a rod-like mesogen able to exist in a thermotropic liquid crystalline state is



(7.13)

The rod-like shape of the mesogen is usually formed by two ring systems (R_1 and R_2, which can be aromatic or aliphatic and may also consist of condensed ring systems). These ring systems are connected by a polar central group (C) and linked to two terminal groups (T_1 and T_2), of which at least one usually is an alkyl chain. However, not all these structural elements necessarily have to be present in a mesogen. Additionally, lateral substituent groups may be present in the mesogen molecular structure (LS_1 and LS_2).

As was the case for LLC, several types of TLC can be differentiated. It is beyond the scope of this section to give a detailed description of all TLC types that have been described in the literature (there are over 20 different types of smectic TLC alone). We will thus restrict the description of different TLCs here to three types: nematic phases, chiral nematic phases (cholesteric phases), and fluid smectic phases (including smectic A and smectic C). Schematic representations of these TLCs are shown in Fig. 7.19.

Above, we have already described a lyotropic nematic phase, formed by elongated micelles. In case of a thermotropic nematic phase, individual rod-like molecules (not micelles) show an orientational long-range order, again in the absence of any positional long-range order. The orientation of the long axes of the rod-like molecules, however, is not the same for all molecules and varies around a preferred orientation, known as the director of the nematic phase ($\hat{n}$). This can be expressed using the order parameter S:

$$S = 0.5\langle 3\ \cos^2 \Theta - 1\rangle \qquad (7.14)$$

where Θ is the angle between the director and the orientation of the molecular length axis of the molecule (see Fig. 7.20). This is, of course, an average value, depending, for example, on the temperature. In the ideal case of complete parallel arrangement of the molecules, S would have the value of unity.

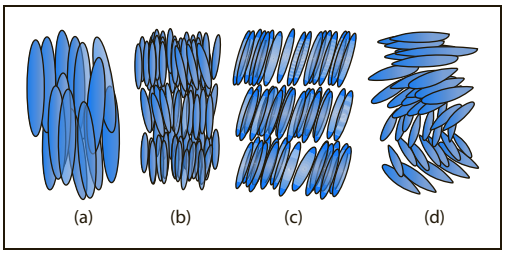


Figure 7.19 Schematic representation of several types of thermotropic liquid crystals: (a) nematic, (b) smectic A, (c) smectic C, and (d) chiral nematic (cholesteric) phase.

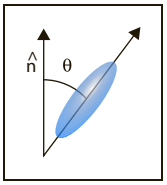


Figure 7.20 Schematic showing the angle Θ between the director (n̂) and the orientation of the molecular length axis of a molecule in a nematic liquid crystal.

The chiral nematic phase can be regarded as a special form of a nematic phase. If the mesogen is chiral (see above), the director field may adopt a helical superstructure, so that we have nematic layers whose directors are shifted by a constant angle from layer to layer. The distance between two nematic layers with the same director is known as the pitch of the chiral nematic phase. Since the pitch height of some cholesteric mesophases is in the order of the wavelength of visible light, they may be colored, and since the pitch height is sensitive to temperature, such liquid crystals may be used as sensitive thermometers, with a specific color indicating a specific temperature.

Smectic phases have a layered structure, similar to the lamellar structure of LLCs. However, in contrast to the lamellar phase, the smectic phase usually does not form a bilayer structure. Depending on the angle the rod-like molecules have with respect to the layer, we can differentiate the smectic A phase (in which the molecules are oriented perpendicular to the layers) from the smectic C phase (in which the molecules are tilted with respect to the layers).

Several drugs have been identified to be able to exist as thermotropic liquid crystals at elevated temperatures,[10] including fenoprofen sodium, fenoprofen calcium,[11] and itraconazole.[12]

Both LLC and TLC can be identified by characteristic appearances (textures) in the polarizing light microscope, as well as by electron microscopic investigation. Also, the liquid crystals show characteristic peak sequences when investigated by X-ray diffraction. Since the distances between the repetition units in liquid crystals are larger than in crystals, the diffraction angles are smaller and, therefore, small angle X-ray diffraction is usually used as an analytical technique, in contrast to wide angle X-ray diffraction, which is usually used in powder diffractometry of crystalline solids.

Liquids

The liquid state of matter is an intermediate state between the solid (and potentially the liquid crystalline state) and the gaseous state of matter. It is thus not surprising that the liquid state of matter shares some commonalities with both solids and gases. As for solids, liquids are practically incompressible under pressure (except if very high pressures are used) and have a high density. This is the reason that solids and liquids are summarized as condensed states of matter. Usually, however, the density of liquids is lower than that of solids for a given material, with water being an important exception, as we have discussed above. Unlike solids, however, the molecules in a liquid can move and change places by diffusing under the influence of heat energy (diffusion). This is a property that liquids have in common with gases and the reason that gases and liquids are summarized as fluid states of matter. While liquids show in general a much higher tendency to be miscible with each other than solids, not all liquids are miscible (unlike gases, which are always completely miscible with each other), and in many cases mixing two liquids will lead to the formation of a two phase system of the two immiscible liquids or a two phase system of a liquid A-rich phase and a liquid B-rich phase if the liquids show partial miscibility. In these cases the two liquids will form an interface with a corresponding interfacial tension. Since the interfacial tension γ is the intensive variable of the interfacial free energy G_s (with the interfacial area A being the extensive variable; $G_s = \gamma A$), two phase liquid systems have a higher energy if the interfacial area between the liquids is increased. An example for this is an emulsion, in which one liquid phase is dispersed in the form of droplets in the other. The system will try to minimize its free energy, and thus the dispersed droplets will fuse together (coalescence) over time to reduce the interfacial energy by reducing the interfacial area. To reduce the surface free energy of emulsions and thereby to stabilize the dispersed nature of the emulsion, surfactants can be added to the emulsion to reduce the interfacial tension between the two liquid phases.

Generally, the principle "like dissolves like" can be applied, and liquids with similar polarity (for example, water and ethanol, or benzene and cyclohexane) will be miscible, whereas liquids with different

polarities (for example, water and benzene) will be immiscible or show partial miscibility.

Another property liquids have in common with gases is that they are isotropic. This means their physical properties are uniform in all directions or orientations. This is not the case for crystalline solids and liquid crystals, which are anisotropic (with the exception of cubic crystals and liquid crystals). The anisotropic nature of most crystals (and liquid crystals) is also the reason for their optical birefringence, making them visible in the polarized light microscope. Conversely, liquids will be invisible in the polarized light microscope under cross polarization.

If we investigate a liquid with X-ray diffraction, we only measure the characteristic halo we have already discussed in the context of amorphous solid materials (amorphous materials are also isotropic and show no long-range order, which would give rise to peaks in a diffractogram). However, also like amorphous materials, liquids are not without near order, and certain distances between the molecules of a liquid may be preferred over others, due to intermolecular interactions. This can also be determined from X-ray diffraction measurements, by calculating the radial distribution function $g(r)$, which can be generated by a Fourier transformation of the diffraction pattern, and presents the average spatial distribution in a liquid (or in a amorphous solid).

An important property relevant for many pharmaceutical applications of liquids is their viscosity. Viscosity is the resistance to flow or, in other words, the resistance of the liquid to be deformed under a shear stress (due to the intermolecular interactions of molecules in a liquid). If a shear stress (a force F [N] applied parallel to the fluid's surface A [m^2], F/A [$N\,m^{-2}$]) is applied to a liquid, this will result in a velocity gradient in the liquid (dv/dx [s^{-1}]). The ratio between the two is called viscosity η [Pa s]

$$\eta = (F/A)/(dv/dx) \tag{7.15}$$

This equation is usually rearranged to give Newton's law of viscosity:

$$F/A = \eta dv/dx \tag{7.16}$$

Liquids can be differentiated by their viscosities and the type of viscosity they have. A Newtonian liquid (ideal viscosity) is a liquid in which η remains constant if the shear stress or shear rate is increased. Water and ethanol are examples of Newtonian liquids. Not all liquids, however, show ideal flow behavior, and these liquids are called non-Newtonian liquids. Many pharmaceutically relevant liquids are non-Newtonian. If the viscosity decreases with increasing shear stress, the liquid shows pseudoplastic flow behavior (also called shear thinning), and in the opposite case, when the viscosity increases as shear stress is increased, the liquid shows dilatant flow behavior (also called shear thickening). Time, however, does not change the viscosity for a given shear stress for pseudoplastic and dilatant liquids (nor for Newtonian liquids). This is, however, not always the case. A pseudoplastic liquid shows a certain viscosity for a certain shear stress. If the stress is kept constant, for some liquids a further decrease in viscosity can be observed. When the shear stress is removed, the system does not immediately return to its original state, but the viscosity gradually increases. This behavior is termed thixotropy. For pharmaceutical suspensions this is advantageous, for the suspension can be homogenized by shaking and can be poured easily. After some time, the viscosity increases again, stabilizing the suspension against sedimentation.

While many polymer solutions used in pharmaceutical applications are pseudoplastic liquids, concentrated pastes may show dilatant flow behavior, and many suspensions and "semisolids," such as creams and ointments, show thixotropy. Note that a semisolid is a pharmaceutical term used to describe creams, ointments, etc. These are solids at rest, but they start to flow (become liquid) at low shear stresses.

To describe pseudoplastic and dilatant liquids, we can extend Newton's viscosity equation to a power law, known as the Ostwald–de Waele equation:

$$F/A = K(dv/dx)^n \tag{7.17}$$

where K is the flow consistency index [Pa s^n]; and n is the flow behavior index [no unit]. $n = 1$ for a Newtonian liquid, $n < 1$ for a pseudoplastic liquid and $n > 1$ for a dilatant liquid.

The viscosity of liquids decreases with increasing temperature, due to the higher molecular mobility. Gases, in contrast, not only have much lower viscosities than liquids but also show an increase in viscosity as temperature is increased (due to higher

collision rates of the gas molecules at elevated temperatures). For example, water has a viscosity of 1.002×10^{-3} Pa s at room temperature and 0.35×10^{-3} Pa s at 80°C. Air, on the other hand, has a viscosity 1.79×10^{-5} Pa s at room temperature. Amorphous solids in the glassy state have viscosities in the order of 10^{12} Pa s or higher.

Gases

Gases play an important role in the pharmaceutical field, for example, in the use of medical gases (e.g., oxygen, nitrous oxide, carbon dioxide, compressed air), as functional excipients in aerosols and inhalers, and in quality control of drugs and dosage forms. Further, oxygen from the air may contribute to oxidative degradation of drugs, and water molecules from air can initiate hydrolytic degradation. Water molecules in air (especially at high relative humidity) may also decrease the physical stability of amorphous drugs or glass solutions, as we have seen, since water is a potent plasticizer, lowering the glass transition temperature of amorphous materials and thus increasing the likelihood of crystallization.

The gaseous state of matter is characterized by very weak interactions between the molecules (for real gases), which in fact are assumed to be completely absent for ideal gases (see below). The consequence of this is that in gases the molecules constantly change their positions by diffusion or convection and have a very low viscosity and density. This makes gases easily compressible under pressure (in contrast to liquids and solids). Also, in contrast to solids and liquids, different gases are always completely miscible with each other. For example, air is a mixture of several gases: approximately 78.1% nitrogen, 20.9% oxygen, 0.9% argon, 0.03% carbon dioxide, and small concentrations of neon, helium, methane, and other gases.

If we are completely disregarding the weak interactions between gas molecules, we can fully describe the behavior of gas by the ideal gas law. Historically, the properties of gases have been described in a set of laws, which we will have a quick look at first.

Boyle's law states that the product of absolute pressure (p) and volume (V) is constant (K_1) at constant temperature:

$$pV = K_1 \tag{7.18}$$

Charles' law states that if a given mass of a gas is heated at constant pressure, the volume of the gas is directly proportional (K_2) to its absolute temperature (T):

$$V/T = K_2 \tag{7.19}$$

Avogadro's law states that equal volumes of pure gases at constant temperature and pressure contain the same number of particles (n):

$$V/n = K_3 \tag{7.20}$$

The volume that one mole of gas molecules occupies (the molar volume) is 22.4 L at 0°C and a pressure of 1 atm. The number of molecules in a mole of gas is 6.022×10^{23}.

These three laws can be regarded as special cases of the ideal gas law:

$$pV = nRT \tag{7.21}$$

where R is the ideal gas constant [8.314 J (mol^{-1} K^{-1})]. Note that K_1 in Boyle's law is nRT, K_2 in Charles' law is nR/p, and K_3 in Avogadro's law is RT/p in the ideal gas law.

Finally, if we take into account the ideal gas law (which assumes no interactions between the molecules forming the gas), we arrive at Dalton's law, which states that the total pressure (p_{tof}) of a mixture of gases equals the sum of their partial pressures (p_1 to p_n):

$$p_{\text{tof}} = p_1 + p_2 + \ldots + p_n \tag{7.22}$$

Related to Dalton's law is *Henry's law*, which states that at constant temperature the amount of a gas (n) that dissolves in a given volume V ($c = n/V$) of a given liquid is directly proportional (K_4) to the partial pressure of that gas in equilibrium with the liquid (p_1).

$$c/p_1 = K_4 \tag{7.23}$$

While all the above laws hold true for many gases over reasonable temperature and pressure ranges, and thus can be used fairly well to describe the behavior of gases, they do not take into account the fact that interactions between the gas molecules do take place and that the gas molecules occupy a part of the total volume of the gas (albeit usually a very small part).

Deviations of the behavior of gases from the ideal situation become more important as, for example, pressure is increased or temperature is decreased. We can also understand this by the fact that gases can be liquefied if the temperature is lowered (this would not be possible if the gas molecules did not interact with each other). On the other hand, many gases behave very closely to ideal gases, and this can be seen, for example, if we determine the molar volumes of some gases. For the gases that make up more than 99% of air, we find that nitrogen, oxygen, and the noble gases indeed have molar volumes of 22.4 L. Other gases, though, already at 0°C and a pressure of 1 atm, have molar volumes that differ slightly from that of ideal gases. Carbon dioxide, for example, has a molar volume of 22.3 L and that of ammonia is 22.1 L.

As stated above, for real gases we have to take into account that the gas molecules occupy a certain volume in the given volume of a gas and that interactions between the gas molecules can occur. These interactions, for example, could be dipole–dipole interactions if the gas molecules contain polar bonds (these interactions are termed Keesom forces). Even in the absence of permanent dipoles in the gas molecules, interaction can occur through transiently induced dipoles (London forces). Note that in the literature the expression "van der Waals force" is sometimes used to describe Keesom and London forces and sometimes specifically for London forces.

The van der Waals equation is one model that takes into account the non-zero volume of the gas molecules and the possible interactions between the gas molecules:

$$nRT = (p + an^2/V_m^2)(V_m - b) \tag{7.24}$$

For one mol of gas the equation simplifies to

$$RT = (p + a/V_m^2)(V_m - b) \tag{7.25}$$

where p is the pressure; T is the temperature; R is the ideal gas constant; V_m is the molar volume; and n is the number of molecules.

The parameters a and b have to be empirically determined for each gas. The parameter a appears in the pressure term of the equation and relates to intermolecular interactions, whereas the parameter b appears in the volume term of the equation and relates to the fact that the gas molecules themselves occupy a certain volume of the gas.

It should be noted that the van der Waals equation is just one of many models that have been developed to better describe the behavior of gases, especially at extreme conditions, and that many other models exist. This is, perhaps, an opportune moment to remind us that a model is a mathematical description of a physical reality, and not the physical reality itself. It is up to the given situation (and possibly the required precision) as to which model is best used in a particular situation.

Plasma

We will finally briefly discuss the plasma state of matter. Plasma is actually the most common state of matter in the universe (for example, stars are matter in the plasma state). Plasma is formed by a phase transition from gases if these are heated to very high temperatures. At a certain temperature the electrons of the gas molecules or atoms leave the atoms, leading to an ionization of the gas. Plasma thus contains charged molecules or atoms and free electrons and conducts electricity (unlike gases). Due to the very high temperature of plasma, it is not particularly useful in the pharmaceutical field. Not all atoms however, need to be ionized for plasma to gain its typical properties. So most plasma consist of ions, electrons, and neutral molecules, which nevertheless are in an activated state, e.g., in the form of radicals (molecules containing one or more unpaired electrons).

It is also possible to create the plasma state from gases by electric discharge under reduced pressure, leading to "cold plasma." Cold plasma created in this way has found medical applications [13] and, for example, cold plasma from argon or oxygen has been used to irradiate polymer coats of tablets and granules.[14],[15] This plasma irradiation leads to the emission of intense UV radiation, which can lead to changes in the polymer structure, influencing, for example, drug release kinetics from these tablets or creating gastro-retentive, floating drug delivery systems.[16]

Thermodynamics

Introduction

Thermodynamics rests upon three basic laws that took over 500 years to establish. Although quantum

mechanics has defined the limits of its scope, the concepts embodied in the three laws have remained unchanged for over a century. Thus, thermodynamics provides unassailable, certain answers. As such, the great value, but also the main challenge, is using the simple concepts to understand complicated physical and biological phenomena. There are many texts available on the subject of thermodynamics ranging from introductory to complex, rigorous treatments. The approach here will involve the development of the concepts with pharmaceutically relevant examples. The purpose is to demonstrate how to make judicious assumptions to allow use of the rigorous definitions in thermodynamics to reveal the certainty in the complex field of pharmaceutics.

To begin, the definitions of system, surroundings, universe, and boundaries are introduced. These, as well as all other definitions, must be clearly understood, otherwise thermodynamics will not be properly used. A *system* is that part of the *universe* under consideration and, as such, is separated from the *surroundings* or, equivalently, the rest of the universe. The focus of the analysis will center on how the properties of a system are altered through an interaction with the surroundings. Properties are those qualitative characteristics (e.g., type of phase, which may be solid, liquid, or gas) and quantitative characteristics (e.g., temperature, pressure) that describe the system. The interaction between the system and surroundings is controlled by the boundary and is revealed in the change in properties.

When a sufficient number of properties of the system have been specified with fixed values, then the system is at equilibrium. Certain systems at equilibrium have a simple equation that provides a relationship among the values of the properties. For example, a system containing an ideal gas (one component) has the properties of pressure, P, volume, V, number of mols, n and temperature, T (K), related by:

$$PV = nRT \tag{7.26}$$

where R is the gas law constant. Such a relationship is referred to as an *equation of state* because it specifies the relationship among the quantitative properties of a system in a definite state. Furthermore, if the system is at equilibrium, only three properties need to be specified, as the fourth may be calculated from the equation of state. Most pharmaceutically relevant systems are extremely complicated, because there are typically many components; the properties of each must be specified for the system to be at equilibrium.

The first law

The first law of thermodynamics is a statement of the principle of conservation of energy; energy may neither be created nor be destroyed. It is mathematically written as

$$\mathrm{d}E = \delta q - \delta W \tag{7.27}$$

where $\mathrm{d}E$ is the differential change in the internal energy, δq is the differential change in the absorbed heat, and δW is the differential change in the expended work or work done.

The change in internal energy of a system in going from state A to state B is given by

$$\Delta E = \int_A^B \mathrm{d}E \tag{7.28}$$

The internal energy is a state function. A change in the value of a state function depends only on the initial and final state and does not depend on how the change in state was achieved. The symbol d represents an exact differential. Another example of a state property is the temperature; that is, the change in temperature only depends on the initial and final temperatures and does not depend on how the temperature was changed (that is, the path followed). A cyclic change in a system describes a series of changes where the initial and final states have the same values for the state properties; one may say, the system "comes to a full circle." For all cyclic processes, the change in all state properties is zero. Finally, the first law provides only a relation for the change in the internal energy and does not provide an absolute value. Thus like temperature, a zero point must be defined as well as a scale for a unit of energy, which were arbitrary until the scientific community reached a consensus.

Although it seems too obvious to point out that if the system has the same value of energy in the initial and final state that the change in energy would be zero, there are quantities that may not be zero even when a system undergoes a cyclic change. Two examples are heat flow and work done, which in the first law

are described by inexact differentials, and the unique symbol δ is used. Neither the heat nor the work is a state function and thus, the integral of the differential depends on the path taken. Mathematically, they are written as

$$q = \int_{A}^{B} \delta q \tag{7.29}$$

$$W = \int_{A}^{B} \delta W \tag{7.30}$$

The work and heat may only be determined if more information is provided concerning how the change in the state of the system was achieved.

Entropy and the second law

Although the first law provides the framework for calculating the change in energy associated with chemical reactions or physical changes in state, there is insufficient information to allow prediction of the likelihood of whether the change will occur. Consider a system composed of two parts that are at different temperatures, T_1 and T_2, separated by an impermeable, adiabatic partition. When the partition is removed, heat will flow from the part at a higher temperature to the part at a lower temperature. According to the first law, the energy of the whole system, the sum of parts one and two, has not changed.

Intuitively it is known that the above change will occur regardless of the fact that the first law does not provide a method of predicting the occurrence. Such changes are described as *spontaneous*, for the obvious reason that they occur without additional stimulation. It should be noted that this spontaneous change involved an increase in the disorder or, if you will, the randomness of the system. Thus, the system initially was separated into two parts at different temperatures, but after thermal contact, a uniform temperature was reached. The *entropy, S*, is the function that provides a quantitative description of the randomness or disorder of the system and is fundamental for predicting the spontaneity of chemical reactions and physical changes. The entropy is a state function that depends only on the initial and final state of the system.

The definition of the entropy change is given by the seemingly surprising form:

$$dS = \delta q_{rev}/T \tag{7.31}$$

where the subscript rev denotes that the heat flow occurs in a reversible manner. By carrying out the integration, the change in entropy for a reversible, isothermal change from state 1 to state 2 is given by

$$\Delta S = \int_{1}^{2} \delta q_{rev}/T = q_{rev}/T \tag{7.32}$$

With the introduction of entropy, the second law may be stated as follows: For any spontaneous process in an isolated system, there is an increase in the value of entropy. Alternatively, the first and second laws may be combined with the classic thermodynamic statement, "the energy of the universe is constant; the entropy is increasing".

Historically, Carnot analyzed the efficiency of such a theoretical cycle, which has come to be known as the Carnot cycle. This can be found in most texts on thermodynamics, although it typically involves isothermal and adiabatic processes in the context of what is known as a heat engine. Nevertheless, the premise is that by permitting the flow of heat into a system, work may be done by the system. The second law dictates that not all of the heat may be converted into work, even if all changes occur in a reversible manner. In fact, the maximum work, W_{max}, that may be obtained is specified by the heat flow into the system and the temperature difference over which the heat engine is operating; that is,

$$W_{max} = q_1(T_1 - T_2)/T_1 \tag{7.33}$$

where $T_1 > T_2$. The proof of this equation can be established by calculating the heat and work for each step and noting that not all of the heat energy may be converted into work. This can be seen from Table 7.3. The heat flow into the system occurs with the second step. The efficiency of an engine ε, is given by the amount of work extracted divided by the heat flow into the system:

$$\varepsilon = W_{tot}/q_1 \tag{7.34}$$

where $W_{tot} = W_{max}$ for reversible changes. The efficiency is proportional to the difference in temperature between the heat reservoirs. In addition, there is no work done unless there is a difference in temperature between the heat reservoirs. Finally, 100% efficiency is obtained only when $T_2 \to 0$, which as will be noted from the third law, is impossible.

Table 7.3 Values for the work and heat and the change in energy and enthalpy for each step for the cyclic change described in text and illustrated in Fig. 7.21

Step	1	2	3	4	Total
W, J	−4.16	1.69	4.16	−1.4	0.29
Q, J	0	5.85	0	−5.85	3.04
ΔE, J	4.16	4.16	−4.16	−4.16	0
ΔH, J	0	5.85	0	−2.74	0

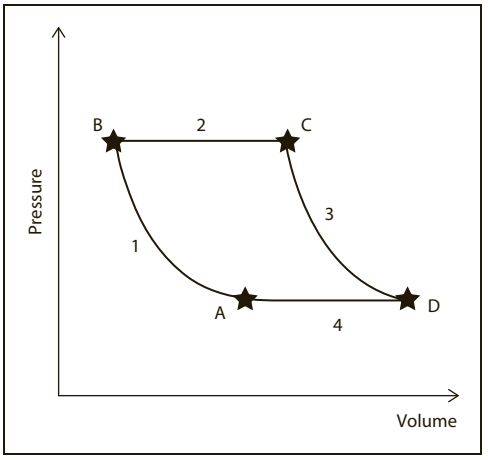


Figure 7.21 Pressure given as a function of volume for an ideal gas. The system undergoes a cyclic change beginning and ending at point A following the paths given by the solid lines.

The above analysis elucidates the connection between entropy and heat flow. The second law provides the quantitative limit on the amount of work that can be done with a cyclic operation performed in a reversible manner.

Given the above background, the entropy changes associated with several reversible processes may be determined. Consider the vaporization of water in the context of the lung, which is known to carry out the important function of humidifying air. Let us assume that initially that the inhaled air contains no water vapor, but is at 310 K, and the final state is air saturated with water at 310 K. To calculate the amount of water that must be evaporated to saturate the air, the saturation vapor pressure of water in air can be found. The value from the internet is 47 mmHg. Using the approach from above, the moles of water that must undergo the phase change from a liquid at 310 K to a vapor at the same temperature is 37 mmHg or (37 × 133 Pa mmHg =) 4921 Pa. The number of moles is found with the ideal gas law:

$$n/V = P/RT = (4921)/(8.314 \times 310) = 1.91 \ \text{mol m}^{-3} \quad (7.35)$$

or for a typical inhalation volume of 0.001 m^3, 1.91 × 10^{-3} mol.

The entropy of vaporization, ΔS_{vap}, is given by

$$\int dS = \int \delta q / T_b \quad (7.36)$$

which may be determined from $\int \delta q = q_p = \Delta H$, but this is the value at the boiling point. We will return to this point below, but for now, consider the problem as occurring at the boiling point. The molar heat of vaporization of water at the boiling point is 40.65 kJ mol^{-1}. Thus

$$\int dS = \Delta H_{vap}/T_m$$
$$\Delta S = 40650/373 = 109 \ \text{J mol}^{-1}\text{K}^{-1} \quad (7.37)$$

In our problem, the number of moles was 1.91 × 10^{-3} leading to the total entropy change of 0.208 J K^{-1}. The positive change in entropy confirms the intuition concerning such an event: gases are in a state of more disorder than liquids, thus the entropy also is greater in the vapor state in comparison to the liquid state.

The discussion, thus far, has been limited to reversible processes that are strictly impossible to achieve in the laboratory (even though such a process may be

approximated very closely). The question arises as to what the entropy change is for an irreversible change. Here the entropy change is given by

$$dS > \delta q_{irr}/T \tag{7.38}$$

Thus, all real processes may be written as

$$dS \geq \delta q/T \tag{7.39}$$

This concept may be extended to determine the condition of spontaneity. Consider a system that is transformed irreversibly from state 1 to state 2 and then reversibly from state 2 back to state 1. The overall change is given by:

$$\int_{\text{State 1}}^{\text{State 2}} \delta q_{irr}/T + \int_{\text{State 1}}^{\text{State 2}} \delta q_{rev}/T < 0 \tag{7.40}$$

$$\int_{\text{State 1}}^{\text{State 2}} \delta q_{irr}/T + \int_{\text{State 1}}^{\text{State 2}} dS < 0 \tag{7.41}$$

which may be rearranged, with changing the limits of integration, to yield

$$\int_{\text{State 1}}^{\text{State 2}} \delta q_{irr}/T < \int_{\text{State 1}}^{\text{State 2}} dS \tag{7.42}$$

or, equivalently, for infinitesimal changes,

$$\delta q_{irr}/T < dS \tag{7.43}$$

This is known as the *Clausius inequality*. For isolated systems, where boundaries do not permit the passage of energy or matter, $\delta q_{irr} = 0$, the result is given

$$dS > 0 \tag{7.44}$$

That is, for every spontaneous change in an isolated system there is an increase in the entropy.

The second law may be generalized in another way. The total entropy for any process is given by the sum of the entropy of the system and the surroundings; that is

$$dS_{tot} = dS_{sys} + dS_{surr} \tag{7.45}$$

For reversible processes, the entropy change in a system is the negative of the entropy change produced in the surroundings. The total entropy, therefore, is zero. For irreversible processes, the total entropy, system plus surroundings, increases. The mathematical statement of this relationship is

$$\sum \Delta S_{tot} = 0 \text{ reversible process} \tag{7.46}$$

$$\sum \Delta S_{tot} > 0 \text{ irreversible process} \tag{7.47}$$

The third law

The third law of thermodynamics simply defines the zero point of the entropy scale. The entropy of a pure, perfectly crystalline substance is zero at absolute zero. Intuitively, a system that has perfect three-dimensional order should have no entropy at the lowest possible temperature. The defining of a zero for the entropy is unlike the other state functions introduced previously. Thus, the value of the entropy, S, of a system in any state, in principle, may be calculated.

What would be the entropy of a crystalline solid at 150 K, S_{150}? This may be calculated as

$$\Delta S = S_{150} - S_0 \tag{7.48}$$

$$\Delta S = \int (C_p/T)dT - 0 \tag{7.49}$$

or:

$$\Delta S = S_{150} \tag{7.50}$$

If the heat capacity over the range of 0 to 150 K is known, the value of the entropy may be calculated.

Free energy

The concept of *free energy* is probably the most useful aspect of thermodynamics. The criteria for determining the spontaneity of a chemical reaction or phase change were presented above; however, it involved carrying out the change in an isolated system. One can imagine how inconvenient and often impossible it would be to apply such a constraint to the laboratory setting. For this sake, additional state functions have been defined to allow prediction of the spontaneity of a change in state. The rationale for the development of other functions was to allow maximum flexibility in their application. The two functions introduced are *Helmholtz free energy, A*, and *Gibbs free energy, G*. The functions for predicting spontaneity are

1. Isolated system: $dS > 0$
2. Isothermal and isochoric system: $dA < 0$
3. Isothermal and isobaric: $dG < 0$
4. Constant volume and entropy: $dE < 0$

Helmholtz free energy is defined as:

$$A \equiv E - TS \tag{7.51}$$

Helmholtz free energy is the energy available to do pressure–volume work for reversible isothermal processes: a decrease in the Helmholtz free energy is equal to the capacity of the system to do work. An alternative view is that, for systems at constant volume and temperature, a change in state is spontaneous if, and only if, there is a decrease in the Helmholtz free energy. Thus, with the introduction of ΔA, the spontaneity of changes occurring at constant volume and temperature may be predicted.

As most reactions carried out in the laboratory are under conditions of constant pressure and temperature, Gibbs free energy is the most useful function and is defined as

$$G \equiv E + PV - TS \tag{7.52}$$

which can be converted into a more usable form by an analogous method used with the Helmholtz function. Taking the differential and applying the constraints of constant pressure and temperature yields

$$dG = dE + PdV - TdS \tag{7.53}$$

but $dE = \delta q - \delta W = TdS - \delta W$; thus, upon substitution,

$$-dG = \delta W - PdV \tag{7.54}$$

A decrease in Gibbs free energy is equal to the non-PV work done by the system or, equivalently,

$$dG = -\delta W_{(\text{non-}PV)} \tag{7.55}$$

which also provides the conditions of a spontaneous change under the constraints of constant temperature and pressure. A direct application of the relationship between Gibbs free energy and non-PV work is used in potentiometry.

These relationships for predicting spontaneity often are expressed in a differential form, which presents the state functions in a concise manner as well as facilitating their use to specific problems. The four differential equations are

$$dE = TdS - PdV \tag{7.56}$$

$$dH = TdS + VdP \tag{7.57}$$

$$dA = -SdT - PdV \tag{7.58}$$

$$dG = -SdT + VdP \tag{7.59}$$

These expressions represent the four fundamental equations of thermodynamics, which in reality are four ways of looking at one fundamental equation describing the conditions of spontaneity.

Example: One mol of liquid water is vaporized reversibly at 100°C and 1 atm pressure. The molar heat of vaporization is 40.65 kJ mol^{-1}. Calculate q_p, ΔH, ΔE, ΔA, ΔG, and ΔS.

Solution:

The value of q_p actually is given in the question, as the heat required to vaporize 1 mol of liquid is the definition of the molar heat of vaporization; thus, q_p = 40.65 kJ. Recognizing that the pressure is constant, $\Delta H = q_p$ = 40.65 kJ. To calculate ΔE, the work first must be determined. The work is given by

$$W = \int PdV = P\Delta V$$

$$W = P(V_g - V_\ell) \tag{7.60}$$

However, the volume of the gas, V_g, is much larger than the volume of the liquid, V_ℓ, which implies that the work is given by

$$W \approx PV_g \tag{7.61}$$

Assuming the gas is ideal, the work is

$$W = nRT = (1\text{ mol})(8.314\text{ J mol}^{-1}\text{K}^{-1})(373\text{ K}) = 3100\text{ J} \tag{7.62}$$

From the above, ΔE may be calculated from

$$\Delta E = q - w = 40650 - 3100 = 37550\text{ J} \tag{7.63}$$

The change in entropy was determined above:

$$\Delta S = \Delta H/T_m = 40650/373 = 109\text{ J K}^{-1} \tag{7.64}$$

Helmholtz free energy is given by

$$\Delta A = \Delta E - T\Delta S = 40650 - (373)(109.0) = -3100\text{ J} \tag{7.65}$$

which also may have been obtained by recognizing that

$$\Delta A = -W_{rev} - 3100 \text{ cal} \quad (7.66)$$

Finally, the change in Gibbs free energy is determined from

$$\Delta G = \Delta E + P\Delta V - T\Delta S$$
$$= 37550 + 3100 - (373)(109) = 0 \text{ cal} \quad (7.67)$$

which, too, may have been obtained by recognizing the absence of non-PV work.

Solutions and phase equilibria

Solutions and solubility

A solution is a chemically and physically homogeneous mixture of two or more substances. The term *solution* generally denotes a homogeneous mixture that is liquid, even though it is possible to have homogeneous mixtures that are solid or gaseous. Thus, it is possible to have solutions of solids in liquids, liquids in liquids, gases in liquids, gases in gases, and solids in solids. The first three of these are most important in pharmacy, and ensuing discussions will be concerned primarily with them.

In pharmacy different kinds of liquid dosage forms are used, and all consist of a dispersion of one or more substances in a liquid phase. Depending on the size of the dispersed particle, they are classified as *true solutions, colloidal solutions*, or *disperse systems*. If sugar is dissolved in water, it is supposed that the ultimate sugar particle is of molecular dimensions and that a true solution is formed. On the other hand, if very fine sand is mixed with water, a suspension of comparatively large particles, each consisting of many molecules, is obtained. Between these two extremes lie the colloidal solutions, the dispersed particles of which are larger than those of true solutions but smaller than the particles present in suspensions. Colloidal solutions, in general, are considered to be thermodynamically stable. In this section only true solutions will be discussed.

It is possible to classify broadly all solutions as one of two types. In the first type, although there may be lesser or greater interaction between the dispersed substance (the solute) and the dispersing medium (the solvent), the solution phase contains the same chemical entity as found in the solid phase; thus, upon removal of the solvent, the solute is recovered unchanged. One example would be sugar dissolved in water where, in the presence of sugar in excess of its solubility, there is an equilibrium between sugar molecules in the solid phase with sugar molecules in the solution phase. A second example would be dissolving silver chloride in water. Admittedly, the solubility of this salt in water is low, but it is finite. In this case the solvent contains silver and chloride ions, and the solid phase contains the same material. Removal of the solvent yields the initial solute in unchanged form.

In the second type the solvent contains a compound that is different from the one in the solid phase. The difference between the compound in the solid phase and solution is due generally to some chemical reaction that has occurred in the presence of solvent. An example would be dissolving aspirin in an aqueous solvent containing some basic material capable of reacting with the acid aspirin. Now the species in solution would not only be undissociated aspirin, but aspirin also as its anion, whereas the species in the solid phase is aspirin in only its undissociated acid form. In this situation, if the solvent were removed, part of the substance obtained (the salt of aspirin) would be different from what was present initially in the solid.

Pharmaceutical solvents

The discussion will focus now on solvents available to pharmacists and on the properties of these solvents. Pharmacists must obtain an understanding of the possible differences in solubility of a given solute in various solvents because they are often called on to select a solvent that will dissolve the solute. Knowledge of the properties of solvents will allow the intelligent selection of suitable solvents.

On the basis of the forces of interaction occurring in solvents, one may broadly classify solvents as one of three types:

1. *Polar solvents* – those made up of strong dipolar molecules having hydrogen bonding (water or hydrogen peroxide)

2. *Semipolar solvents* – those also made up of strong dipolar molecules but that do not form hydrogen bonds (acetone or pentyl alcohol)
3. *Non-polar solvents* – those made up of molecules having a small or no dipolar character (benzene, vegetable oil, or mineral oil).

Naturally, there are many solvents that may fit into more than one of these broad classes; for example, chloroform is a weak dipolar compound but generally is considered non-polar in character, and glycerin could be considered a polar or semipolar solvent even though it is capable of forming hydrogen bonds.

Colligative properties of solutions

Up to this point our concern has been with dissolving a solute in a solvent. Once the dissolution has been brought about, naturally the solution has a number of properties that are different from that of the pure solvent. Of very great importance are the colligative properties that a solution possesses.

The colligative properties of a solution are those that depend on the number of solute particles in solution, irrespective of whether these are molecules or ions, large or small. Ideally, the effect of a solute particle of one species is considered to be the same as that of an entirely different kind of particle, at least in dilute solution. Practically, there may be differences that may become substantial as the concentration of the solution is increased.

The colligative properties that will be considered are

1. Osmotic pressure
2. Vapor-pressure lowering
3. Boiling-point elevation
4. Freezing-point depression.

Of these four, all of which are related, osmotic pressure has the greatest direct importance in the pharmaceutical sciences. It is the property that largely determines the physiological acceptability of a variety of solutions used for therapeutic purposes.

Methods to increase solubility of poorly soluble drugs

A large number of promising drug candidates do not make it to the market because of poor bioavailability, due primarily to their poor solubility in aqueous medium. Recently, several strategies have been used to improve solubility profile of these drugs and include the following:

1. Use of buffers
2. Use of cosolvents
3. Use of surfactants
4. Complexation
5. Solid dispersions.

Use of buffers

The idea behind the use of buffers to improve solubility is to create and maintain pH conditions in a system that causes the drug to be in its ionized state. The ionized fraction of a drug is much more soluble in water, due to its increased polarity relative to the un-ionized fraction. Buffers can also help in reducing the likelihood of drug precipitation when drug solution is diluted in an aqueous medium. Consistent with the principles of solubility changes with pH, acidic drugs are formulated under relatively basic conditions while the opposite is true for the basic drugs. Some examples of drugs that are formulated with buffer systems are Amikacin sulfate (pH 3.5 to 5.5, citrate buffer) and Midazolam hydrochloride (pH 3).[17–19] The drugs that make good candidates for use of pH variation or buffers are the ones that have the ability to ionize within a pH range of 2 to 8.

Use of co-solvents

A common way to increase drug solubility is through the use of a water-miscible organic solvent. This strategy is based on the fact that poor solubility of drugs in water results from the great difference in polarity of the two components, water being of very high polarity and the drug having low polarity. Addition of a co-solvent with a polarity value of less than that of water reduces the difference between polarity of the drug and water co-solvent system, thereby improving solubility. Commonly used co-solvents for this purpose are the hydrogen bonding organic solvents such as ethyl alcohol, propylene glycol, and glycerin.

The polarity scale of solvents is defined by a property known as the dielectric constant. This value for water is 80, and for ethyl alcohol, propylene

glycol, and glycerin, it is 24, 32, and 42, respectively. Most poorly soluble drugs have dielectric constant values of less than 20. Examples of some parenteral solution that contain cosolvents include chlordiazepoxide (25% propylene glycol), diazepam (10% ethyl alcohol and 40% propylene glycol), and digoxin (10% ethyl alcohol and 40% propylene glycol). Non-polar and nonionizable drugs are good candidates for cosolvent systems.[17–19]

Use of Surfactants

Surfactants are molecules with well defined polar and non-polar regions that allow them to aggregate in solution to form micelles. Non-polar drugs can partition into these micelles and be solubilized. Depending on the nature of the polar area, surfactants can be nonionic (e.g., polyethylene glycol), anionic (e.g., sodium dodecyl sulfate), cationic (e.g., trialkylammonium), and zwitterionic (e.g., glycine and proteins). Among these, the most commonly used ones are the anionic and nonionic surfactants. Since the process of solubilization occurs due to presence of micelles, generally high concentrations of surfactants are needed to significantly improve drug solubility. One example of surfactant based solution is Taxol (paclitaxel), an anti-cancer drug that is solubilized in a 50% solution of Cremophor. Other examples include valrubicin in 50% Cremophor, and cyclosporine in 65% Cremophor.[17–19]

Complexation

Complexation is the association between two or more molecules to form a noncovalent-based complex that has higher solubility than the drug itself. From the solubility standpoint, complexes can be put into two categories, the stacking complexes and inclusion complexes. Stacking complexation is driven by association of non-polar areas of the drug and complexing agent. This results in exclusion of the non-polar areas from contact with water, thereby reducing the total energy of the system. This aggregation is favored by large, planar, non-polar regions on the molecules. Stacking can be homogeneous or mixed, but results in a clear solution.

Inclusion complexes are formed by insertion of drug molecule into a cavity formed by the complexing agent. In this arrangement the non-polar area of the drug molecule is excluded from water, due to its insertion in the complexing agent. One requirement for the complexing agent in such systems is that it has a non-polar core and a polar exterior. The most commonly used inclusion complexing molecules are cyclodextrins. The cyclic oligomers of glucose are relatively soluble in water and have cavities large enough to accept non-polar portions of many drug molecules. Cyclodextrins can consist of six, seven, or eight sugar residues and are classified as α, β and γ, respectively. Due to geometric considerations, steroid molecules are very suitable for inclusion into cyclodextrin complexes.

Solid dispersions

Solid dispersion refers to the dispersion of one or more active ingredients in an inert carrier or matrix at solid state, prepared by the melting (fusion), solvent, or the melting-solvent method. It has also been defined as the product formed by converting a fluid drug–carrier combination to the solid state. The term co-precipitate or co-evaporate has also been used frequently when a solid dispersion is prepared by the solvent method.

Classification of solid dispersions

Solid dispersions can be classified as follows:

1. Simple eutectic mixtures
2. Solid solutions
3. Glass solutions of suspensions
4. Compound or complex formation between the drug and the carriers
5. Amorphous precipitations of drug in crystalline carrier.

Simple eutectic mixtures

A simple eutectic mixture consists of two compounds that are completely miscible in the liquid state but only to a very limited extent in the solid state. A eutectic mixture of a sparingly water-soluble drug and a highly water-soluble carrier may be regarded thermodynamically as an intimately blended physical mixture of its two crystalline components. These components are assumed to crystallize simultaneously in very small particulate sizes. The increase in specific surface area, therefore, is mainly responsible for the increased rate of dissolution of a poorly water-soluble drug.

Differential thermal analysis (DTA) of binary mixtures normally exhibits two endotherms, but a binary mixture of eutectic composition usually exhibits a single major endotherm. In the case of a simple eutectic system, the thaw points of binary mixtures of varying compositions are equal to the eutectic temperature of the system.

Solid solutions

A solid solution consists of a solid solute dissolved in a solid solvent. The particle size in solid solution is reduced to molecular level. Successful solubilization of itraconazole has been achieved using solid solution techniques. Solid solutions of lower drug concentrations generally give faster dissolution rate, and drug dissolution improves considerably with an increase in molecular weight of a water-soluble polymer, such as polyethylene glycol.

Glass solutions of suspensions

A glass solution is a homogeneous system in which a glassy or a vitreous form of the carrier solubilizes drug molecules. PVP has been used as a carrier in several formulations. In its matrix form, PVP dissolved in an organic solvent, undergoes a transition to a glassy state upon evaporation of the solvent.

Compound or complex formation between drug and carriers

This system is characterized by complexation of two components in a binary system during solid dispersion preparation. The availability of a drug from the complex is dependent on the solubility, dissociation constant, and intrinsic absorption rate of the complex. α, β and γ Cyclodextrins in combination with polyethylene glycol (PEG) 6000, have been used to formulate such systems.

Amorphous precipitation

Amorphous precipitation occurs when the drug precipitates as an amorphous form in the inert carrier. The high-energy state of the drug in this system generally produces much greater dissolution rates than the corresponding crystalline forms of the drug.

Separation methods

Separation may be defined as an operation that brings about isolation and/or purification of a single chemical constituent or a group of chemically related substances. Most medicinal agents require some degree of purification before being incorporated into desirable dosage forms. Many times the analysis of pharmaceutical preparations requires separation of the chief constituent from other formulation constituents before quantitative measurement can be made.

Although the problems of separation are the concern chiefly of pharmaceutical manufacturers, at times they may be encountered by the pharmacist in the prescription laboratory; hence, all pharmacy practitioners should have knowledge of the underlying principles and the techniques employed in the basic processes of separation.

The processes of separation may be divided into two general categories – simple and complex – depending on the complexity of the method used.

Simple processes bring about separation of constituents through a single mechanical manipulation. Processes in this category are limited usually to separations of relatively simple mixtures or solutions. Some examples of this type are the use of:

- A separatory funnel or pipette to separate two immiscible liquids such as water and ether
- A distillation process to separate two miscible liquids such as benzene and chloroform
- A garbling process to separate solids
- Centrifugation, filtration, and expression processes to separate solids from liquids.

Complex processes usually require formation of a second phase by the addition of either a solid, liquid, or gas plus mechanical manipulation to bring about effective separation. One example is the separation of aspirin (acetylsalicylic acid) from salicylic acid. In this mixture, salicylic acid is considered to be an impurity, and to separate the impurity from the desired constituent, a suitable solvent is added to the mixture for the purpose of recrystallizing only the acetylsalicylic acid. The contaminant remains in solution and is removed in the filtrate during the filtration process.

Only selected processes involving separations are covered here. Other methods are discussed under the headings of Complex Formation, Colloidal Dispersions and Coarse Dispersions.

Ionic solutions and electrolytic equilibria

Electrolytes

Electrolytes are substances containing free ions, thus rendering the substance electrically conductive. The most typical electrolyte is an *ionic solution* typified by solutions of acids, bases, or salts. As most drugs are weak acids or bases, it is essential to understand the properties of ionic solutions. *Colligative properties* are properties of solutions that depend on the number of molecules in a given volume of solvent rather than the weight concentration of the molecules. The colligative properties of solutions of electrolytes depend on the total number of entities in solution, including ions. In order to determine which species are present in ionic solutions, it is mperative to understand *ionic equilibria* and their impact on subsequent drug activity. An understanding of these fundamental concepts and an ability to manipulate and predict the subsequent drug properties is crucial in pharmaceutical disciplines.

Pharmaceutical significance

pK_a is one of the most important physicochemical properties of a molecule and the impact of pH on drug systems is widespread. Both solubility and lipophilicity are both governed by pK_a; therefore understanding and predication of absorption, distribution, metabolism, and excretion (ADME) behaviour is impacted. The metabolic profile is highly influenced by the parent compound's pK_a which is also extremely relevant in metabolite identification. Phase II reactions, mechanism-based inhibition are also influenced by pK_a. Receptor binding can also be strongly influenced by pK_a because most drugs are ionized in physiological conditions.

Salt formation

When the first "drugs" or alkaloids were isolated from plant materials they were purified as well-crystallising salts such as morphine hydrochloride, atropine sulfate, codeine phosphate, quinine sulfate and pilocarpine nitrate. In contrast to the free bases, the salts were found to be water soluble and also more stable, rendering them more suitable for use as therapeutic agents. Around 50% of drugs are administered as salts.[20] Salt formation is a simple way of modifying the properties of a drug having ionizable functional groups in order to overcome some undesirable characteristic of the parent drug, normally poor solubility. This affords the opportunity to modify other physicochemical characteristics, such as melting point, hygroscopicity, chemical stability, dissolution rate, solution pH, and crystal form; and mechanical properties, such as hardness and elasticity of the potential drug substance and to develop dosage forms with acceptable bioavailability, stability, manufacturability, and patient compliance.

Salts are formed when a compound that is ionized in solution forms a strong ionic interaction with an oppositely charged compound leading to the precipitation of the salt form. The counterions are attracted by intermolecular coulombic forces. These interactions change the potential energy landscape and lead to stronger interaction between the charged active pharmaceutical ingredient and polar aqueous solvents, which can result in enhanced dissolution rates and higher apparent solubility on physiological time scales, resulting in increased drug delivery rates *in vivo*. For the salt to be dissolved the solvent must overcome the crystal lattice energy of the solid and create space for the solute. Thus, the solubility of the salt depends on its polarity, lipophilicity, ionization potential, and size. A salt's solubility also depends on the properties of the solvent and solid, such as the crystal packing and the presence of solvates.

The advantages and disadvantages of salt formation for manipulation of drug properties are summarized in Table 7.4. A large number of different salt forms are potentially available for application as the counterion and the following criteria are desirable for a particular salt form:

- High aqueous solubility, over a wide pH range, depending on the intended pharmaceutical profile
- High degree of crystallinity
- Low hygroscopicity, for consistent performance
- Optimal chemical and solid-state stability under accelerated conditions.

A serious deficiency in any of these characteristics should exclude the salt for further development. Other influential criteria are:

Table 7.4 Advantages and disadvantages of salt formation (data from Kumar *et al.*[21])

Advantages
Altered solubility and dissolution rate
Controlled-release potential
Improved thermal, hydrolytic and photostability
Reduced hygroscopicity
Improved permeability
Improved organoleptic properties
Improved drug efficacy
Reduced pain on injection
Altered melting point resulting in improved milling and formulation properties
Ease of purification and handling
Improved compactability
Extended patent protection
Disadvantages
Only suitable for ionizable compounds
Decreased percentage of active content
Increased potential for formation of solvates and polymorphs
Reduced dissolution rate or solubility for hydrochloride salts in gastric fluid
Increased chance of poor solid-state stability at the microenvironment pH of the salt, e.g. precipitation of the free acid in the gastrointestinal environment
Corrosiveness of salts, resulting in tableting problems
Possible dissociation of hydrochloride and hydrobromide salts, resulting in the release of hydrohalide gas or reaction with excipients or process-related chemicals
Additional step in synthesis of medicinal product

- Limited number of polymorphs
- Ease of synthesis, handling and formulation development.

The *solubility product* of a salt, K_{sp}, needs to be taken into account when predicting the solubility of a salt in a particular environment that contains other salts with a common counterion.

In spite of the abundance of available counterions, few are used frequently. USP (2013) showed that salt forms (56.15%) are generally preferred over free acid or base forms of a drug (43.85%).[20] Hydrochloride (63%) and sodium (40%) salts remain the favourite counterions in salt formation with basic and acidic drugs, respectively.[21] Because of the low solubility of many basic drugs, where pH_{max} (pH of maximum solubility of the salt) is very low, most common carboxylic acids do not form acceptable salts and it is anticipated that the use of relatively strong counterions will continue in the future. Similarly, 14 out of 19 salt forms of new chemical entities approved by the FDA from 1995 to 2006 are prepared with strong alkalis such as NaOH and KOH, and this trend is also expected to continue in the future.[22]

If a salt, NaA, is added to water to give a concentration C_s, the following reactions occur:

$$Na^+ \ A^- \xrightarrow{H_2O} Na^+ + A^-$$

$$A^- + H_2O \rightleftharpoons HA + OH^-$$

If the pH of the solution is lowered, more of the A^- would be converted to the un-ionized acid, HA, in accordance with Le Chatelier's principle. Eventually, a pH will be obtained below which the amount of HA formed exceeds its *intrinsic aqueous solubility*, S_0, and the acid will precipitate from solution; this pH can be designated as pH_p. At this point, at which the amount of HA formed just equals S_0, a mass balance on the total amount of drug in solution yields

$$C_s = [HA] + [A^-] = S_0 + [A^-] \tag{7.68}$$

Replacing $[A^-]$ as a function of hydroniumion concentration gives

$$C_s = S_0 + \frac{K_a C_s}{[H_3O^+]_p + K_a} \tag{7.69}$$

where K_a is the ionization constant for the conjugate acid, HA, and $[H_3O^+]_p$ refers to the hydroniumion concentration above which precipitation will occur. This equation can be rearranged to give

$$[H_3O^+]_p = K_a \frac{S_0}{C_s - S_0} \tag{7.70}$$

Taking logarithms gives

$$pH_p = pK_a + \log \frac{C_s - S_0}{S_0} \tag{7.71}$$

Thus, the pH below which precipitation occurs is a function of the amount of salt added initially, the pK_a and the solubility of the free acid formed from the salt.

The analogous equation for salts of weak bases and strong acids (such as pilocarpine hydrochloride, cocaine hydrochloride, or codeine phosphate) is

$$pH_p = pK_a + \log \frac{S_0}{C_s - S_0} \tag{7.72}$$

in which pK_a refers to the protonated form of the weak base.

For both acids and bases, when pH = pK_a, $[H_3O^+] = K_a$. If either is substituted the solution is as below,

$$C_s = S_0 \left(\frac{[H_3O^+] + [H_3O^+]}{[H_3O^+]} \right) \tag{7.73}$$

It can be seen that at 50% ionization, the solubility is always equal to twice the intrinsic solubility (S_0).

Ionic liquids

Ionic liquids (ILs) are salt-like materials that are liquid below 100°C and whose melts are composed of discrete cations and anions, thus there is no molecular species present. Although they have been known for over a century, interest is increasing due to their appealing solvent properties. They are miscible with water or organic solvents, their use can be classified as process chemicals (e.g., solvents, separation media) and performance chemicals (e.g., electrolytes, lubricants) and they are useful solvents for extraction processes.

Other properties of ILs are that they have practically no vapor pressure and are reported to have a wide window of electrochemical stability, good electrical conductivity, high ionic mobility, and excellent chemical stability. The third and most recent generation of ILs involve active pharmaceutical ingredients, which are being used to produce ILs with biological activity.[23]

Drug stability

One of the most diversified and fruitful areas of study is the investigation of the effect of hydrogen-ion concentration on the stability or, in more general terms, the reactivity of pharmaceutical systems. The evidence for enhanced stability of systems when these are maintained within a narrow range of pH, as well as of progressively decreasing stability as the pH departs from the optimum range, is abundant. Stability (or instability) of a system may result from gain or loss of a proton (hydrogen ion) by a substrate molecule (often accompanied by an electronic rearrangement) that reduces (or increases) the reactivity of the molecule. *Instability* results when the substance desired to remain unchanged is converted to one or more other, unwanted, substances. In aqueous solution, instability may arise through the catalytic effect of acids or bases: the former by transferring a proton to the substrate molecule, the latter by accepting a proton.

Specific illustrations of the effect of hydrogen-ion concentration on the stability of medicinals are myriad; only a few will be given here, these being chosen to show the importance of pH adjustment of solutions that require sterilization.

Morphine solutions are not decomposed during a 60 minute exposure at a temperature of 100°C if the pH is less than 5.5; neutral and alkaline solutions, however, are highly unstable. Minimum hydrolytic decomposition of solutions of cocaine occurs in the pH range 2 to 5; in one study a solution of cocaine hydrochloride, initially at pH 5.7, remained stable during two months (although the pH dropped to 4.2 in this time), whereas another solution buffered to about pH 6 underwent approximately 30% hydrolysis in the same time. Similarly, solutions of procaine hydrochloride containing some hydrochloric acid showed no appreciable decomposition; when dissolved in water alone, 5% of the procaine hydrochloride hydrolyzed, whereas when buffered to pH 6.5, from 19 to 35% underwent decomposition by hydrolysis. Solutions of thiamine hydrochloride may be sterilized by autoclaving without appreciable decomposition if the pH is below 5; above this, thiamine hydrochloride is unstable.

The stability of many disperse systems, and especially of certain emulsions, is often pH dependent. Information concerning specific emulsion systems, and the effect of pH upon them, may be found under the heading Colloidal Dispersions.

Drug activity

Drugs that are weak acids or weak bases, and hence may exist in ionized or nonionized form (or a mixture of both), may be active in one form but not in the other; often such drugs have an optimum pH range for maximum activity. Thus, mandelic acid, benzoic acid, or salicylic acid have pronounced antibacterial activity in their nonionized forms but have practically no such activity in the equivalent ionized form. Accordingly, these substances require an acidic environment to function effectively as antibacterial agents. For example, sodium benzoate is effective as a preservative in 4% concentration at pH 7, in 0.06 to 0.1% concentration at pH 3.5 to 4, and in 0.02 to 0.03% concentration at pH 2.3 to 2.4. Other antibacterial agents are active principally, if not entirely, in cationic form. Included in this category are the acridines and quaternary ammonium compounds.

Drug absorption

The degree of ionization and lipoid solubility of a drug are two important factors that determine the rate of absorption of drugs from the gastrointestinal tract, and indeed their passage through cellular membranes generally. Drugs that are weak organic acids or bases, and that in nonionized form are soluble in lipids, apparently are absorbed through cellular membranes by virtue of the lipoidal nature of the membranes. Completely ionized drugs, on the other hand, are absorbed poorly, if at all. Rates of absorption of a variety of drugs are related to their ionization constants and in many cases may be predicted quantitatively on the basis of this relationship. Thus, not only the degree of the acidic or basic character of a drug, but also consequently the pH of the physiological medium (e.g., gastric or intestinal fluid, plasma, cerebrospinal fluid) in which a drug is dissolved or dispersed (because this pH determines the extent to which the drug will be converted to ionic or nonionic form) become important parameters of drug absorption. Further information on drug absorption is given in Chapter 8 under the heading Drug Absorption, Distribution, Metabolism and Excretion.

Tonicity, osmoticity, osmolality and osmolarity

Basic definitions

If a solution is placed in contact with a membrane that is permeable to molecules of the solvent, but not to molecules of the solute, the movement of solvent through the membrane is called *osmosis*. Such a membrane often is called *semipermeable*. As the several types of membranes of the body vary in their permeability, it is well to note that they are *selectively* permeable. Most normal living-cell membranes maintain various solute concentration gradients. A selectively permeable membrane may be defined either as one that does not permit free, unhampered diffusion of all the solutes present or as one that maintains at least one solute concentration gradient across itself. Osmosis, then, is the diffusion of water through a membrane that maintains at least one solute concentration gradient across itself.

Assume that solution A is on one side of the membrane, and solution B of the same solute but of a higher concentration is on the other side; the solvent will tend to pass into the more concentrated solution until equilibrium has been established. The pressure required to prevent this movement is the osmotic pressure. It is defined as the excess pressure, or pressure greater than that above the pure solvent, that must be applied to solution B to prevent passage of solvent through a perfect semipermeable membrane from A to B. The concentration of a solution with respect to effect on osmotic pressure is related to the number of particles (un-ionized molecules, ions, macromolecules, aggregates) of solute(s) in solution and, thus, is affected by the degree of ionization or aggregation of the solute. See the Solutions and Phase Equilibria section for a review of colligative properties of solutions.

Body fluids, including blood and lacrimal fluid, normally have an osmotic pressure that often is described as corresponding to that of a 0.9%w/v solution of sodium chloride. The body also attempts to keep the osmotic pressure of the contents of the gastrointestinal tract at about this level, but there the normal range is much wider than that of most body fluids. The 0.9%w/v sodium chloride solution is said to be *isoosmotic* with physiological fluids. In medicine, the term isotonic, meaning equal tone, is commonly used interchangeably with iso-osmotic. However, terms such as isotonic and tonicity should be used *only* with reference to a physiological fluid. Iso-osmotic actually is a physical term that compares the osmotic pressure (or another colligative property, such as freezing-point depression) of two liquids, neither of which may be a physiological fluid, or which may be a physiological fluid only under certain circumstances. For example, a solution of boric acid that is iso-osmotic with both blood and lacrimal fluid is isotonic only with the lacrimal fluid. This solution causes hemolysis of red blood cells because molecules of boric acid pass freely through the erythrocyte membrane, regardless of concentration. Thus, isotonicity infers a sense of physiological compatibility where iso-osmoticity need not. As another example, a *chemically defined elemental diet* or enteral nutritional fluid can be iso-osmotic with the contents of the gastrointestinal tract but would not be considered a physiological fluid or suitable for parenteral use.

A solution is isotonic with a living cell if there is no net gain or loss of water by the cell, or no other change in the cell, when it is in contact with that solution. Physiological solutions with an osmotic pressure lower than that of body fluids, or of 0.9% sodium chloride solution, are referred to commonly as being *hypotonic*. Physiological solutions having a greater osmotic pressure are termed *hypertonic*.

Such qualitative terms are of limited value, and it has become necessary to state osmotic properties in quantitative terms. To do so, a term must be used that will represent all the particles that may be present in a given system. The term used is *osmol:* the weight, in grams, of a solute, existing in a solution as molecules (and/or ions, macromolecules, aggregates, etc.), which is osmotically equivalent to a mole of an ideally behaving nonelectrolyte. Thus, the osmol weight of a nonelectrolyte, in a dilute solution, generally is equal to its gram molecular weight. A *milliosmol*, abbreviated mOsm, is the weight stated in milligrams.

If one extrapolates this concept of relating an osmol and a mole of a nonelectrolyte as being equivalent, then one also may define an osmol in the following ways. It is the amount of solute that will provide 1 Avogadro's number (6.02×10^{23}) of particles in solution, and it is the amount of solute that, on dissolution in 1 kg of water, will result in an

osmotic pressure increase of 17 000 torr at 0°C or 19 300 torr at 37°C. One mOsmol is 1/1000 of an osmol. For example, 1 mol of anhydrous glucose is equal to 180 gram. One osmol of this nonelectrolyte is also 180 gram. One mOsmol would be 180 mg. Thus, 180 mg of this solute dissolved in 1 kg of water will produce an increase in osmotic pressure of 19.3 torr at body temperature.

For a solution of an electrolyte such as sodium chloride, one molecule of sodium chloride represents one sodium and one chloride ion. Hence, 1 mol will represent 2 osmol of sodium chloride theoretically. Accordingly, 1 osmol NaCl = 58.5 g/2 or 29.25 g. This quantity represents the sum total of 6.02×10^{23} ions as the total number of particles. Ideal solutions infer very dilute solutions or infinite dilution.

However, as pH or concentration is increased, other factors enter. Strong electrolyte, interionic attraction causes a decrease in their effect on colligative properties. In addition, the charge of ions must also follow an electrical gradient which operates to intensify or reduce their colligative effect *in vivo* physiological conditions. Body pH is actively maintained at differing values throughout the gastrointestinal tract with more minor variations in other organs. A combination of electrochemical gradient and chemical concentration maintains pH at different values across membranes, often forcing a change in state of organic acids or bases between ionized (multiple species) and un-ionized (one species) states. The body uses these systems for absorption of nutrition and medications but also excretion of waste products.

Therefore, it is very difficult and often impossible to predict accurately the osmoticity of a solution. It may be possible to do so for a dilute solution of a single pure and well-characterized solute entering a similarly well defined environment, but not for most parenteral and enteral medicinal and/or nutritional fluids; experimental determination is likely required to predict behavior *in vivo*.

Therapeutic considerations

Generally it is accepted that osmotic effects have a major place in the maintenance of homeostasis (the state of equilibrium in the living body, with respect to various functions and to the chemical composition of the fluids and tissues, e.g., temperature, heart rate, blood pressure, water content, or blood sugar). To a great extent these effects occur within or between cells and tissues where they cannot be measured. One of the most troublesome problems in clinical medicine is the maintenance of adequate body fluids and proper balance between extracellular and intracellular fluid volumes in seriously ill patients. It should be kept in mind, however, that fluid and electrolyte abnormalities are not diseases but are the manifestations of disease.

The physiological mechanisms that control water intake and output appear to respond primarily to serum osmoticity. Renal regulation of output is influenced by variation in rate of release of pituitary antidiuretic hormone (ADH) and other factors in response to changes in serum osmoticity. Osmotic changes also serve as a stimulus to moderate thirst. This mechanism is sufficiently sensitive to limit variations in osmoticity in the normal individual to less than about 1%. Body fluid continually oscillates around a narrow genetically determined set point in the normal range of 280 to 295 mOsmol L^{-1}. An increase of plasma osmoticity of 1% will stimulate ADH release, resulting in a reduction of urine flow, and, at the same time, stimulate thirst that results in increased water intake. Both the increased renal reabsorption of water (without solute) stimulated by circulating ADH and the increased water intake tend to lower serum osmoticity.

The transfer of water through the cell membrane occurs so rapidly that any lack of osmotic equilibrium between the two fluid compartments in any given tissue usually is corrected within a few seconds and, at most, within a minute or so. However, this rapid transfer of water does not mean that complete equilibration occurs between the extracellular and intracellular compartments throughout the entire body within this same short period of time. The reason is that fluid usually enters the body through the gut and then must be transported by the circulatory system to all tissues before complete equilibration can occur. In the normal person it may require 30 to 60 minutes to achieve reasonably good equilibration throughout the body after drinking water. Osmoticity is the property that largely determines the physiological acceptability of a variety of solutions used for therapeutic and nutritional purposes.

Pharmaceutical and therapeutic consideration of osmotic effects has been, to a great extent, directed

toward the side effects of ophthalmic and parenteral medicinals due to abnormal osmoticity, and either to formulating to avoid the side effects or to finding methods of administration to minimize them. More recently this consideration has been extended to total (central) parenteral nutrition, to enteral hyperalimentation ("tube" feeding), and to concentrated-fluid infant formulas.[24,25] Also, in recent years, the importance of osmometry of serum and urine in the diagnosis of many pathological conditions has been recognized.

There are a number of examples of the direct therapeutic effect of osmotic action, such as the *intravenous* (IV) use of mannitol as a diuretic that is filtered at the glomeruli and thus increases the osmotic pressure of tubular urine. Water must then be reabsorbed against a higher osmotic gradient than otherwise, so reabsorption is slower and diuresis is observed. The same fundamental principle applies to the IV administration of 30% urea used to affect intracranial pressure in the control of cerebral edema. Peritoneal dialysis fluids tend to be somewhat hyperosmotic to withdraw water and nitrogenous metabolites. Two to 5% sodium chloride solutions or dispersions in an oleaginous base (Muro; Bausch and Lomb) and a 40% glucose ointment are used topically for corneal edema. Ophthalgan (Wyeth-Ayerst) is ophthalmic glycerin employed for its osmotic effect to clear edematous cornea to facilitate an ophthalmoscopic or gonioscopic examination. Glycerin solutions in 50% concentration (Osmoglyn; Alcon) and isosorbide solution (Ismotic; Alcon) are oral osmotic agents for reducing intraocular pressure.

The osmotic principle also applies to plasma extenders, such as PVP and to saline laxatives, such as magnesium sulfate, magnesium citrate solution, magnesium hydroxide (via gastric neutralization), sodium sulfate, sodium phosphate, sodium biphosphate oral solution, and enema (Fleet).

An interesting osmotic laxative that is a nonelectrolyte is a lactulose solution. Lactulose is a nonabsorbable disaccharide that is colon-specific, wherein colonic bacteria degrade some of the disaccharide to lactic and other simple organic acids. These, in total, lead to an osmotic effect and laxation. An extension of this therapy is illustrated by Cephulac (Marion Merrell Dow) solution, which uses the acidification of the colon via lactulose degradation to serve as a trap for ammonia migrating from the blood to the colon. The conversion of ammonia of blood to the ammonium ion in the colon ultimately is coupled with the osmotic effect and laxation, thus expelling undesirable levels of blood ammonia. This product is employed to prevent and treat frontal systemic encephalopathy.

Osmotic laxation is observed with the oral or rectal use of glycerin and sorbitol. Epsom salt has been used in baths and compresses to reduce edema associated with sprains. Another approach is the indirect application of the osmotic effect in therapy via osmotic pump drug delivery systems.[26]

Undesirable effects of abnormal osmoticity

Ophthalmic medication

It is generally accepted that ophthalmic preparations intended for instillation into the cul-de-sac of the eye should, if possible, be approximately isotonic to avoid irritation. It also has been stated that the abnormal tonicity of contact lens solutions can cause the lens to adhere to the eye and/or cause burning or dryness and photophobia.

Neonatal enteral and total parenteral medication

Adult tolerances of osmoticity cannot be expected in pediatric and neonatal therapy. Paracetamol solutions have an osmolality approaching 15,000 mOsm L^{-1} with a target of less than 500 mOsmol/L suitable for enternal feed. Modifications, or dilutions of these formulations must be considered to prevent the risks of *pneumatosis intestinalis* or hypernatremia,[25] particularly in the cases of significant imbalance of ADH caused by existing trauma or acute diarrhea states.[27,28]

Because of the different fluid and protein requirements of neonates and pediatric patients, the final concentration of glucose and amino acids are often different from those of an adult. It is now expected that these variations are available to the clinician and that calculation or active measurement of the osmolarity of a system should be made. Many automated compounding systems are now capable of calculation of the full bag osmolarity, using previously recorded individual coefficients of variations for

the individual components. Large validation cycles allow these calculations to be clinically relied upon, but pharmacists must take particular care with regard to the extemporaneous addition of compounds to these systems, for these concentrated systems are not governed by the simpler calculations.

Hyperosmotic agents

Therapies directly applying osmotic gradients therapeutically are few. However, pediatric and mature cystic fibrosis patients infrequently make use of salt solutions in the range 295 to 700 mOsm L^{-1} for their direct osmotic effect. Upon nebulization of these solutions, water movement is increased through the lungs' transepithelial surface to dilute any mucus. Higher osmolarities produce transepithelial movement through tight junctions,[29,30] further accelerating tracheobronchial mucocillary clearance.[31]

Diagnostic contrast agents

Radiopharmaceutical and tomography contrast agents demand a pharmaceutical concentration to be held in a specific area of interest to allow appropriate imaging. This requirement can produce localized concentrations in the region of 600 mOsm L^{-1} resulting in tissue shrinkage and the potential for resultant cell death.[32] Since dilution of the agent is not possible until after treatment, reformulation with alternative agents could be considered.

Parenteral medication

Osmoticity is of great importance in parenteral injections, its effects depending on such factors as the degree of deviation from tonicity, the concentration, the location of the injection, the volume injected, the speed of the injection, and the rapidity of dilution and diffusion. When formulating hypotonic parenterals, they usually have tonicity adjusted by the addition of glucose or sodium chloride. Hypertonic parenteral drug solutions cannot be adjusted, but if prepared from a dry powder, they may be reconstituted in a different solvent volume. Hypotonic and hypertonic solutions usually are administered slowly, in small volumes, or into a large vein such as the subclavian, where dilution and distribution occur rapidly. Solutions that differ from the serum in tonicity generally cause tissue irritation, pain on injection, and electrolyte shifts, the effect depending on the degree of deviation from tonicity:

- Excessive infusion of *hypotonic* fluids may cause swelling of red blood cells, hemolysis, and water invasion of the body's cells in general. When this is beyond the body's tolerance for water, water intoxication results, with convulsions and edema, such as pulmonary edema.
- Excessive infusion of *isotonic* fluids can cause an increase in extracellular fluid volume, which can result in circulatory overload.
- Excessive infusion of *hypertonic* fluids leads to a wide variety of complications. For example, the sequence of events when the body is presented with a large IV load of hypertonic fluid, rich in glucose, is as follows: hyperglycemia, glycosuria and intracellular dehydration, osmotic diuresis, loss of water and electrolytes, dehydration, and coma.

One cause of osmotic diuresis is the infusion of glucose at a rate faster than the ability of the patient to metabolize it (as greater than perhaps 400 to 500 mg kg^{-1} per hour for an adult on total parenteral nutrition). A heavy load of unmetabolizable glucose increases the osmoticity of blood and acts as a diuretic; the increased solute load requires more fluid for excretion, 10 to 20 mL of water being required to excrete each gram of glucose. Solutions such as those for total parenteral nutrition should be administered by means of a metered constant-infusion apparatus over a lengthy period (usually more than 24 hours) to avoid sudden hyperosmotic glucose loads. Such solutions may cause osmotic diuresis; if this occurs, water balance is likely to become negative because of the increased urinary volume, and electrolyte depletion may occur because of excretion of sodium and potassium secondary to the osmotic diuresis. If such diuresis is marked, body weight falls abruptly and signs of dehydration appear. Urine should be monitored for signs of osmotic diuresis, such as glycosuria and increased urine volume.

If the IV injection rate of hypertonic solution is too rapid, there may be catastrophic effects on the circulatory and respiratory systems. Blood pressure may fall to dangerous levels, cardiac irregularities or arrest may ensue, respiration may become shallow and irregular, and there may be heart failure and pulmonary edema. Probably the precipitating factor is a bolus of concentrated solute suddenly reaching

the myocardium and the chemoreceptors in the aortic arch and carotid sinus.[33]

Abrupt changes in serum osmoticity can lead to cerebral hemorrhage. It has been shown experimentally that rapid infusions of therapeutic doses of hypertonic saline with osmotic loads produce a sudden rise in cerebrospinal fluid (CSF) pressure and venous pressure, followed by a precipitous fall in CSF pressure. This particularly may be conducive to intracranial hemorrhage, for the rapid infusion produces an increase in plasma volume and venous pressure at the same time the CSF pressure is falling. During the CSF pressure rise, there is a drop in hemoglobin and hematocrit, reflecting a marked increase in blood volume.

Hyperosmotic medications, such as sodium bicarbonate (osmolarity of 1560 at $1\,mEq\,mL^{-1}$), which are administered intravenously, should be diluted prior to use and should be injected slowly to allow dilution by the circulating blood. Rapid *push* injections may cause a significant increase in blood osmoticity.[34]

Safety, therefore, demands that all IV injections, especially of highly osmotic solutions, be performed slowly, usually being given preferably over a period not less than that required for a complete circulation of the blood (1 minute). The exact danger point varies with the state of the patient, the concentration of the solution, the nature of the solute, and the rate of administration.

Hyperosmotic solutions also should not be discontinued suddenly. In dogs, marked increase in levels of intracranial pressure have occurred when hyperglycemia produced with glucose infusions was suddenly reversed by stopping the infusion and administering saline. It also has been shown that the CSF pressure in humans rises during treatment of diabetic ketoacidosis in association with a fall in the plasma concentration of glucose and a fall in plasma osmolality. These observations may be explained by the different rates of decline in glucose content of the brain and of plasma. The concentration of glucose in the brain may fall more slowly than in the plasma, causing a shift of fluid from the extracellular fluid space to the intracellular compartment of the CNS, resulting in increased intracranial pressure.

Clinical applications

Although there are many issues with abnormal osmoticity, most pharmacists are concerned with preventable adverse effects, such as thrombophlebitis and pain at the injection site. The understanding of these potential risks from hyperosmotic parenteral medications has fine-tuned IV administration techniques. The site of administration – peripheral versus central venous catheter – plays a significant role in determining the final concentration of parenteral medications infused IV. Attention should be directed toward establishing the optimal osmolarity of IV administered parenteral medications via the peripheral venous route that will result in the least adverse effects.

Since the introduction of parenteral nutrition support, hyperosmoticity of these nutrition solutions remains a concern. The commonly accepted osmolarity of less than $900\,mOsmol\,L^{-1}$ has been quoted for safe peripheral administration of parenteral nutrition solutions.[35,36] All attempts should be made to prepare solutions with osmoticity close to that of serum osmoticity or no greater than $900\,mOsmol\,L^{-1}$. This can be achieved by carefully selecting the diluent for dilution and determining the final concentration of the parenteral medication. Glucose 5% in Water for Injection and Sodium Chloride 0.9% have been used routinely as diluents. When comparing the two diluents, parenteral medications diluted with Glucose 5% in Water for Injection have a lower osmolarity than do solutions diluted with Sodium Chloride 0.9% at the same final concentration.

Several studies have been conducted to determine optimal final concentration of commonly used parenteral medications.[37–39] The published final concentrations for most parenteral medications are recommended for peripheral as well as central venous catheter IV administration for patients with no special needs, such as fluid restriction. In the event that fluid restriction is required or the recommended final concentration is not achievable, the parenteral medication should be administered via a central venous catheter, by which immediate dilution and distribution is achieved rapidly. This will minimize potential for phlebitis and pain at the injection site.

Osmoticity issues associated with parenteral medications are also applicable to total parenteral nutrition (TPN) solutions, especially via peripheral venous

administration. Peripheral parenteral nutrition support remains an integral part of therapeutic options for hospitalized patients. The peripheral route of administration often is preferred for patients who require short-term therapy or supplemental nutrition support.

Methods of adjusting tonicity

There are several methods for adjusting the tonicity of an aqueous solution, provided, of course, that the solution is hypotonic when the drug and additives are dissolved. The most prominent of these methods are the freezing-point depression method, the sodium chloride equivalent method, and the isotonic solution *V*-value method. The first two of these methods can be used with a three-step problem-solving process, based on sodium chloride.

1. Identify a reference solution and the associated tonicity parameter.
2. Determine the contribution of the drug(s) and additive(s) to the total tonicity.
3. Determine the amount of sodium chloride needed by subtracting the contribution of the actual solution from the reference solution.

The result of the third step also indicates whether the actual solution is hypotonic, isotonic, or hypertonic. If the actual solution contributes less to the total tonicity than the reference solution, then the actual solution is hypotonic. If, however, the actual solution contributes a greater amount to tonicity than the reference solution, the actual solution is hypertonic and can be adjusted to isotonicity only by dilution. This may not be possible on therapeutic grounds.

The amount of sodium chloride resulting in the third step also can be converted into an amount of other materials, such as glucose, to render the actual solution isotonic.

Freezing-point-depression method

The freezing-point method makes use of a *D value* (found in Appendix A) which has the units of degree centigrade/(x% drug). For example, in Appendix A, dexamethasone sodium phosphate has *D* values of 0.050°/(0.5% drug), 0.180°/(2.0% drug), 0.52°/(6.75% drug), etc. It is apparent that the *D* value is nearly proportional to concentration. If a *D* value is needed for a concentration of drug not listed in Appendix A, a *D* value can be calculated from the appendix by direct proportion, using a *D* value closest to the concentration of drug in the actual solution.

The reference solution for the freezing-point-depression method is 0.9% sodium chloride, which has a freezing-point depression of $\Delta T_f = 0.52°C$. Using the three steps described above, the dexamethasone sodium phosphate solution in Example 1 can be rendered isotonic as follows:

Example 1	
Dexamethasone Sodium Phosphate	0.1%
Purified Water qs	30 mL

Mft Isotonic Solution

Step 1 – Reference solution: 0.9% sodium chloride.

$\Delta T_f = 0.52°C$

$D = 0.050°/0.5\%$ (dexamethasone sodium phosphate)

Step 2 – Contribution of drug.

$$\frac{0.050°}{0.5\%\ \text{drug}} \times 0.1\%\ \text{drug} = 0.010° \qquad (7.74)$$

Step 3 – Reference solution – Actual solution.

$0.52° - 0.01° = 0.51°$

Sodium chloride needed.

$$\frac{0.883\ \text{g NaCl}}{100\ \text{mL}} \times 30\ \text{mL} = 0.265\ \text{g NaCl} \qquad (7.75)$$

$$\frac{0.9\%\ \text{NaCl}}{0.52°} \times 30\ \text{mL} = 0.265\ \text{g NaCl} \qquad (7.76)$$

The above solution could be made isotonic with any appropriate material other than sodium chloride by using the *D* value for that material. For example, to make the solution isotonic with glucose with a *D* value, $D = 0.091°/1\%$;

$$\frac{5.60\ \text{g Dextrose}}{100\ \text{mL}} \times 30\ \text{mL} = 1.68\ \text{g Dextrose} \qquad (7.77)$$

$$\frac{1\%\ \text{Dextrose}}{0.091°} \times 0.51° = 5.60\%\ \text{Dextrose} \qquad (7.78)$$

Example 2	
Naphazoline HCl (N.HCl)	0.02%
Zinc Sulfate	0.25%
Purified Water qs	30 mL

Mft Isotonic solution

Step 1 – Reference solution: 0.9% sodium chloride.

$\Delta T_f = 0.52^\circ C$

$D = 0.14^\circ/1\%$ (naphazoline HCl)

$D = 0.086^\circ/1\%$ (zinc sulfate)

Step 2 – Contribution of drugs.

$$\frac{0.086^\circ}{1\%\ \ ZnSO_4} \times 0.25\%\ \ ZnSO_4 = 0.022^\circ \tag{7.79}$$

$$\frac{0.14^\circ}{1\%\ N.HCl} \times 0.02\%\ N.HCl = 0.003^\circ \tag{7.80}$$

Step 3 – Reference solution – Actual solution.

$0.52^\circ - 0.025^\circ = 0.495^\circ$

Sodium chloride needed.

$$\frac{0.857\ g\ NaCl}{100\ mL} \times 30\ mL = 0.257\ g\ NaCl \tag{7.81}$$

$$\frac{0.9\%\ NaCl}{0.52^\circ} \times 0.495^\circ = 0.857\%\ NaCl \tag{7.82}$$

The above solution could be made isotonic with any appropriate material, other than sodium chloride, by using the *D* value for that material.

For example, to make the solution isotonic with glucose with a *D* value, $D = 0.091^\circ/1\%$;

$$\frac{5.44\ g\ Dextrose}{100\ mL} \times 30\ mL = 1.63\ g\ Dextrose \tag{7.83}$$

$$\frac{1\%\ Dextrose}{0.091^\circ} \times 0.495^\circ = 5.44\%\ Dextrose \tag{7.84}$$

Sodium chloride equivalent method

A sodium chloride equivalent, *E value*, is defined as the weight of sodium chloride that will produce the same osmotic effect as 1 g of the drug. For example, in Appendix A, dexamethasone sodium phosphate has an *E* value of 0.18 g NaCl/g drug at 0.5% drug concentration, 0.17 g NaCl/g drug at 1% drug concentration and a value of 0.16 g NaCl/g drug at 2% drug. This slight variation in the sodium chloride equivalent with concentration is due to changes in interionic attraction at different concentration of drug; the *E* value is not directly proportional to concentration, as was the freezing-point depression.

The reference solution for the sodium chloride equivalent method is 0.9% sodium chloride, as it was for the freezing-point-depression method.

The dexamethasone sodium phosphate solution in Example 1 can be rendered isotonic, using the sodium chloride equivalent method as follows:

Example 1	
Dexamethasone Sodium Phosphate	0.1%
Purified Water qs	30 mL

Mft Isotonic Solution

Step 1 – Reference solution: 0.9% sodium chloride.

$$\frac{0.9\ g\ NaCl}{100\ mL} \times 30\ mL = 0.270\ g\ NaCl \tag{7.85}$$

$E = 0.18$ g NaCl/g drug

Step 2 – Contribution of drug.

$$\frac{0.18\ g\ NaCl}{1\ g\ drug} \times \frac{0.1\ g\ drug}{100\ mL} \times 30\ mL = 0.0054\ g\ NaCl \tag{7.86}$$

Step 3 – Reference solution – Actual solution.

0.270 g NaCl – 0.0054 g NaCl = 0.265 g NaCl

The above solution can be made isotonic with a material other than sodium chloride, such as glucose, by using the *E* value of that material. For example, to make the solution isotonic with glucose, $E = 0.16$ g NaCl/g glucose, the amount of sodium chloride needed in Step 3, can be converted to glucose as follows:

$$\frac{1\ g\ Dextrose}{0.16\ g\ NaCl} \times 0.265\ g\ NaCl = 1.66\ g\ Dextrose \tag{7.87}$$

Example 2	
Naphazoline HCl (N.HCl)	0.02%
Zinc Sulfate	0.25%
Purified Water qs	30 mL

Mft Isotonic Solution

Step 1 – Reference solution: 0.9% sodium chloride.

$$\frac{0.9\text{ g NaCl}}{100\text{ mL}} \times 30\text{mL} = 0.270\text{ g NaCl} \qquad (7.88)$$

E = 0.27 g NaCl/g N.HCl

E = 0.15 g NaCl/g $ZnSO_4$

Step 2 – Contribution of drugs.

$$\frac{0.27\text{ g NaCl}}{1\text{ g N.HCl}} \times \frac{0.02\text{ g N.HCl}}{100\text{mL}} \times 30\text{ mL} = 0.002\text{ g NaCl} \qquad (7.89)$$

$$\frac{0.15\text{ g NaCl}}{1\text{ g } ZnSO_4} \times \frac{0.25\text{ g}ZnSO_4}{100\text{mL}} \times 30\text{ mL} = 0.011\text{ g NaCl} \qquad (7.90)$$

0.002 g NaCl + 0.011 g NaCl = 0.013 g NaCl

Step 3 – Reference solution − Actual solution.

0.270 g NaCl − 0.013 g NaCl = 0.257 g NaCl

The above solution can be made isotonic with a material other than sodium chloride, such as glucose, by using the E value of that material. For example, to make the solution isotonic with glucose, E = 0.16 g NaCl/g glucose, the amount of sodium chloride needed in *Step 3* can be converted to glucose as follows:

$$\frac{1\text{ g Dextrose}}{0.16\text{ g NaCl}} \times 0.257\text{ g NaCl} = 1.61\text{ g Dextrose} \qquad (7.91)$$

Isotonic solution V-values

The V-value of a drug is the volume of water to be added to a specified weight of drug (0.3 g or 1.0 g, depending on the table used) to prepare an isotonic solution. Appendix B gives such values for some commonly used drugs. The reason for providing data for 0.3 g of drug is for convenience in preparing 30 mL (approximately 1 fluid ounce) of solution, a commonly prescribed volume. The basic principle underlying the use of V-values is to prepare an isotonic solution of the prescribed drug and then dilute this solution to final volume with a suitable isotonic vehicle.

The two solutions in the previous examples can be prepared as follows using the V-value method:

Example 1	
Dexamethasone Sodium Phosphate	0.1%
Purified Water qs	30 mL

Mft Isotonic Solution

Step 1 – The V-value for dexamethasone sodium phosphate can be calculated from the sodium chloride equivalent, E, as outlined in the footnote in Appendix B.

$$\frac{100\text{ mL Soln}}{0.9\text{ g NaCl}} \times \frac{0.17\text{ g NaCl}}{1\text{ g drug}} \times 0.3\text{ g drug} = 5.67\text{ mL Soln} \qquad (7.92)$$

for a dilute solution:

5.67 mL Soln ≅ 5.67 mL H_2O

where V = (5.67 mL H_2O)/(0.3 g drug)

Step 2 – Amount of drug needed.

$$\frac{0.1\text{ g drug}}{100\text{ mL}} \times 30\text{ mL} = 0.030\text{ g drug} \qquad (7.93)$$

Volume of water needed to prepare an isotonic solution.

$$\frac{5.67\text{ mL } H_2O}{0.3\text{ g drug}} \times 0.030\text{ g} = 0.57\text{ mL } H_2O \qquad (7.94)$$

Step 3 – To prepare the solution, dissolve 0.030 g of drug in 0.57 mL water, and qs to volume with a suitable isotonic vehicle, such as 0.9% sodium chloride solution, 5.51% glucose, or an isotonic phosphate buffer.

Example 2	
Naphazoline HCl (N.HCl)	0.02%
Zinc Sulfate	0.25%
Purified Water qs	30 mL

Mft Isotonic Solution

Step 1 – The *V*-value for naphazoline HCl can be calculated from the sodium chloride equivalent, *E*, as outlined in the footnote in Appendix B; the *V*-value for zinc sulfate is taken directly from Appendix B.

$$\frac{100\text{ mL Soln}}{0.9\text{ g NaCl}} \times \frac{0.27\text{ g NaCl}}{1\text{ g N.HCl}} \times 0.3\text{ g N.HCl} = 9.00\text{ mL Soln} \quad (7.95)$$

for a dilute solution:

$9.00\text{ mL Soln} \cong 9.00\text{ mL } H_2O$

where $V = (9.00\text{ mL } H_2O)/(0.3\text{ g N.HCl})$

$V = 5.00\text{ mL } H_2O/0.3\text{ g } ZnSO_4$

Step 2 – Amount of drugs needed.

$$\frac{0.25\text{ g } ZnSO_4}{100\text{ mL}} \times 30\text{ mL} = 0.075\text{ g } ZnSO_4 \quad (7.96)$$

$$\frac{0.02\text{ g N.HCl}}{100\text{ mL}} \times 30\text{ mL} = 0.006\text{ g N.HCl} \quad (7.97)$$

Volume of water needed to prepare an isotonic solution:

$$\frac{5.00\text{ mL } H_2O}{0.3\text{ g } ZnSO_4} \times 0.075\text{ g } ZnSO_4 = 1.25\text{ mL } H_2O \quad (7.98)$$

$$\frac{9.00\text{ mL } H_2O}{0.3\text{ g N.HCl}} \times 0.006\text{ g drug} = 0.18\text{ mL } H_2O \quad (7.99)$$

Step 3 – To prepare the solution, dissolve 0.006 g of naphazoline HCl and 0.075 g zinc sulfate in 1.43 mL water, and qs to volume with a suitable isotonic vehicle, such as 0.9% sodium chloride solution, 5.51% glucose, or an isotonic phosphate buffer.

Chemical kinetics

This section is intended as a general introduction to Chemical Kinetics. A comprehensive review of experimental approaches and interpretation of data can be found in several texts, such as the books by House, Epenson, and Houston, and the compilation of information relative to kinetic studies on pharmaceuticals by Garrett.[40–43]

Chemical reactions

A chemical reaction is said to have occurred when one or more molecules undergoes a process in which electrons are either lost or gained by an atom or molecule, or the electrons go through a transition process in which they are shared differently between atoms which result in the breaking or forming of bonds. These result in the formation of one or more new chemical species with different chemical structures and properties than that of the original starting material. Such chemical processes usually result in changes in energy and/or degree of randomness in going from the initial to the final state which is the basis for thermodynamics. Thermodynamic parameters, such as ΔG, ΔE, ΔH, and ΔS, are state functions that only depend on the initial and final states of a chemical process (usually defined as the state of the reactants and products at certain temperatures, pressures and physical states) and are independent of the pathway taken to get to the final state from the initial state. Spontaneous reactions are said to occur when the reactants proceed to products when the energy contained within the products is less than the energy contained in the reactants (i.e., $\Delta G < 0$) which usually result in the release of heat (i.e., $\Delta H < 0$) and/or an increase in randomness of the chemical system (i.e., $\Delta S > 0$). However, it has been observed that in some cases, whereas some reactions are thermodynamically favorable to proceed spontaneously, the conversion of reactants to products may proceed at very slow rates over relatively long periods of time. This serves to point out that thermodynamics is essentially a snapshot of the differences between the properties of the product and reactant states of a chemical reaction which provides no indication of the chemical processes or the time that it took to go from reactant to product state.

Chemical kinetics is the discipline that is concerned with the mechanism by which a chemical process gets to its final state from its initial state and the rate in which this reaction proceeds. Therefore, chemical kinetics involves the study of rate of chemical change and the way in which this rate is influenced by the conditions of the concentration of reactants, products, and other chemical species that may be present, and by factors such as solvent, pressure, and temperature. From these studies, one or more mechanisms

involving a series of elementary processes may be postulated to explain how the reactants are converted to products during a chemical process.

Applied to pharmaceutics, chemical kinetic information permits a rational approach to the stabilization of drug products, and prediction of shelf life and optimum storage conditions.

Reaction mechanism

There are two basic ways in which chemical reactions can occur. One method involves the absorption of electromagnetic radiation which excites certain electrons within an atom or molecule to a higher energy state or even the ejection of the electron creating a free radical which is a very reactive chemical species. This may be indicated by the elementary processes such as

$$A + h\nu \rightarrow A^*$$

and

$$A + h\nu \rightarrow A^{\bullet} + e^-$$

where $h\nu$ represents a quantum of electromagnetic radiation absorbed by chemical species A, A* represents the higher energy, excited state of chemical species A, $A^{\bullet}$ represents the free radical of species A, and e^- represents an electron. If the excited electrons were originally involved in a bond between atoms, then the bond may be weakened or broken which may cause the molecule to dissociate into smaller molecules or possibly cause the molecule to internally rearrange its bonds as shown by the elementary processes

$$A + h\nu \rightarrow B + C$$

or

$$A + h\nu \rightarrow H$$

where species B and C are the products of the disintegration of species A, and H is a resulting product caused by the rearrangement of species A upon absorption of a quantum of electromagnetic energy. If an excited molecule collides with another atom/molecule under the right conditions, a new bond may form creating a new molecule as shown by the elementary process

$$A^* + D \rightarrow F$$

where D represent a reactant species that collides and reacts with the excited species A* to produce the product species F. At other times, the excited electrons may revert back to a lower energy level or even the original energy level through a release of electromagnetic radiation as shown by the elementary process

$$A^* \rightarrow A + h\nu$$

The other common method in which a reaction can occur is when a transfer of energy occurs when an atom or molecule collides with another atom, molecule or even the wall of a container. For example, an atom or molecule with a certain amount of kinetic and potential energy collides with a wall of a container that is at a higher temperature than that of the atom or molecule. The atom/molecule absorbs some of this thermal energy resulting in an increase in its kinetic energy, which causes it to increase its velocity, or, in the case of a molecule, may absorb enough energy to disrupt bonds within the molecule. A similar process can occur when there is a collision between atoms/molecules where there may be a transfer of energy. In such cases where the atoms/molecules collide and bounce off one another, one atom/molecule may increase its kinetic or potential energy at the cost of energy of the other atom/molecule. Such processes can be represented by

$$A + W \rightarrow A^* + W$$

where W represents either a molecule or the wall of a container in which chemical species A has collided creating a higher energy, activated species A*. It should be noted that W in such cases has lost some of its energy upon such collisions. The higher energy atom/molecule may then go on to collide with other atoms/molecules. If there is sufficient energy between the colliding molecules/atoms and other conditions, such as intermolecular orientation, are right, intermolecular interactions may be sufficient to cause the colliding entities to "stick" together creating an intermediate species as indicated by the elementary process

$$A^* + B \rightarrow [A - -B]^* \rightarrow AB^*$$

where [A– –B]* and AB* represent intermediate or transition state species. During this process, either a transfer of energy can occur before the entities

separate creating an excited species, certain electrons of the two entities can form a bond creating a new chemical species, or the transition state entity can break apart to form a new chemical species as shown by the elementary processes

$$AB^* \rightarrow A + B^*$$

or

$$AB^* \rightarrow C$$

or

$$AB^* \rightarrow D + F$$

Thus, when a chemical reaction does occur, it may occur via a mechanism in a single reaction step, known as an elementary process, or by a series of two or more elementary processes which, when totaled, will give the net chemical reaction. For example,

Rxn 1 $A^* + B \rightarrow AB^*$

Rxn 2 $AB^* \rightarrow D + F^*$

Rxn 3 $F^* \rightarrow 2G$

which when summed together gives

$$A^* + B + AB^* + F^* \rightarrow AB^* + D + F^*2G$$

However, because the transition state AB* and the activated molecule F* appear in both reactant and product sides of the reaction in the same stoichiometric quantities, they can be treated as intermediates and removed from the reaction to give the net reaction

$$A^* + B \rightarrow D + 2G$$

Reaction rate

The rate of a reaction is the velocity with which a reactant or reactants undergoes a chemical change. Experimentally, the rate of a reaction must be determined by directly or indirectly following the change in the concentration of the reactants or products as a function of time. When there is more than one reactant, such changes need to be normalized according to the stoichiometry of the reaction. For a reaction of the type

$$aA + bB + \ldots \rightarrow cC + dD + \ldots$$

where the uppercase letters represent chemical species and the lowercase letters represent stoichiometric coefficients, the rate in which reactants go to products can be determined by following the rate of the disappearance of the reactants as a function of time.

$$\text{Rate} = -\frac{\mathrm{d}[A]}{a\mathrm{d}t} = -\frac{\mathrm{d}[B]}{b\mathrm{d}t} \tag{7.100}$$

The brackets denote concentration (usually molar concentration unless otherwise indicated) and d represents the derivative function. The negative sign signifies that the concentration of the reactants is decreasing, as the rate must always be positive as long as the reaction is progressing from reactants to products.

The rate at which a reaction proceeds for the reaction type shown above also can be determined by following the appearance of the products as a function of time.

$$\text{Rate} = +\frac{\mathrm{d}[C]}{c\mathrm{d}t} = +\frac{\mathrm{d}[D]}{d\mathrm{d}t} \tag{7.101}$$

where the positive signs indicate that the concentrations of the products are increasing. Note that these two expressions for rate are only for the type of reaction where the reactants go irreversibly to products, without going through any intermediates.

If $[A]_0$, $[B]_0$, $[C]_0$, and $[D]_0$ represent the initial concentration (i.e., $t = 0$) of each of the reactants and products, at some time t (i.e., $t = t$), the concentration of A decreases by aX (i.e., $[A]_t = [A]_0 - aX$) and the concentration of B decreases by bX (i.e., $[B]_t = [B]_0 - bX$). Similarly, the concentrations of the products C and D increase by cX and dX, respectively (i.e., $[C]_t = [C]_0 + cX$ and $[D]_t = [D]_0 + dX$) after some time t. Thus, upon normalization, the rate expressed in equations (7.101) and (7.102) can be shown to reduce to equation (7.103).

$$\text{Rate} = +\frac{\mathrm{d}X}{\mathrm{d}t} \tag{7.102}$$

The *law of mass action* relates these experimentally determined rates to the concentration of all of the reacting species. This law states that, at a given temperature, the rate of the reaction is at each instant proportional to the product of the concentration of each of the reacting species raised to a power equal to the number of molecules of each of these species participating in the process. Accordingly, the law of

mass action applied to the above reaction gives the following rate equation:

$$\text{Rate} = k[A]^n[B]^m \tag{7.103}$$

where the proportionality constant k (referred to as the *specific rate constant* or as the *rate constant*) should be independent of the concentrations of all chemical species at a given temperature. The exponents, n and m, are known as the *order of the reaction* with respect to the components A and B, respectively; their sum represents the overall order of the reaction.

Equation (7.103) can be applied to each individual elementary process which makes up a reaction. In such cases, the exponents of each of the reacting species are equal to their stoichiometric coefficients for the balanced equation representing the processes. These exponents indicate the number of molecules/atoms of each reacting species that participate in a simultaneous collision to form the reactants with the rate of the process controlled by the specific rate constant, k, during that specific elementary process. It is interesting to note that statistically, collisions involving more than two bodies are extremely rare and collisions involving more than three bodies are nearly impossible; the specific rate constants for these rare processes will be very small and the reactions very slow.

It is important to note that for a *net chemical reaction*, which is the sum of all of the elementary processes, there is no requirement that the order of the reaction with respect to a chemical species be identical to its stoichiometric coefficient indicated in the net chemical equation. This is because chemical species that appeared as both reactants and products in the various elementary processes have been removed to create a balanced net equation. Further, it may be necessary for some elementary processes to occur more than once in order to arrive at net balanced equation. Additionally, some elementary processes may be reversible (i.e., products revert to reactants) during an overall chemical reaction. Therefore, unlike for elementary processes in which the species which enter into equation (7.103), can only be reactants, equation (7.103) for a net chemical reaction can include products as well as reactants. However, a proper rate equation for a net chemical equation should not contain any chemical species that exists as an intermediate during a chemical reaction.

It should be noted that unless the stoichiometric coefficient of the reactant or product that is being followed to determine the rate of the reaction is *unity* (one), the rate of the reaction is not equivalent to the change in the concentration of the chemical species with respect to time. For the case where there is only one chemical reactant, which has a stoichiometric coefficient that is greater than unity, authors of articles and textbooks on kinetics often base the reaction rate only on the disappearance of the reactant without accounting for the stoichiometry. When this occurs, the resulting rate constant will be greater than the true rate constant by a factor equal to the stoichiometric coefficient. Thus, care must be taken to determine how the rates of reactions were determined when comparing rate constants of a reaction.

Drug stabilization

Some drug decomposition reactions, such as photolytic and oxidative reactions, are relatively easy to avoid by protecting the components from light (photodecomposition) or exclusion of oxygen and by use of chain-terminating reagents or free-radical scavengers to minimize free-radical-mediated reactions. Solvolysis reactions, however, cannot be stopped by such procedures, but several techniques may be employed to retard reactions sufficiently to permit the formulation of a suitable drug product. The following approaches may be useful in attempts to retard solvolytic reactions.

Selection of optimum pH, buffer, and solvent

Consideration of the mechanism of the reaction and the way in which the reaction rate is influenced by pH, buffer species, and solvent permits the selection of the optimum conditions for drug stability. Often, however, ideal conditions for maximum stability may be unacceptable from the viewpoint of pharmaceutically acceptable formulation or therapeutic efficacy; thus, it may be necessary to prepare a formulation with conditions less than optimum for drug stability. If a suitable compromise between conditions for maximum stability and conditions for a pharmaceutically acceptable formulation cannot be achieved,

techniques, such as those described below, may be useful in retarding solvolysis reactions.

Specific complexing agents

The technique of stabilization by forming complexes in solution was introduced by Higuchi and Lachman[9] who demonstrated that the rate of hydrolysis of the ester function of benzocaine was retarded significantly in the presence of caffeine, a reagent with which the benzocaine formed a soluble complex. It was demonstrated further that, in these systems, the complexed drug did not hydrolyze at all and that the observed rate of hydrolysis could be ascribed to the concentration of the free or uncomplexed drug that was in equilibrium with the drug complex.

There are many recognized examples in which drug stabilization occurs by disrupting the kinetic mechanisms of degradation. Boric acid chelation of the catechol function of epinephrine stabilizes epinephrine against attack by bisulfite and sulfite. The complex of povidone (polyvinylpyrrolidone) and iodine was used for many years as a topical antiseptic because of its higher iodine concentration, slow release of iodine from the complex, lower toxicity, and its ability to stabilize and protect the iodine from degradation before application.

Surfactants

It has been demonstrated that the incorporation of benzocaine into surfactant micelles could retard significantly the rate of ester hydrolysis. Nonionic and anionic surfactants retarded the hydroxide-ion-catalyzed hydrolysis, but cationic surfactants somewhat increased the rate of hydroxide-ion-catalyzed hydrolysis. Similar observations have been reported for a number of drugs that are sufficiently lipophilic to be solubilized by surfactant micelles.

Suspensions

If the solubility of a labile drug is reduced and the drug is prepared in a suspension form, the rate at which the drug degrades will be related only to the concentration of dissolved drug rather than to the total concentration of drug in the product. Thus it has been demonstrated that penicillin G procaine suspensions degraded at a rate proportional to the low concentration of penicillin in solution. Because the penicillin in solution was in equilibrium with excess solid penicillin G procaine, the penicillin concentration in solution was constant and the observed order of reaction was apparently zero order.

Refrigeration

Storage below room temperature usually will retard solvolytic reactions. Storage in the frozen state generally is an effective means of retarding degradative reactions. Several antibiotics are sold as frozen solutions in flexible plastic bags. An exception is sodium ampicillin dissolved in 5% dextrose solution, which showed approximately 10% decomposition after 4 h of storage at 5°C and more than 13% loss after storage for the same period in the frozen state at −20°C.

Stability testing of pharmaceutical products

If a product is to be marketed, it must be stable over relatively long storage times at room temperature or at the actual temperature at which it will be shipped and stored prior to its ultimate use. Thus, the rate of degradation may have to be studied over an undesirably long period of time in order to determine the product's stability under normal storage conditions.

To avoid this undesirable delay in evaluating possible formulations, the manufacturer attempts to predict stability under conditions of room temperature or actual storage conditions by using data for the rate of decomposition obtained at several elevated temperatures. This is accomplished using an Arrhenius plot to predict, from high-temperature data, the rate of product breakdown to be expected at actual lower temperature storage conditions.

Prediction based on data obtained at elevated temperatures generally is satisfactory for solution dosage forms. Success is more uncertain when nonhomogeneous products are involved. Suspensions of drugs may not provide linear Arrhenius plots because often there is the possibility that the solid phase, which exists at elevated temperature, may not be the same solid phase that exists at room temperature. Such differences in the solubility of the several

solid phases may invalidate the usual Arrhenius plots due to a change in mechanism as the phase changes with increase in temperature. These difficulties should be anticipated when polymorphic crystal forms or several different solvates are known to exist for a specific solute. Also, when solid dosage forms (e.g., tablets) are subjected to high temperatures, changes in the quantity of moisture in the product may greatly influence the stability of the product.

Arrhenius plots also suffer limitations when applied to reactions that have relatively low activation energies and, therefore, are not accelerated greatly by an increase in temperature. Where usually it is desirable to determine drug stability by analyzing samples for the amount of intact drug remaining (in instances where there is very little drug decomposition and particularly when it is not convenient to accelerate the reaction by increasing temperature) it sometimes is advantageous to determine initial reaction rates from the determination of the amount of reaction product formed.

Using modern methods of analysis, such as high-performance liquid chromatography (HPLC), it is often possible to measure the rate of formation of a degradation product. By using this technique, very small amounts of degradation (less than 1% loss of parent compound) can be detected, resulting in a more sensitive indication of product stability than can be obtained by analyzing potency.

Because manufacturers are interested primarily in the time required to produce just a few-percent breakdown in their product, it is not uncommon to employ terminology such as $t_{0.90}$ or $t_{0.95}$, which is the time required for the drug to decompose to 90 or 95%, respectively, of original potency.

An Arrhenius-type plot, analogous to that illustrated in Fig. 7.22 can be obtained by plotting the natural logarithm of the specific rate constants versus the reciprocal of absolute temperature. The rate constant at the temperature of interest can be determined and applied to the appropriate kinetic model to determine the time required for the product to decrease in potency to 90% of original potency.

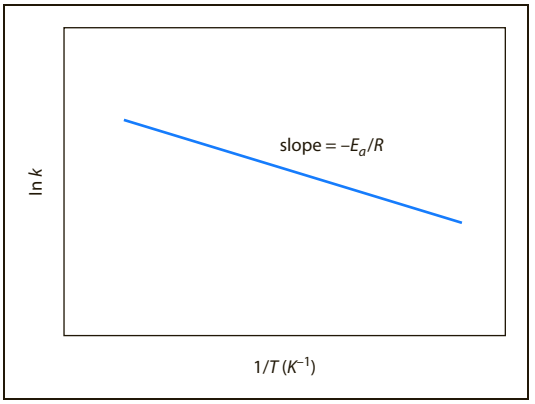


Figure 7.22 Variation of the rate constant with reciprocal absolute temperature, illustrating the Arrhenius equation.

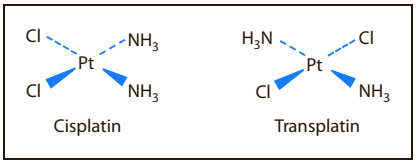


Figure 7.23 A **coordination complex** is called a *chelate* if the same substrate (metal ion) binds with two or more sites on a ligand.

Complex formation

In chemistry and chemical processes the word *complex* usually refers to molecules or molecular assemblies formed by combination of *substrates*, *S*, and *ligands*, *L*. Most often, complex (S_mL_n) formation is a reversible process:

$$mS + nL \rightleftharpoons S_mL_n \tag{7.104}$$

where *m* substrate molecules, associate with *n* ligand molecules to form a complex of *m*:*n* stoichiometry. In this context, *complex formation*, *complexation*, *binding*, *association*, and *chelation* are often synonymous. The substrate and ligand are kept together by relatively strong coordinate covalent bonds or by weak non-covalent forces such as hydrogen bonding, van der Waals forces, electrostatic interactions, dipole forces, charge transfer, release of conformational strain, or hydrophobic interactions. The complex formation changes the physicochemical properties of its constituents, both of the substrate and the ligand, including their aqueous solubility, molar absorptivity, NMR chemical shifts, adsorption to solid surfaces, partitioning behavior, conductivity, chemical reactivity and/or pK_a values. By studying such properties, for example of the substrate as a function of the

ligand concentration, the complex can be identified and quantitatively described. Furthermore, the methods of chemical kinetics and thermodynamics can be applied to describe the formation and dissociation of a complex. Although most frequently substrate and ligand molecules are associated by weak chemical forces, there are complexes where bonds are quite strong and formation of some metal complexes are virtually irreversible. Complexes are usually broadly classified into two groups based on type of S–L bonding involved, namely *coordination complexes* and *molecular complexes*.

Coordination complexes consist of ionic substrates, most frequently transition metal ions, with bases or, in other words, products of Lewis acid–base reactions where the metal ion (an acid) accepts a pair of electrons from the ligand (the base) to form a coordinate covalent bond. Examples of such complexes are $[Ag(NH_3)_2]^+$, $[Co(NH_3)_6]^{3+}$ and $[Fe(CN)_6]^{4-}$. Other common types of coordination complexes are organometallic complexes that are complexes formed between organic groups and metal atoms such as vitamin B12 (a porphyrin containing a cobalt atom), and cluster complexes where the central metal ion consists of a three-dimensional cell of several directly bonded metal ions such as triruthenium dodecacarbonyl ($Ru_3(CO)_{12}$).

Molecular complexes consist of non-covalently bound substrates and ligands. These include complexes of relatively small substrates and ligands such as drug–cyclodextrin complexes, complexes between small substrates and a large ligand such as drug–protein complexes (e.g., plasma protein binding) and complexes between large substrates and a small ligand such as some protein–polyalcohol complexes. Molecular complexes also include molecular dimers, ion-pairs, intramolecular interactions (such as base–base interactions in the DNA helix) and clathrate compounds (cage compounds) where a cage-like lattice of one type of molecules (e.g., hydroquinone molecule) entraps a second type of molecules (e.g., methanol molecule). Pharmaceutical co-crystals can also be considered a type of molecular complex with components subjected to hydrogen bonding and other forces in the crystal lattice. Examples of these types of molecular complexes include isoniazid and 4-aminosalicylic acid where the carboxylic acid function can be shown to interact with the pyridine nitrogen.

Interfacial phenomena

Very often it is desirable or necessary in the development of pharmaceutical dosage forms to produce multiphasic dispersions by mixing together two or more ingredients that are not mutually miscible and capable of forming homogeneous solutions. Examples of such dispersions include

- Suspensions (solid in liquid)
- Emulsions (liquid in liquid)
- Foams (vapor in liquids).

Because these systems are not homogeneous and thermodynamically stable, over time they will show some tendency to separate on standing. By doing so, this produces the minimum possible surface area of contact between phases. Thus, suspended particles agglomerate and sediment, emulsified droplets cream and coalesce, and the bubbles dispersed in foams collapse to produce unstable and nonuniform dosage forms. One way to prevent or slow down this natural tendency for further phase separation is to add materials that can accumulate at the interface to provide some type of energy barrier to aggregation and coalescence. Such materials are said to exhibit *surface activity* or to act as *surface-active agents*.

Colloidal dispersions

The British chemist Thomas Graham applied the term "colloid" (derived from the Greek word for glue) about 1850 to polypeptides such as albumin and gelatin, to polysaccharides such as acacia, starch, and dextrin, and to inorganic compounds such as gelatinous metal hydroxides and Prussian blue (ferric ferrocyanide). Contemporary colloid and surface chemistry deals with an unusually wide variety of industrial and biological systems.

Within the field of pharmacy, the colloidal systems we commonly come across include some protein and polymer solutions, micellar systems, liquid crystals and emulsions, suspensions, aerosols, foams and other drug delivery systems that fall within the colloidal size

range. In some instances, what was formally referred to as colloidal systems have been replaced by the term nanotechnology (structures that have one or more dimension between approximately 1 and 100 nm).

Colloidal systems and interfaces

Except for high-molecular-weight polymers, most soluble substances can be prepared as either low-molecular-weight solutions, colloidal dispersions, or coarse suspensions, depending upon the choice of dispersion medium and dispersion technique. Colloidal dispersions consist of at least two phases: one or more dispersed or internal phases, and a continuous or external phase called the *dispersion medium* or *vehicle*. Colloidal dispersions are distinguished from solutions and coarse dispersions by the particle size of the dispersed phase, not its composition. Whilst somewhat arbitrary, colloidal dispersions can be characterized as containing particles in the size range of between approximately 1 nm and 1 μm; however, a smaller size range of up to 500 nm is also quoted. Thus, blood, cell membranes, micelles, thinner nerve fibers, milk, rubber latex, fog, and beer foam are colloidal systems. Some materials, such as emulsions and suspensions of most organic drugs, are coarser than true colloidal systems but exhibit similar behavior. Even though serum albumin, acacia, and povidone form true or molecular solutions in water, the size of the individual solute molecules places such solutions in the colloidal range (particle size >1 nm).

In general, there are several features that distinguish colloidal dispersions from coarse suspensions and emulsions. Colloidal particles are usually too small for visibility in a light microscope, because at least one of their dimensions measures 1 µm or less. They are, however, often visible in an ultramicroscope, and almost always in an electron microscope. Conversely, coarse suspended particles are usually visible to the naked eye and always in a light microscope. In addition, colloidal particles, as opposed to coarse particles, pass through ordinary filter paper but are retained by dialysis or ultrafiltration membranes. Also, unlike coarse particles, colloidal particles diffuse very slowly and undergo little or no sedimentation or creaming. Brownian motion maintains the dispersion of the colloidal internal phases.

An appreciable fraction of atoms, ions, or molecules of colloidal particles are located in the boundary layer between the particle and the dispersion medium. The boundary layer between a particle and air is commonly referred to as a *surface*, whereas the boundary layer between a particle and a liquid or solid is commonly referred to as an *interface*. The ions or molecules within the particle and within the medium are surrounded on all sides by similar ions or molecules and have balanced force fields; however, the ions or molecules at surfaces or interfaces are subjected to unbalanced forces of attraction. Consequently, a surface free-energy component is added to the total free energy of colloidal particles and becomes important as the particles become smaller and a greater fraction of their atoms, ions, or molecules are located in the surface or interfacial region. As a result, the solubility of very fine solid particles and the vapor pressure of very small liquid droplets are greater than the corresponding values for coarse particles and drops of the same materials.

Coarse dispersions

For the purpose of the present discussion, a dispersed system, or dispersion, will be regarded as a two-phase system in which one phase is distributed as particles or droplets in the second, or continuous, phase. In these systems, the dispersed phase frequently is referred to as the discontinuous or internal phase, and the continuous phase is called the external phase or dispersion medium. Discussion will be restricted to those solid–liquid and liquid–liquid dispersions that are of pharmaceutical significance, namely, suspensions and emulsions. However, more complicated phase systems (e.g., a combination of liquid and liquid crystalline phases) can exist in emulsions.

All dispersions may be classified into three groups based of the size of the dispersed particles. One such group, colloidal dispersions, is where the size of the dispersed particles is in the range of approximately 1 nm to 0.5 µm. Molecular dispersions are the second group in this classification. The third group, consisting of *coarse dispersions* in which the particle size exceeds 0.5 µm, is the subject of this discussion. Knowledge of coarse dispersions is essential for the preparation

of both pharmaceutical suspensions (solid–liquid dispersions) and emulsions (liquid–liquid dispersions).

Table 7.5 contains examples of pharmaceutical suspensions and emulsions. Pharmaceutical course dispersions are administered via several routes of administration and include many different types of active ingredients.

The dispersion step

The pharmaceutical formulator is concerned primarily with producing a smooth, uniform, easily flowing (pouring or spreading) suspension or emulsion in which dispersion of particles can be effected with minimum expenditure of energy.

In preparing suspensions, particle–particle attractive forces need to be overcome by the high shearing action of such devices as the colloid mill, or by use of surface-active agents. The latter greatly facilitate wetting of lyophobic powders and assist in the removal of surface air that shearing alone may not remove; thus, the clumping tendency of the particles is reduced. Moreover, lowering of the surface free energy by the

Table 7.5 Examples of pharmaceutical/cosmetic suspension and emulsion products

Suspensions		**Emulsions**	
Name	**Route of administration**	**Name**	**Route of administration**
Milk of Magnesia® (magnesium hydroxide)	Oral	Mineral Oil	Oral
Nystatin Oral Suspension, USP	Oral	Restasis® (cyclosporine ophthalmic emulsion)	Eye
Cortisporin® Ophthalmic and Otic suspensions (neomycin/ polymyxin, bacitracin, hydrocortisone)	Ear, eye	Intralipid®,Liposyn® (intravenous fat emulsion)	Intravenous
Ibuprofen oral suspension, USP	Oral	Lipomul®	Oral
Tobradex® (tobramycin, dexamethasone)	Eye	Simethicone Emulsion, USP	Oral,-manufacturing aid
Tussionex® (chlorpheniramine/hydrocodone sustained release)	Oral	Propofol Injectable Emulsion, USP	Intravenous
Prednisolone Acetate Ophthalmic Suspension, USP	Eye	Lubriderm® (emollient)	Topical
NPH Insulin	Subcutaneous	Lidocaine/Prilocaine cream (EMLA®)	Topical
Sterile Procaine Penicillin G Injectable Suspension, USP	Intramuscular	Diazemuls® (diazepam)	Intravenous
Griseofulvin Oral Suspension, USP	Oral		
Phenytoin Oral Suspension, USP	Oral		
Sulfamethoxazole/Trimethoprim Oral Suspension	Oral		

adsorption of these agents directly reduces the thermodynamic driving force opposing dispersion of the particles.

In emulsification, shear rates are frequently necessary for dispersion of the internal phase into fine droplets. The shear forces are opposed by forces operating to resist distortion and subsequent breakup of the droplets. Again surface-active agents help greatly by lowering interfacial tension, which is the primary reversible component resisting droplet distortion. Surface-active agents also may play an important role in determining whether an oil-in-water (O/W) or a water-in-oil (W/O) emulsion preferentially survives the shearing action.

Once the process of dispersion begins there develops simultaneously a tendency for the system to revert to an energetically more stable state, manifested by flocculation, coalescence, sedimentation, crystal growth, and caking phenomena. If these physical changes are not inhibited or controlled, successful dispersions will not be achieved or will be lost during shelf-life.

Interfacial properties

Because suspensions and emulsions are dispersions of one phase within another, the process of dispersion creates a tremendous increase in interfacial area between the dispersed particles or droplets and the dispersion medium. When considering the interfacial properties of dispersed particles, two factors must be taken into account, regardless of whether the dispersed phase is solid or liquid. The first relates to an increase in the free energy of the surface as the particle size is reduced and the specific surface increased. The second deals with the presence of an electrical charge on the surface of the dispersed particles.

Surface free energy

When solid and liquid materials are reduced in size, they tend to agglomerate or stick together. This clumping, which can occur either in an air or liquid medium, is an attempt by the particles to reduce the excess free energy of the system. The increase in surface free energy is related to the increase in surface area produced when the mean particle size is reduced. It may be expressed as

$$\Delta F = \gamma \Delta A \qquad (7.105)$$

where ΔF is the increase in surface free energy in ergs, ΔA is the increase in surface area in cm^2, and γ is the interfacial tension in dyn cm^{-1}, between the dispersed particle or droplet and the dispersion medium. The smaller ΔF is, the more thermodynamically stable is the suspension of particles. A reduction in ΔF is effected often by the addition of a wetting agent which is adsorbed at the interface between the particle and the vehicle, thereby reducing the interfacial tension. This causes the particles to remain dispersed and settle relatively slowly. Unfortunately, in solid–liquid suspensions, the particles can form a hard cake at the bottom of the container when they eventually settle. Such a sediment, which can be extremely difficult to redisperse, can lead to dosing errors when the product is administered to the patient.

Surface potential

Both attractive and repulsive forces exist between particles in a liquid medium. The balance between these opposing forces determines whether two particles approaching each other actually make contact or are repulsed at a certain distance of separation. Although much of the theoretical work on electrical surface potentials has been carried out on lyophobic colloids, the theories developed in this area have been applied to suspensions and emulsions.

Suspensions

A *pharmaceutical suspension* may be defined as a coarse dispersion containing finely divided insoluble material suspended in a liquid medium. Because some products occasionally are prepared in a dry form to be placed in suspension at the time of dispensing by the addition of an appropriate liquid vehicle, this definition is extended to include these products.

Suspension dosage forms are given by the oral route, injected intramuscularly or subcutaneously, instilled intranasally, inhaled into the lungs, applied to the skin as topical preparations, or used for ophthalmic or otic purposes in the eye or ear, respectively. They are an important class of dosage form which can offer several advantages. Suspensions offer an alternative oral dosage form for patients who cannot swallow a tablet or capsule such as pediatric and geriatric patients. Oral antibiotics, analgesic and antipyretic drugs are commonly administered as suspensions to

these groups of patients. Suspensions are often used to deliver poorly water-soluble drugs which cannot be formulated as aqueous solutions. In early drug development studies of potentially new drug candidates, suspension dosage forms are frequently used to deliver drugs to animals, particularly when the drug is given orally. In addition, drugs that have an unpleasant taste may preferably be formulated as a suspension to reduce interaction of drug with taste receptors in the mouth. Because suspended drug must undergo a dissolution step prior to crossing biological membranes, suspensions offer a way to provide sustained release of drug by parenteral, topical, and oral routes of administration.

There are certain criteria that a well-formulated suspension should meet. The dispersed particles should be of such a size that they do not settle rapidly in the container. However, in the event that sedimentation does occur, the sediment must not form a hard cake. Rather, it should be capable of redispersion with a minimum of effort on the part of the patient. Finally, the product should be easy to pour, have a pleasant taste, and be resistant to microbial attack.

The three major concerns associated with suspensions are:

1. Ensuring adequate dispersion of the particles in the vehicle
2. Minimizing settling of the dispersed particles
3. Preventing caking of these particles when a sediment forms.

Much of the following discussion will deal with the factors that influence these processes and the ways in which settling and caking can be minimized.

Flocculation and deflocculation

Zeta potential, ζ, is a measurable indication of the potential existing at the surface of a particle. When ζ is relatively high (25 mV or more), the repulsive forces between two particles exceed the attractive London forces. Accordingly, the particles are dispersed and are said to be *deflocculated*. Even when brought close together by random motion or agitation, deflocculated particles resist collision due to their high surface potential.

The addition of a preferentially adsorbed ion whose charge is opposite in sign to that on the particle leads to a progressive lowering of ζ. At some concentration of the added ion, the electrical forces of repulsion are lowered sufficiently and the forces of attraction predominate. Under these conditions the particles may approach each other more closely and form loose aggregates, termed *flocs*. Such a system is said to be *flocculated*.

Some workers restrict the term "flocculation" to the aggregation brought about by chemical bridging; aggregation involving a reduction of repulsive potential at the double layer is referred to as *coagulation*. Other workers regard flocculation as aggregation in the secondary minimum of the potential energy curve of two interacting particles and coagulation as aggregation in the primary minimum. In the present chapter the term *flocculation* is used for all aggregation processes, irrespective of mechanism.

The continued addition of the flocculating agent can reverse the above process, if the zeta potential increases sufficiently in the opposite direction. Thus, the adsorption of anions onto positively charged, deflocculated particles in suspension will lead to flocculation. The addition of more anions eventually can generate a net negative charge on the particles. When this has achieved the required magnitude, deflocculation may occur again. The only difference from the starting system is that the net charge on the particles in their deflocculated state is negative rather than positive. Some of the major differences between suspensions of flocculated and deflocculated particles are presented in Table 7.6.

Flocculation kinetics

The rate at which flocculation occurs is a consideration in the stability of suspended dispersions. Whether flocculation is judged to be rapid or slow depends on the presence of a repulsive barrier between adjacent particles. In the absence of such a barrier, and for a monodispersed system, rapid flocculation occurs at a rate given by the Smoluchowski equation.

$$\delta N/\delta \mathrm{t} = -4\,\pi DRN^2 \tag{7.106}$$

where $\delta N/\delta t$ is the disappearance rate of particles per mL, R is the distance between the centers of the two particles in contact, N is the number of particles per mL, and D is the diffusion coefficient. Under these

Table 7.6 Relative properties of flocculated and deflocculated particles in suspension

Deflocculated	Flocculated
1. Particles exist in suspension as separate entities.	1. Particles form loose aggregates.
2. Rate of sedimentation is slow, as each particle settles separately and particle size is minimal.	2. Rate of sedimentation is high, as particles settle as a floc, which is a collection of particles.
3. A sediment is formed slowly.	3. A sediment is formed rapidly.
4. The sediment eventually becomes very closely packed, due to weight of upper layers of sedimenting material. Repulsive forces between particles are overcome and a hard cake is formed that is difficult, if not impossible, to redisperse.	4. The sediment is packed loosely and possesses a scaffold-like structure. Particles do not bond tightly to each other and a hard, dense cake does not form. The sediment is easy to redisperse, so as to reform the original suspension.
5. The suspension has a pleasing appearance, as the suspended material remains suspended for a relatively long time. The supernate also remains cloudy, even when settling is apparent.	5. The suspension is somewhat unsightly, due to rapid sedimentation and the presence of an obvious, clear supernatant region. This can be minimized if the volume of sediment is made large. Ideally, volume of sediment should encompass the volume of the suspension.

conditions the rate is proportional to the square of the particle concentration. The presence or absence of an energy barrier is influenced strongly by the type and concentration of any electrolyte present. When an energy barrier does exist between adjacent particles, the flocculation rate likely will be much smaller than predicted by equation (7.106).

Emulsions

An *emulsion* is a dispersed system containing at least two immiscible liquid phases. The majority of conventional emulsions in pharmaceutical use have dispersed particles ranging in diameter from 0.1 to 100 µm. As with suspensions, emulsions are thermodynamically unstable as a result of the excess free energy associated with the surface of the droplets. The dispersed droplets, therefore, strive to come together and reduce the surface area. In addition to this flocculation effect, also observed with suspensions, the dispersed particles can coalesce, or fuse, and this can result in the eventual destruction of the emulsion. To minimize this effect, a third component, the *emulsifying agent*, is added to the system to improve its stability. The choice of emulsifying agent is critical to the preparation of an emulsion possessing optimum stability. The efficiency of present-day emulsifiers permits the preparation of emulsions that are stable for many months and even years, even though they are thermodynamically unstable.

In recent years, it has been recognized that complex multiple-phase combinations can exist in emulsions. Thus, liquid crystalline phases and gel structures can form from the combination of the basic three-component mixture of water, oil, and surfactant (emulsifying agent). Often, these structures confer significant stability to the emulsion and therefore are to be desired. Such multiple-phase emulsions and their stability have been reviewed by Eccleston.[41]

Emulsions are widely used in pharmacy and medicine, and emulsified materials can possess advantages not observed in formulations in other dosage forms. For example, certain medicinal agents that have an objectionable taste have been made more palatable for oral administration when formulated in an emulsion. The principles of emulsification have been applied extensively in the formulation of dermatological creams and lotions. Intravenous emulsions of contrast media have been developed to assist the physician in undertaking X-ray examinations of the body organs while exposing the patient to the minimum of radiation. Considerable attention has been directed towards the use of sterile, stable intravenous emulsions containing fat, carbohydrate, and vitamins all in one preparation. Such products are administered to patients unable to assimilate these

vital materials by the normal oral route. Emulsions are also used to deliver nutrients via the enteral route in the form of nutritional supplements. More recently, emulsions have been used to deliver poorly water-soluble drugs, such as general anesthetics and anti-cancer compounds, via the intravenous route.

Emulsions offer potential in the design of systems capable of giving controlled rates of drug release and affording protection to drugs susceptible to oxidation or hydrolysis. There is still a need for well-characterized dermatologic products with reproducible properties, regardless of whether these products are antibacterial, sustained-release, protective, or emollient lotions, creams, or ointments. In addition, emulsions may provide a useful way to deliver poorly water-soluble drugs via enteral and parenteral routes. The principle of emulsification is also involved in an increasing number of aerosol products.

The pharmacist must be familiar with the types of emulsions and the properties and theories underlying their preparation and stability.

Rheology

Rheology is the branch of physics that deals with deformation, including flow, of matter. Although this definition was proposed in 1929, the recognition of rheological phenomena dates back to antiquity.[44] The earliest application of rheology (ca. 1600 BC) is associated with the Egyptian Amenemhet, who made a 7° correction to the drainage angle of a water clock in order to account for the temperature-dependent variation in water flow during the course of a day. Archimedes's claim (ca. 250 BC) "Give me but one firm spot on which to stand, and I will move the earth." was based on the application of solid mechanics, the oldest branch of the physical sciences.[45]

Reiner[46] describes a simple mechanical experiment in which he lets three different materials – a pencil, a ball of plasticine, and a known mass of water – fall from some height onto the surface of a table. Newton's second law tells us that $F = ma$, where F is the force acting upon each of these materials of mass m, and a is the acceleration of the center of mass of each material. Since F is proportional to m, a is the same for each of these materials. Consequently, these three bodies fall toward the table in exactly the same manner. Their material differences do not become apparent until they reach the tabletop. At that point, the pencil rebounds somewhat, the plasticine stays put, and the water spreads over the tabletop and, on reaching the edge, flows off. These very different outcomes, which mechanics is unable to explain, are the focus of rheology.

The ubiquity of rheological phenomena in pharmacy is evident in the levigation or mixing of ointments on slabs, the use of a mortar and pestle to prepare suspensions and emulsions, the flow of emulsions through colloid mills and pumps, the use of roller mills for compacting powders or processing ointments, and the mechanical properties of glass or plastic containers and of rubber or polymeric closures. Squeezing ointments, creams, or toothpaste from a collapsible tube, spreading lotion on the skin, or spraying liquids from atomizers or aerosol cans all involve rheological phenomena. The fluidity of solutions to be injected by syringe or infused intravenously, the flexibility of tubing used in catheters, and the strength of sutures and ligatures are important rheological properties. Drug release from dosage forms and delivery systems is often controlled or modulated by the rheological properties of the formulation matrix. Diffusion, a process occurring at the molecular level, is governed, in part, by the rheological behavior of the molecule's environment. Rheological principles govern the circulation of blood and lymph through capillaries and large vessels, the flow of mucus, the transit of the luminal contents through the gastrointestinal tract, the bending of bones, the stretching of cartilage, and the contraction of muscles.

The centrality of rheological behavior to many unit operations in pharmaceutical manufacturing, to drug product functionality and stability, and to patient or consumer use of dosage forms and delivery systems necessitates a thorough understanding of rheology and the measurement of rheological behavior.

Appendix A: sodium chloride equivalents, freezing-point depressions, and hemolytic effects of certain medicinals in aqueous solution

	0.5 %		1 %		2 %		3 %		5 %		Iso-osmotic concentration[a]				
	E	*D*	*E*	*D*	*E*	*D*	*E*	*D*	*E*	*D*	%	*E*	*D*	H	pH
Acetrizoate methylglucamine	0.09		0.08		0.08		0.08		0.08	12.12	0.07			0	7.1
Acetrizoate sodium	0.10	0.027	0.10	0.055	0.10	0.109	0.10	0.163	0.10	0.273	9.64	0.09	0.52	0	6.9†
Acetylcysteine	0.20	0.055	0.20	0.113	0.20	0.227	0.20	0.341			4.58	0.20	0.52	100*	2.0
Adrenaline HCl											4.24			68	4.5
Alphaprodine HCl	0.19	0.053	0.19	0.105	0.18	0.212	0.18	0.315			4.98	0.18	0.52	100	5.3
Alum (potassium)			0.18				0.15		0.15		6.35		0.14	24*	3.4
Amantadine HCl	0.31	0.090	0.310	0.180	0.31	0.354					2.95	0.31	0.52	91	5.7
Aminoacetic acid	0.42	0.119	0.41	0.235	0.41	0.47					2.20	0.41	0.52	0*	6.2
Aminohippuric acid	0.13	0.035	0.13	0.075											
Aminophylline				0.098[c]											
Ammonium carbonate	0.70	0.202	0.70	0.405							1.29	0.70	0.52	97	7.7
Ammonium chloride			1.12								0.8	1.12	0.52	93	5.0
Ammonium lactate	0.33	0.093	0.33	0.185	0.33	0.37					2.76	0.33	0.52	98	5.9
Ammonium nitrate	0.69	0.200	0.69	0.400							1.30	0.69	0.52	91	5.3
Ammonium phosphate, dibasic	0.58	0.165	0.55	0.315							1.76	0.51	0.52	0	7.9

(continued overleaf)

	0.5 %		1 %		2 %		3 %		5 %		Iso-osmotic concentration[a]				
	E	*D*	*E*	*D*	*E*	*D*	*E*	*D*	*E*	*D*	%	*E*	*D*	H	pH
Ammonium sulfate	0.55	0.158	0.55	0.315							1.68	0.54	0.52	0	5.3
Amobarbital sodium			0.25	0.143[c]			0.25				3.6	0.25	0.52	0	9.3
d-Amphetamine HCl											2.64			98	5.7
Amphetamine phosphate			0.34	0.20			0.27	0.47			3.47	0.26	0.52	0	4.5
Amphetamine sulfate			0.22	0.129[c]			0.21	0.36			4.23	0.21	0.52	0	5.9
Amprotropine phosphate											5.90			0	4.2
Amylcaine HCl			0.22				0.19				4.98	0.18		100	5.6
Anileridine HCl	0.19	0.052	0.19	0.104	0.19	0.212	0.18	0.316	0.18	0.509	5.13	0.18	0.52	12	2.6
Antazoline phosphate											6.05			90	4.0
Antimony potassium tartrate			0.18				0.13		0.10						
Antipyrine			0.17	0.10			0.14	0.24	0.14	0.40	6.81	0.13	0.52	100	6.1
Apomorphine HCl			0.14	0.080[c]											
Arginine glutamate	0.17	0.048	0.17	0.097	0.17	0.195	0.17	0.292	0.17	0.487	5.37	0.17	0.52	0	6.9
Ascorbic acid				0.105[c]							5.05	0.52[b]	100*	2.2	
Atropine methylbromide			0.14				0.13		0.13		7.03	0.13			
Atropine methylnitrate											6.52			0	5.2
Atropine sulfate			0.13	0.075			0.11	0.19	0.11	0.32	8.85	0.10	0.52	0	5.0
Bacitracin			0.05	0.03			0.04	0.07	0.04	0.12					

(continued overleaf)

	0.5 %		1 %		2 %		3 %		5 %		Iso-osmotic concentration[a]				
	E	*D*	*E*	*D*	*E*	*D*	*E*	*D*	*E*	*D*	%	*E*	*D*	H	pH
Barbital sodium			0.30	0.171[c]			0.29	0.50			3.12	0.29	0.52	0	9.8
Benzalkonium chloride			0.16				0.14		0.13						
Benztropine mesylate	0.26	0.073	0.21	0.115	0.15	0.170	0.12	0.203	0.09	0.242					
Benzyl alcohol			0.17	0.09[c]			0.15								
Bethanechol chloride	0.50	0.140	0.39	0.225	0.32	0.368	0.30	0.512			3.05	0.30		0	6.0
Bismuth potassium tartrate			0.09				0.06		0.05						
Bismuth sodium tartrate			0.13				0.12		0.11		8.91	0.10		0	6.1
Boric acid	0.50	0.288[c]									1.9	0.47	0.52	100	4.6
Brompheniramine maleate	0.10	0.026	0.09	0.05	0.08	0.084									
Bupivacaine HCl	0.17	0.048	0.17	0.096	0.17	0.193	0.17	0.29	0.17	0.484	5.38	0.17	0.52	83	6.8
Butabarbital sodium	0.27	0.078	0.27	0.155	0.27	0.313	0.27	0.47			3.33	0.27	0.52	0	6.8
Butacaine sulfate			0.20	0.12			0.13	0.23	0.10	0.29					
Caffeine and sodium benzoate			0.26	0.15			0.23	0.40			3.92	0.23	0.52	0	7.0
Caffeine and sodium salicylate			0.12	0.12			0.17	0.295	0.16	0.46	5.77	0.16	0.52	0	6.8
Calcium aminosalicylate											4.80			0	6.0
Calcium chloride			0.51	0.298[c]							1.70	0.53	0.52	0	5.6

(continued overleaf)

	0.5 %		1 %		2 %		3 %		5 %		Iso-osmotic concentration[a]				
	E	*D*	*E*	*D*	*E*	*D*	*E*	*D*	*E*	*D*	%	*E*	*D*	H	pH
Calcium chloride ($6H_2O$)			0.35	0.20							2.5	0.36	0.52	0	5.7
Calcium chloride, anhydrous			0.68	0.39							1.3	0.69	0.52	0	5.6
Calcium disodium edetate	0.21	0.061	0.21	0.120	0.21	0.240	0.20	0.357			4.50	0.20	0.52	0	6.1
Calcium gluconate			0.16	0.091[c]			0.14	0.24							
Calcium lactate			0.23	0.13			0.12	0.36			4.5	0.20	0.52	0	6.7
Calcium lactobionate	0.08	0.022	0.08	0.043	0.08	0.085	0.07	0.126	0.07	0.197					
Calcium levulinate			0.27	0.16			0.25	0.43			3.58			0	7.2
Calcium pantothenate			0.129								5.50			0	7.4
Camphor			0.12[d]												
Capreomycin sulfate	0.04	0.011	0.04	0.02	0.04	0.042	0.04	0.063	0.04	0.106					
Carbachol				0.205[c]							2.82			0	5.9
Carbenicillin sodium	0.20	0.059	0.20	0.118	0.20	0.236	0.20	0.355			4.40	0.20	0.52	0	6.6
Carboxymethylcellulose sodium	0.03	0.007	0.03	0.017	0.145										
Cephaloridine	0.09	0.023	0.07	0.041	0.06	0.074	0.06	0.106	0.05						
Chloramine-T											4.10			100*	9.1
Chloramphenicol				0.06[d]											

(continued overleaf)

	0.5 %		1 %		2 %		3 %		5 %		Iso-osmotic concentration[a]				
	E	*D*	*E*	*D*	*E*	*D*	*E*	*D*	*E*	*D*	%	*E*	*D*	*H*	pH
Chloramphenicol sodium succinate	0.14	0.038	0.14	0.078	0.14	0.154	0.13	0.230	0.13	0.382	6.83	0.13	0.52	partial	6.1
Chlordiazepoxide HCl	0.24	0.068	0.22	0.125	0.19	0.220	0.18	0.315	0.17	0.487	5.50	0.16	0.52	66	2.7
Chlorobutanol (hydrated)			0.24	0.14											
Chloroprocaine HCl	0.20	0.054	0.20	0.108	0.18	0.21									
Chloroquine phosphate	0.14	0.039	0.14	0.082	0.14	0.162	0.14	0.242	0.13	0.379	7.15	0.13	0.52	0	4.3
Chloroquine sulfate	0.10	0.028	0.09	0.050	0.08	0.090	0.07	0.127	0.07	0.195					
Chlorpheniramine maleate	0.17	0.048	0.15	0.085	0.14	0.165	0.13	0.22	0.09	0.265					
Chlortetracycline HCl	0.10	0.030	0.10	0.061	0.10	0.121									
Chlortetracycline sulfate			0.13	0.08			0.10	0.17							
Citric acid			0.18	0.10			0.17	0.295	0.16	0.46	5.52	0.16	0.52	100*	1.8
Clindamycin phosphate	0.08	0.022	0.08	0.046	0.08	0.095	0.08	0.144	0.08	0.242	10.73	0.08	0.52	58*	6.8
Cocaine HCl			0.16	0.090[c]			0.15	0.26	0.14	0.40	6.33	0.14	0.52	47	4.4
Codeine phosphate			0.14	0.080[c]			0.13	0.23	0.13	0.38	7.29	0.12	0.52	0	4.4
Colistimethate sodium	0.15	0.045	0.15	0.085	0.15	0.170	0.15	0.253	0.14	0.411	6.73	0.13	0.52	0	7.6
Cupric sulfate			0.18	0.100[c]			0.15		0.14		6.85	0.13		trace*	3.9
Cyclizine HCl	0.20	0.060													
Cyclophosphamide	0.10	0.031	0.10	0.061	0.10	0.125									

(continued overleaf)

	0.5 %		1 %		2 %		3 %		5 %		Iso-osmotic concentration[a]				
	E	*D*	*E*	*D*	*E*	*D*	*E*	*D*	*E*	*D*	%	*E*	*D*	H	pH
Cytarabine	0.11	0.034	0.11	0.066	0.11	0.134	0.11	0.198	0.11	0.317	8.92	0.10	0.52	0	8.0
Deferoxamine mesylate	0.09	0.023	0.09	0.047	0.09	-0.093	0.09	0.142	0.09	0.241					
Demecarium bromide	0.14	0.038	0.12	0.069	0.10	0.108	0.08	0.139	0.07	0.192					
Dexamethasone sodium phosphate	0.18	0.050	0.17	0.095	0.16	0.18	0.15	0.260	0.14	0.410	6.75	0.13	0.52	0	8.9
Dextroamphetamine HCl	0.34	0.097	0.34	0.196	0.34	0.392					2.64	0.34	0.52		
Dextroamphetamine phosphate			0.25	0.14			0.25	0.44			3.62	0.25	0.52	0	4.7
Dextroamphetamine sulfate	0.24	0.069	0.23	0.134	0.22	0.259	0.22	0.380			4.16	0.22	0.52	0	5.9
Dextrose			0.16	0.091[c]			0.16	0.28	0.16	0.46	5.51	0.16	0.52	0	5.9
Dextrose (anhydrous)			0.18	0.101[c]			0.18	0.31			5.05	0.18	0.52	0	6.0
Diatrizoate sodium	0.10	0.025	0.09	0.049	0.09	0.098	0.09	0.149	0.09	0.248	10.55	0.09	0.52	0	7.9
Dibucaine HCl				0.074[c]											
Dicloxacillin sodium (1 H_2O)	0.10	0.030	0.10	0.061	0.10	0.122	0.10	0.182							
Diethanolamine	0.31	0.089	0.31	0.177	0.31	0.358					2.90	0.31	0.52	100	11.3
Dihydrostreptomycin sulfate			0.06	0.03			0.05	0.09	0.05	0.14	19.4	0.05	0.52	0	6.1
Dimethpyrindene maleate	0.13	0.039	0.12	0.07	0.11	0.12									
Dimethyl sulfoxide	0.42	0.122	0.42	0.245	0.42	0.480					2.16	0.42	0.52	100	7.6

(continued overleaf)

	0.5 %		1 %		2 %		3 %		5 %		Iso-osmotic concentration[a]				
	E	*D*	*E*	*D*	*E*	*D*	*E*	*D*	*E*	*D*	%	*E*	*D*	H	pH
Diperodon HCl	0.15	0.045	0.14	0.079	0.13	0.141									
Diphenhydramine HCl				0.161[c]							5.70			88*	5.5
Diphenidol HCl	0.16	0.045	0.16	0.09	0.16	0.180									
Doxapram HCl	0.12	0.035	0.12	0.070	0.12	0.140	0.12	0.210							
Doxycycline hyclate	0.12	0.035	0.12	0.072	0.12	0.134	0.11	0.186	0.09	0.264					
Dyphylline	0.10	0.025	0.10	0.052	0.09	0.104	0.09	0.155	0.08	0.245					
Echothiophate iodide	0.16	0.045	0.16	0.090	0.16	0.179									
Edetate disodium	0.24	0.070	0.23	0.132	0.22	0.248	0.21	0.360			4.44	0.20	0.52	0	4.7
Edetate trisodium monohydrate	0.29	0.079	0.29	0.158	0.28	0.316	0.27	0.472			3.31	0.27	0.52	0	8.0
Emetine HCl				0.058[c]				0.17		0.29					
Ephedrine HCl			0.30	0.165[c]			0.28				3.2	0.28		96	5.9
Ephedrine sulfate			0.23	0.13			0.20	0.35			4.54	0.20	0.52	0	5.7
Epinephrine bitartrate			0.18	0.104			0.16	0.28	0.16	0.462	5.7	0.16	0.52	100*	3.4
Epinephrine hydrochloride			0.29	0.16[b]			0.26				3.47	0.26			
Ergonovine maleate				0.089[c]											
Erythromycin lactobionate	0.08	0.020	0.07	0.040	0.07	0.078	0.07	0.115	0.06	0.187					

(continued overleaf)

	0.5 %		1 %		2 %		3 %		5 %		Iso-osmotic concentration[a]				
	E	*D*	*E*	*D*	*E*	*D*	*E*	*D*	*E*	*D*	%	*E*	*D*	*H*	pH
Ethyl alcohol											1.39			100	6.0
Ethylenediamine				0.253[c]							2.08			100*	11.4
Ethylmorphine HCl			0.16	0.088[c]			0.15	0.26	0.15	0.43	6.18	0.15	0.52	38	4.7
Eucatropine HCl				0.11[d]											
Ferric ammonium citrate (green)											6.83			0	5.2
Floxuridine	0.14	0.040	0.13	0.076	0.13	0.147	0.12	0.213	0.12	0.335	8.47	0.12	0.52	3*	4.5
Fluorescein sodium			0.31	0.181[c]			0.27	0.47			3.34	0.27	0.52	0	8.7
Fluphenazine 2-HCl	0.14	0.041	0.14	0.082	0.12	0.145	0.09	0.155							
D-Fructose											5.05			0*	5.9
Furtrethonium iodide	0.24	0.070	0.24	0.133	0.22	0.250	0.21	0.360			4.44	0.20	0.52	0	5.4
Galactose											4.92			0	5.9
Gentamicin sulfate	0.05	0.015	0.05	0.030	0.05	0.060	0.05	0.093	0.05	0.153					
D-Glucuronic acid											5.02			48*	1.6
Glycerin			0.203[c]								2.6			100	5.9
Glycopyrrolate	0.15	0.042	0.15	0.084	0.15	0.166	0.14	0.242	0.13	0.381	7.22	0.12	0.52	92*	4.0
Gold sodium thiomalate	0.10	0.032	0.10	0.061	0.10	0.111	0.09	0.159	0.09	0.250					

(continued overleaf)

	0.5 %		1 %		2 %		3 %		5 %		Iso-osmotic concentration[a]				
	E	*D*	*E*	*D*	*E*	*D*	*E*	*D*	*E*	*D*	%	*E*	*D*	H	pH
Hetacillin potassium	0.17	0.048	0.17	0.095	0.17	0.190	0.17	0.284	0.17	0.474	5.50	0.17	0.52	0	6.3
Hexafluorenium bromide	0.12	0.033	0.11	0.065											
Hexamethonium tartrate	0.16	0.045	0.16	0.089	0.16	0.181	0.16	0.271	0.16	0.456	5.68	0.16	0.52		
Hexamethylene sodium acetaminosalicylate	0.18	0.049	0.18	0.099	0.17	0.199	0.17	0.297	0.16	0.485	5.48	0.16	0.52	0*	4.0
Hexobarbital sodium				0.15[c]											
Hexylcaine HCl											4.30			100	4.8
Histamine 2HCl	0.40	0.115	0.40	0.233	0.40	0.466					2.24	0.40	0.52	79*	3.7
Histamine phosphate				0.149[c]							4.10	0	4.6		
Histidine HCl											3.45			40	3.9
Holocaine HCl			0.20	0.12											
Homatropine hydrobromide			0.17	0.097[c]			0.16	0.28	0.16	0.46	5.67	0.16	0.52	92	5.0
Homatropine methylbromide			0.19	0.11			0.15	0.26	0.13	0.38					
4-Homosulfanilamide HCl											3.69			0	4.9
Hyaluronidase	0.01	0.004	0.01	0.007	0.01	0.013	0.01	0.02	0.01	0.033					
Hydromorphone HCl											6.39			64	5.6
Hydroxyamphetamine HBr				0.15[d]							3.71			92	5.0

(continued overleaf)

	0.5 %		1 %		2 %		3 %		5 %		Iso-osmotic concentration[a]				
	E	*D*	*E*	*D*	*E*	*D*	*E*	*D*	*E*	*D*	%	*E*	*D*	H	pH
8-Hydroxyquinoline sulfate											9.75			59*	2.5
Hydroxystilbamidine isethionate	0.20	0.06	0.16	0.090	0.12	0.137	0.10	0.17	0.07	0.216					
Hyoscyamine hydrobromide											6.53			68	5.9
Imipramine HCl	0.20	0.058	0.20	0.110	0.13	0.143									
Indigotindisulfonate sodium	0.30	0.085	0.30	0.172											
Intracaine HCl											4.97			85	5.0
Iodophthalein sodium				0.07[c]							9.58			100	9.4
Isometheptene mucate	0.18	0.048	0.18	0.095	0.18	0.196	0.18	0.302			4.95	0.18	0.52	0	6.2
Isoproterenol sulfate	0.14	0.039	0.14	0.078	0.14	0.156	0.14	0.234	0.14	0.389	6.65	0.14	0.52	trace	4.5
Kanamycin sulfate	0.08	0.021	0.07	0.041	0.07	0.083	0.07	0.125	0.07	0.210					
Lactic acid				0.239[c]							2.30			100*	2.1
Lactose			0.07	0.040[c]			0.08		0.09		9.75	0.09		0*	5.8
Levallorphan tartrate	0.13	0.036	0.13	0.073	0.13	0.143	0.12	0.210	0.12	0.329	9.40	0.10	0.52	59*	6.9
Levorphanol tartrate	0.12	0.033	0.12	0.067	0.12	0.136	0.12	0.203							
Lidocaine HCl				0.13[c]							4.42			85	4.3
Lircomycin HCl	0.16	0.045	0.16	0.090	0.15	0.170	0.14	0.247	0.14	0.40	6.60	0.14	0.52	0	4.5

(continued overleaf)

	0.5 %		1 %		2 %		3 %		5 %		Iso-osmotic concentration[a]				
	E	*D*	*E*	*D*	*E*	*D*	*E*	*D*	*E*	*D*	%	*E*	*D*	H	pH
Lobeline HCl				0.090*											
Lyapolate sodium	0.10	0.025	0.09	0.051	0.09	0.103	0.09	0.157	0.09	0.263	9.96	0.09	0.52	0	6.5^{+}
Magnesium chloride				0.45							2.02	0.45		0	6.3
Magnesium sulfate			0.17	0.094[c]			0.15	0.26	0.15	0.43	6.3	0.14	0.52	0	6.2
Magnesium sulfate, anhydrous	0.34	0.093	0.32	0.184	0.30	0.345	0.29	0.495			3.18	0.28	0.52	0	7.0
Mannitol				0.098[c]						5.07			0*	6.2	
Maphenide HCl		0.27	0.075	0.27	0.153	0.27	0.303	0.26	0.448		3.55	0.25	0.52		
Menadiol sodium diphosphate											4.36			0	8.2
Menadione sodium bisulfite					0.12[d]						5.07			0	5.3
Menthol															
Meperidine HCl					0.125[c]						4.80			98	5.0
Mepivacaine HCl	0.21	0.060	0.21	0.116	0.20	0.230	0.20	0.342			4.60	0.20	0.52	45	4.5
Merbromin				0.08[b]											
Mercuric cyanide			0.15	0.06*			0.14		0.13						
Mersalyl															
Mesoridazine besylate	0.10	0.024	0.07	0.04	0.05	0.058	0.04	0.071	0.03	0.087					

(continued overleaf)

	0.5 %		1 %		2 %		3 %		5 %		Iso-osmotic concentration[a]				
	E	*D*	*E*	*D*	*E*	*D*	*E*	*D*	*E*	*D*	%	*E*	*D*	H	pH
Metaraminol bitartrate	0.20	0.06	0.20	0.112	0.19	0.21	0.18	0.308	0.17	0.505	5.17	0.17	0.52	59	3.8
Methacholine chloride				0.184[c]							3.21			0	4.5
Methadone HCl				0.101[c]							8.59			100*	5.0
Methamphetamine HCl				0.213[c]							2.75			97	5.9
Methdilazine HCl	0.12	0.035	0.10	0.056	0.08	0.08	0.06	0.093	0.04	0.112					
Methenamine			0.23				0.24				3.68	0.25		100	8.4
Methiodal sodium	0.24	0.068	0.24	0.136	0.24	0.274	0.24	0.41			3.81	0.24	0.52	0	5.9
Methitural sodium	0.26	0.074	0.25	0.142	0.24	0.275	0.23	0.407			3.85	0.23	0.52	78	9.8
Methocarbamol	0.10	0.03	0.10	0.06											
Methotrimeprazine HCl	0.12	0.034	0.10	0.060	0.07	0.077	0.06	0.094	0.04	0.125					
Methoxyphenamine HCl	0.26	0.075	0.26	0.150	0.26	0.300	0.26	0.450			3.47	0.26	0.52	96	5.4
p-Methylaminoethanol-phenol tartrate	0.18	0.048	0.17	0.095	0.16	0.19	0.16	0.282	0.16	0.453	5.83	0.16	0.52	0	6.2
Methyldopate HCl	0.21	0.063	0.21	0.122	0.21	0.244	0.21	0.365			4.28	0.21	0.52	partial	3.0
Methylergonovine maleate	0.10	0.028	0.10	0.056											
N-Methylglucamine	0.20	0.057	0.20	0.111	0.18	0.214	0.18	0.315	0.18	0.517	5.02	0.18	0.52	4	11.3
Methylphenidate HCl	0.22	0.065	0.22	0.127	0.22	0.258	0.22	0.388			4.07	0.22	0.52	66	4.3

(continued overleaf)

	0.5 %		1 %		2 %		3 %		5 %		Iso-osmotic concentration[a]				
	E	*D*	*E*	*D*	*E*	*D*	*E*	*D*	*E*	*D*	%	*E*	*D*	H	pH
Methylprednisolone sodium succinate	0.10	0.025	0.09	0.051	0.09	0.102	0.08	0.143	0.07	0.20					
Minocycline HCl	0.10	0.030	0.10	0.058	0.09	0.107	0.08	0.146							
Monoethanolamine	0.53	0.154	0.53	0.306							1.70	0.53	0.52	100	11.4
Morphine HCl			0.15	0.086[c]			0.14								
Morphine sulfate			0.14	0.079[c]			0.11	0.19	0.09	0.26					
Nalorphine HCl	0.24	0.07	0.21	0.121	0.18	0.210	0.17	0.288	0.15	0.434	6.36	0.14	0.52	63	4.1
Naloxone HCl	0.14	0.042	0.14	0.083	0.14	0.158	0.13	0.230	0.13	0.367	8.07	0.11	0.52	35	5.2
Naphazoline HCl			0.27	0.14[d]			0.24				3.99	0.22		100	5.3
Neoarsphenamine											2.32		17	7.80	
Neomycin sulfate			0.11	0.063[c]			0.09	0.16	0.08	0.232					
Neostigmine bromide			0.22	0.127[c]			0.19				4.98			0	4.6
Neostigmine methylsulfate			0.20	0.115[c]			0.18		0.17		5.22	0.17			
Nicotinamide			0.26	0.148[c]			0.21	0.36			4.49	0.20	0.52	100	7.0
Nicotinic acid			0.25	0.144[c]											
Nikethamide				0.100[c]							5.94			100	6.9
Novobiocin sodium	0.12	0.033	0.10	0.057	0.07	0.073									

(continued overleaf)

	0.5 %		1 %		2 %		3 %		5 %		Iso-osmotic concentration[a]				
	E	*D*	*E*	*D*	*E*	*D*	*E*	*D*	*E*	*D*	%	*E*	*D*	H	pH
Oleandomycin phosphate	0.08	0.017	0.08	0.038	0.08	0.084	0.08	0.129	0.08	0.255	10.82	0.08	0.52	0	5.0
Orphenadrine citrate	0.13	0.037	0.13	0.074	0.13	0.144	0.12	0.204	0.10	0.285					
Oxophenarsine HCl											.67			trace*	2.3
Oxymetazoline HCl	0.22	0.063	0.22	0.124	0.20	0.232	0.19	0.335			4.92	0.18	0.52	86	5.7
Oxyquinoline sulfate	0.24	0.068	0.21	0.113	0.16	0.182	0.14	0.236	0.11	0.315					
D-Pantothenyl alcohol	0.20	0.053	0.18	0.100	0.17	0.193	0.17	0.283	0.16	0.468	5.60	0.16	0.52	92	6.8
Papaverine HCl			0.10	0.061[c]											
Paraldehyde	0.25	0.071	0.25	0.142	0.25	0.288	0.25	0.430			3.65	0.25	0.52	97	5.3
Pargyline HCl	0.30	0.083	0.29	0.165	0.29	0.327	0.28	0.491			3.18	0.28	0.52	91	3.8
Penicillin G, potassium			0.18	0.102[c]			0.17	0.29	0.16	0.46	5.48	0.16	0.52	0	6.2
Penicillin G, procaine				0.06[d]											
Penicillin G, sodium			0.18	0.100[c]			0.16	0.28	0.16	0.46	5.90			18	5.2
Pentazocine lactate	0.15	0.042	0.15	0.085	0.15	0.169	0.15	0.253	0.15	0.42					
Pentobarbital sodium				0.145[c]							4.07			0	9.9
Pentolinium tartrate				0.09[d]							5.95			55*	3.4
Phenacaine HCl				0.09											

(continued overleaf)

	0.5 %		1 %		2 %		3 %		5 %		Iso-osmotic concentration[a]				
	E	*D*	*E*	*D*	*E*	*D*	*E*	*D*	*E*	*D*	%	*E*	*D*	H	pH
Pheniramine maleate				0.09[d]											
Phenobarbital sodium			0.24	0.135[c]			0.23	0.40			3.95	0.23	0.52	0	9.2
Phenol	0.35	0.20									2.8	0.32	0.52	0*	5.6
Phentolamine mesylate	0.18	0.052	0.17	0.096	0.16	0.173	0.14	0.244	0.13	0.364	8.23	0.11	0.52	83	3.5
Phenylephrine HCl			0.32	0.184[c]			0.30				3.0	0.30		0	4.5
Phenylephrine tartrate												5.90		58*	5.4
Phenylethyl alcohol	0.25	0.070	0.25	0.141	0.25	0.283									
Phenylpropanolamine HCl			0.38	0.219[c]							2.6	0.35		95	5.3
Physostigmine salicylate			0.16	0.090[c]											
Physostigmine sulfate				0.074[c]											
Pilocarpine HCl			0.24	0.138[c]			0.22	0.38			4.08	0.22	0.52	89	4.0
Pilocarpine nitrate			0.23	0.132[c]			0.20	0.35			4.84	0.20	0.52	88	3.9
Piperocaine HCl				0.12[d]							5.22			65	5.7
Polyethylene glycol 300	0.12	0.034	0.12	0.069	0.12	0.141	0.12	0.216	0.13	0.378	6.73	0.13	0.52	53	3.8
Polyethylene glycol 400	0.08	0.022	0.08	0.047	0.09	0.098	0.09	0.153	0.09	0.272	8.50	0.11	0.52	0	4.4
Polyethylene glycol 1500	0.06	0.015	0.06	0.036	0.07	0.078	0.07	0.120	0.07	0.215	10.00	0.09	0.52	4	4.1

(continued overleaf)

	0.5 %		1 %		2 %		3 %		5 %		Iso-osmotic concentration[a]				
	E	*D*	*E*	*D*	*E*	*D*	*E*	*D*	*E*	*D*	%	*E*	*D*	H	pH
Polyethylene glycol 1540	0.02	0.005	0.02	0.012	0.02	0.028	0.03	0.047	0.03	0.094					
Polyethylene glycol 4000	0.02	0.004	0.02	0.008	0.02	0.02	0.020	0.033	0.02	0.067					
Polymyxin B sulfate			0.09	0.052			0.06	0.10	0.04	0.12					
Polysorbate 80	0.02	0.005	0.02	0.010	0.02	0.02	0.020	0.032	0.02	0.055					
Polyvinyl alcohol (99% hydrol)	0.02	0.004	0.02	0.008	0.02	0.020	0.02	0.035	0.03	0.075					
Polyvinylpyrrolidone	0.01	0.003	0.010	0.006	0.01	0.01	0.01	0.017	0.01	0.035					
Potassium acetate	0.59	0.172	0.59	0.342							1.53	0.59	0.52	0	7.6
Potassium chlorate											1.88			0	6.9
Potassium chloride			0.76	0.439[c]							1.19	0.76	0.52	0	5.9
Potassium iodide			0.34	0.196[c]							2.59	0.34	0.52	0	7.0
Potassium nitrate			0.56	0.324[c]							1.62	0.56	0	5.9	
Potassium phosphate			0.46	0.27							2.08	0.43	0.52	0	8.4
Potassium phosphate, monobasic			0.44	0.25							2.18	0.41	0.52	0	4.4
Potassium sulfate			0.44								2.11	0.43		0	6.6
Pralidoxime chloride	0.32	0.092	0.32	0.183	0.32	0.364					2.87	0.32	0.52	0	4.6
Prilocaine HCl	0.22	0.062	0.22	0.125	0.22	0.250	0.22	0.375			4.18	0.22	0.52	45	4.6

(continued overleaf)

	0.5 %		1 %		2 %		3 %		5 %		Iso-osmotic concentration[a]				
	E	*D*	*E*	*D*	*E*	*D*	*E*	*D*	*E*	*D*	%	*E*	*D*	H	pH
Procainamide HCl			0.22	0.13			0.19	0.33	0.17	0.49					
Procaine HCl			0.21	0.122[c]			0.19	0.33	0.18		5.05	0.18	0.52	91	5.6
Prochlorperazine edisylate	0.08	0.020	0.06	0.033	0.05	0.048	0.03	0.056	0.02	0.065					
Promazine HCl	0.18	0.050	0.13	0.077	0.09	0.102	0.07	0.112	0.05	0.137					
Proparacaine HCl	0.16	0.044	0.15	0.086	0.15	0.169	0.14	0.247	0.13	0.380	7.46	0.12	0.52		
Propiomazine HCl	0.18	0.050	0.15	0.084	0.12	0.133	0.10	0.165	0.08	0.215					
Propoxycaine HCl											6.40			16	5.3
Propylene glycol											2.00			100	5.5
Pyrathiazine HCl	0.22	0.065	0.17	0.095	0.11	0.123	0.08	0.140	0.06	0.17					
Pyridostigmine bromide	0.22	0.062	0.22	0.125	0.22	0.250	0.22	0.377			4.13	0.22	0.52	0	7.2
Pyridoxine HCl											3.05			31*	3.2
Quinacrine methanesulfonate				0.06[c]											
Quinine bisulfate			0.09	0.05			0.09	0.16							
Quinine dihydrochloride			0.23	0.130[c]			0.19	0.33	0.18		5.07	0.18	0.52	trace*	2.5
Quinine hydrochloride			0.14	0.077[c]			0.11	0.19							
Quinine and urea HCl			0.23	0.13			0.21	0.36			4.50	0.20	0.52	64	2.9

(continued overleaf)

	0.5 %		1 %		2 %		3 %		5 %		Iso-osmotic concentration[a]				
	E	*D*	*E*	*D*	*E*	*D*	*E*	*D*	*E*	*D*	%	*E*	*D*	H	pH
Resorcinol		0.161[c]									3.30			96	5.0
Rolitetracycline	0.11	0.032	0.11	0.064	0.10	0.113	0.09	0.158	0.07	0.204					
Rose Bengal	0.08	0.02	0.07	0.04	0.07	0.083	0.07	0.124	0.07	0.198	14.9	0.06	0.52		
Rose Bengal B	0.08	0.022	0.08	0.044	0.08	0.087	0.08	0.131	0.08	0.218					
Scopolamine HBr			0.12	0.07			0.12	0.21	0.12	0.35	7.85	0.11	0.52	8	4.8
Scopolamine methylnitrate			0.16				0.14		0.13	6.95	0.13	0	6.0		
Secobarbital sodium			0.24	0.14			0.23	0.40			3.9	0.23	0.52	trace	9.8
Silver nitrate			0.33	0.190[c]							2.74	0.33	0.52	0*	5.0
Silver protein, mild			0.17	0.10			0.17	0.29	0.16	0.46	5.51	0.16	0.52	0	9.0
Silver protein, strong				0.06[d]											
Sodium acetate			0.46	0.267							2.0	0.45	0.52		
Sodium acetazolamide	0.24	0.068	0.23	0.135	0.23	0.271	0.23	0.406			3.85	0.23	0.52		
Sodium aminosalicylate				0.170[c]							3.27			0	7.3
Sodium ampicillin	0.16	0.045	0.16	0.090	0.16	0.181	0.16	0.072	0.16	0.451	5.78	0.16	0.52	0	8.5
Sodium ascorbate											3.00			0	6.9
Sodium benzoate			0.40	0.230[c]							2.25	0.40	0.52	0	7.5

(continued overleaf)

	0.5 %		1 %		2 %		3 %		5 %		Iso-osmotic concentration[a]				
	E	*D*	*E*	*D*	*E*	D	*E*	*D*	*E*	D	%	*E*	*D*	H	pH
Sodium bicarbonate			0.65	0.375							1.39	0.65	0.52	0	8.3
Sodium biphosphate (H_2O)			0.40	0.23							2.45	0.37	0.52	0	4.1
Sodium biphosphate ($2H_2O$)			0.36								2.77	0.32		0	4.0
Sodium bismuth thioglycollate	0.20	0.055	0.19	0.107	0.18	0.208	0.18	0.303	0.17	0.493	5.29			0	8.3
Sodium bisulfite			0.61	0.35							1.5	0.61	0.52	0*	3.0
Sodium borate			0.42	0.241[c]							2.6	0.35	0.52	0	9.2
Sodium bromide											1.60			0	6.1
			0.32				0.28				3.3	0.27		0	8.0
Sodium carbonate, monohydrated			0.60	0.346							1.56	0.58	0.52	100	11.1
Sodium cephalothin	0.18	0.05	0.17	0.095	0.16	0.179	0.15	0.259	0.14	0.400	6.80	0.13	0.52	partial	8.5
Sodium chloride			1.00	0.576[c]			1.00	1.73	1.00	2.88	0.9	1.00	0.52	0	6.7
Sodium citrate			0.31	0.178[c]			0.30	0.52			3.02	0.30		0	7.8
Sodium colistimethate	0.16	0.045	0.15	0.087	0.14	0.161	0.14	0.235	0.13	0.383	6.85	0.13	0.52	0	8.4
Sodium hypophosphite											1.60			0	7.3
Sodium iodide			0.39	0.222[c]							2.37	0.38	0.52	0	6.9
Sodium iodohippurate											5.92			0	7.3

(continued overleaf)

	0.5 %		1 %		2 %		3 %		5 %		Iso-osmotic concentration[a]				
	E	*D*	*E*	*D*	*E*	*D*	*E*	*D*	*E*	*D*	%	*E*	*D*	H	pH
Sodium lactate											1.72			0	6.5
Sodium lauryl sulfate	0.10	0.029	0.08	0.046	0.07	0.068	0.05	0.086							
Sodium mercaptomerin											5.30			0	8.4
Sodium metabisulfite			0.67	0.386[c]							1.38	0.65	0.52	5*	4.5
Sodium methicillin	0.18	0.050	0.18	0.099	0.17	0.192	0.16	0.281	0.15	0.445	6.00	0.15	0.52	0	5.8
Sodium nafcillin	0.14	0.039	0.14	0.078	0.14	0.158	0.13	0.219	0.10	0.285					
Sodium nitrate			0.68								1.36	0.66		0	6.0
Sodium nitrite			0.84	0.480[c]							1.08	0.83		0*	8.5
Sodium oxacillin	0.18	0.050	0.17	0.095	0.16	0.177	0.15	0.257	0.14	0.408	6.64	0.14	0.52	0	6.0
Sodium phenylbutazone	0.19	0.054	0.18	0.104	0.17	0.202	0.17	0.298	0.17	0.488	5.34	0.17	0.52		
Sodium phosphate			0.29	0.168			0.27	0.47			3.33	0.27	0.52	0	9.2
Sodium phosphate, dibasic ($2H_2O$)			0.42	0.24							2.23	0.40	0.52	0	9.2
Sodium phosphate, dibasic ($12H_2O$)			0.22				0.21				4.45	0.20		0	9.2
Sodium propionate			0.61	0.35							1.47	0.61	0.52	0	7.8
Sodium salicylate			0.36	0.210[c]							2.53	0.36	0.52	0	6.7
Sodium succinate	0.32	0.092	0.32	0.184	0.31	0.361					2.90	0.31	0.52	0	8.5

(continued overleaf)

	0.5 %		1 %		2 %		3 %		5 %		Iso-osmotic concentration[a]				
	E	*D*	*E*	*D*	*E*	*D*	*E*	*D*	*E*	*D*	%	*E*	*D*	H	pH
Sodium sulfate, anhydrous			0.58	0.34							1.61	0.56	0.52	0	6.2
Sodium sulfite, exsiccated			0.65	0.38							1.45			0	9.6
Sodium sulfobromophthalein	0.07	0.019	0.06	0.034	0.05	0.060	0.05	0.084	0.04	0.123					
Sodium tartrate	0.33	0.098	0.33	0.193	0.33	0.385					2.72	0.33	0.52	0	7.3
Sodium thiosulfate			0.31	0.181[c]							2.98	0.30	0.52	0	7.4
Sodium warfarin	0.18	0.049	0.17	0.095	0.16	0.181	0.15	0.264	0.15	0.430	6.10	0.15	0.52	0	8.1
Sorbitol (*A* H_2O)											5.48			0	5.9
Sparteine sulfate	0.10	0.03	0.10	0.056	0.10	0.111	0.10	0.167	0.10	0.277	9.46	0.10	0.52	19*	3.5
Spectinomycin HCl	0.16	0.045	0.16	0.092	0.16	0.185	0.16	0.280	0.16	0.460	5.66	0.16	0.52	3	4.4
Streptomycin HCl			0.17	0.10[c]			0.16	0.16							
Streptomycin sulfate			0.07	0.036[c]			0.06	0.10	0.06	0.17					
Sucrose			0.08	0.047[c]			0.09	0.16	0.09	0.26	9.25	0.10	0.52	0	6.4
Sulfacetamide sodium			0.23	0.132[c]			0.23	0.40			3.85	0.23	0.52	0	8.7
Sulfadiazine sodium			0.24	0.14			0.24	0.38			4.24	0.21	0.52	0	9.5
Sulfamerazine sodium			0.23	0.13			0.21	0.36			4.53	0.20	0.52	0	9.8
Sulfapyridine sodium			0.23	0.13			0.21	0.36			4.55	0.20	0.52	5	10.4
Sulfathiazole sodium			0.22	0.13			0.20	0.35			4.82	0.19	0.52	0	9.9
Tartaric acid				0.143[c]							3.90			75*	1.7

(continued overleaf)

	0.5 %		1 %		2 %		3 %		5 %		Iso-osmotic concentration[a]				
	E	*D*	*E*	*D*	*E*	*D*	*E*	*D*	*E*	*D*	%	*E*	*D*	H	pH
Tetracaine HCl			0.18	0.109[c]			0.15	0.26	0.12	0.35					
Tetracycline HCl			0.14	0.081[c]		0.10									
Tetrahydrozoline HCl											4.10			60*	6.7
Theophylline				0.02*											
Theophylline sodium glycinate											2.94			0	8.9
Thiamine HCl				0.139[c]							4.24			87*	3.0
Thiethylperazine maleate	0.10	0.030	0.09	0.050	0.08	0.089	0.07	0.119	0.05	0.153					
Thiopental sodium				0.155[c]							3.50			74	10.3
Thiopropazate diHCl	0.20	0.053	0.16	0.090	0.12	0.137	0.10	0.170	0.08	0.222					
Thioridazine HCl	0.06	0.015	0.05	0.025	0.04	0.042	0.03	0.055	0.03	0.075					
Thiotepa	0.16	0.045	0.16	0.090	0.16	0.182	0.16	0.278	0.16	0.460	5.67	0.16	0.52	10*	8.2
Tridihexethyl chloride	0.16	0.047	0.16	0.096	0.16	0.191	0.16	0.28	0.16	0.463	5.62	0.16	0.52	97	5.4
Triethanolamine	0.20	0.058	0.21	0.121	0.22	0.252	0.22	0.383			4.05	0.22	0.52	100	10.7
Trifluoperazine 2HCl	0.18	0.052	0.18	0.100	0.13	0.144									
Triflupromazine HCl	0.10	0.031	0.09	0.051	0.05	0.061	0.04	0.073	0.03	0.092					
Trimeprazine tartrate	0.10	0.023	0.06	0.035	0.04	0.045	0.03	0.052	0.02	0.061					
Trimethadione	0.23	0.069	0.23	0.133	0.22	0.257	0.22	0.378			4.22	0.21	0.52	100	6.0
Trimethobenzamide HCl	0.12	0.033	0.10	0.062	0.10	0.108	0.09	0.153	0.08	0.232					

(continued overleaf)

	0.5 %		1 %		2 %		3 %		5 %		Iso-osmotic concentration[a]				
	E	*D*	*E*	*D*	*E*	*D*	*E*	*D*	*E*	*D*	%	*E*	*D*	H	pH
Tripelennamine HCl				0.13[d]							5.50			100	6.3
Tromethamine	0.26	0.074	0.26	0.15	0.26	0.30	0.26	0.45			3.45	0.26	0.52	0	10.2
Tropicamide	0.10	0.03	0.09	0.050											
Trypan blue	0.26	0.075	0.26	0.150											
Tryparsamide				0.11[c]											
Tubocurarine chloride				0.076[c]											
Urea			0.59	0.34							1.63	0.55	0.52	100	6.6
Urethan				0.18[b]							2.93			100	6.3
Uridine	0.12	0.035	0.12	0.069	0.12	0.138	0.12	0.208	0.12	0.333	8.18	0.11	0.52	0*	6.1
Valethamate bromide	0.16	0.044	0.15	0.085	0.15	0.168	0.14	0.238	0.11	0.324					
Vancomycin sulfate	0.06	0.015	0.05	0.028	0.04	0.049	0.04	0.066	0.04	0.098					
Viomycin sulfate			0.08	0.05			0.07	0.12	0.07	0.20					
Xylometazoline HCl	0.22	0.065	0.21	0.121	0.20	0.232	0.20	0.342			4.68	0.19	0.52	88	5.0
Zinc phenolsulfonate											5.40		0*		5.4
Zinc sulfate			0.15	0.086[c]			0.13	0.23	0.12	0.35	7.65	0.12 0.52			

[a] The unmarked values were taken from Hammarlund *et al.*[26–29] and Sapp *et al.*[30]

[b] Adapted from Lund *et al.*[25]

[c] Adapted from *British Pharmaceutical Codex*.[31]

[d] Obtained from several sources.

E, sodium chloride equivalents; *D*, freezing-point depression, °C; H, hemolysis, %, at the concentration that is isoosmotic with 0.9% NaCl, based on freezing-point determination or equivalent test; pH, approximate pH of solution studied for hemolytic action; *, change in appearance of erythrocytes and/or solution[30–32]; † pH determined after addition of blood.

Note: See also Budavari S, ed. *Merck Index*, 11th edn, Rahway, NJ: Merck, 1988: MISC 79–103.

Appendix B: isotonic solution values[33]

Drug (0.3 g)	Water needed for isotonicity (mL)	Drug (0.3 g)	Water needed for isotonicity (mL)	Drug (0.3 g)	Water needed for isotonicity (mL)
Alcohol	21.7	Epinephrine bitartrate	6.0	Silver nitrate	11.0
Ammonium chloride	37.3	Epinephrine hydrochloride	9.7	Silver protein, mild	5.7
Amobarbital sodium	8.3	Ethylmorphine hydrochloride	5.3	Sodium acetate	15.3
Amphetamine phosphate	11.3	Fluorescein sodium	10.3	Sodium bicarbonate	21.7
Amphetamine sulfate	7.3	Glycerin	11.7	Sodium biphosphate, anhydrous	15.3
Antipyrine	5.7	Holocaine hydrochloride	6.7	Sodium biphosphate	13.3
Apomorphine hydrochloride	4.7	Homatropine hydrobromide	5.7	Sodium bisulfite	20.3
Ascorbic acid	6.0	Homatropine methylbromide	6.3	Sodium borate	14.0
Atropine methylbromide	4.7	Hyoscyamine sulfate	4.7	Sodium iodide	13.0
Atropine sulfate	4.3	Neomycin sulfate	3.7	Sodium metabisulfite	22.3
Bacitracin	1.7	Oxytetracycline hydrochloride	4.3	Sodium nitrate	22.7
Barbital sodium	10.0	Penicillin G, potassium	6.0	Sodium phosphate	9.7
Bismuth potassium tartrate	3.0	Penicillin G, sodium	6.0	Sodium propionate	20.3
Boric acid	16.7	Pentobarbital sodium	8.3	Sodium sulfite, exsiccated	21.7
Butacaine sulfate	6.7	Phenobarbital sodium	8.0	Sodium thiosulfate	10.3
Caffeine and sodium benzoate	8.7	Physostigmine salicylate	5.3	Streptomycin sulfate	2.3
Calcium chloride	17.0	Pilocarpine hydrochloride	8.0	Secobarbital sodium	8.0

Drug (0.3 g)	Water needed for isotonicity (mL)	Drug (0.3 g)	Water needed for isotonicity (mL)	Drug (0.3 g)	Water needed for isotonicity (mL)
Calcium chloride (6 H_2O)	11.7	Pilocarpine nitrate	7.7	Sulfacetamide sodium	7.7
Chlorobutanol (hydrated)	8.0	Piperocaine hydrochloride	7.0	Sulfadiazine sodium	8.0
Chlortetracycline sulfate	4.3	Polymyxin B sulfate	3.0	Sulfamerazine sodium	7.7
Cocaine hydrochloride	5.3	Potassium chloride	25.3	Sulfapyridine sodium	7.7
Cupric sulfate	6.0	Potassium nitrate	18.7	Sulfathiazole sodium	7.3
Dextrose, anhydrous	6.0	Potassium phosphate, monobasic	14.7	Tetracaine hydrochloride	6.0
Dibucaine hydrochloride	4.3	Procainamide hydrochloride	7.3	Tetracycline hydrochloride	4.7
Dihydrostreptomycin sulfate	2.0	Procaine hydrochloride	7.0	Viomycin sulfate	2.7
Ephedrine hydrochloride	10.0	Scopolamine hydrobromide	4.0	Zinc chloride	20.3
Ephedrine sulfate	7.7	Scopolamine methylnitrate	5.3	Zinc sulfate	5.0

This table of isotonic solution values above shows volumes in mL of water to be added to 300 mg of the specified drug in sterile water to produce an isotonic solution. The addition of an isotonic vehicle (commonly referred to as diluting solution) to make 30 mL yields a 1% solution. Solutions prepared as directed above are iso-osmotic with 0.9% sodium chloride solution but may not be isotonic with blood (see Appendix A for hemolysis data).

The V values for drugs that do not appear in the table above but are listed in Appendix A can be calculated from the sodium chloride equivalent for 1% drug.

Example: Calculate the V value for anileridine HCl (Appendix A defines E = 0.19).

$$\frac{100 \text{ ml Soln}}{0.9 \text{ NaCl}} \times \frac{0.19 \text{ g NaCl}}{1 \text{ g drug}} \times 0.3 \text{ g drug} = 6.33 \text{ mL Soln}$$

for dilute solution

$$6.33 \text{ mL soln} \cong 6.33 \text{ mL water}$$

$$\therefore V = 6.33 \text{ mL water}/0.3 \text{ g drug}.$$

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8

Pharmacokinetics and pharmacodynamics

Basic pharmacokinetics and pharmacodynamics

The goal of pharmacotherapy is to provide optimal drug therapy in the treatment or prevention of disease. A major barrier to the achievement of this goal is the large variability in the pharmacological effect that is observed following drug administration (Fig 8.1).[1] The ability to implement drug therapy in a safe and rational manner necessitates an understanding of the factors that cause this variability. One of the most important factors is the concentration of drug that is achieved at the site of action.

The critical nature of the concentration versus effect relationship

The quantitative response to a drug depends highly on the concentration of drug at the site of action. In most situations one cannot quantify drug concentration at the actual site of action. Rather, drug concentrations are measured in an easily accessible site that is believed to be in equilibrium with the site of action

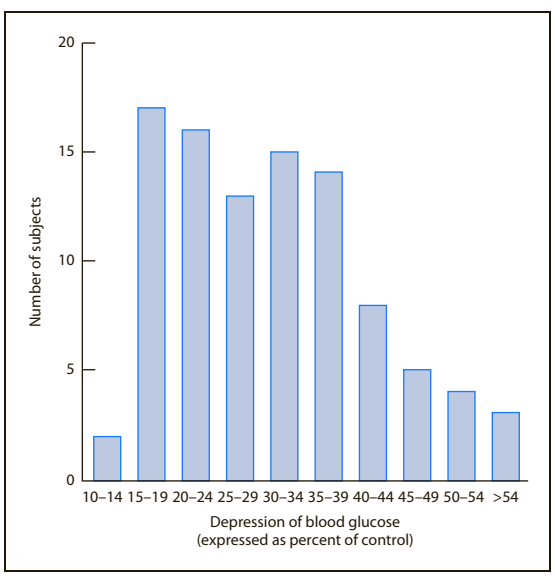

Figure 8.1 Decrease in blood glucose in 97 subjects 30 min after an intravenous dose of 1 g of tolbutamide. Note the large variability observed after the equivalent dose was administered in this group. (Data from Swerdloff RS *et al.* Influence of age on the intravenous tolbutamide response test. *Diabetes* 1967; 16: 161–170.)

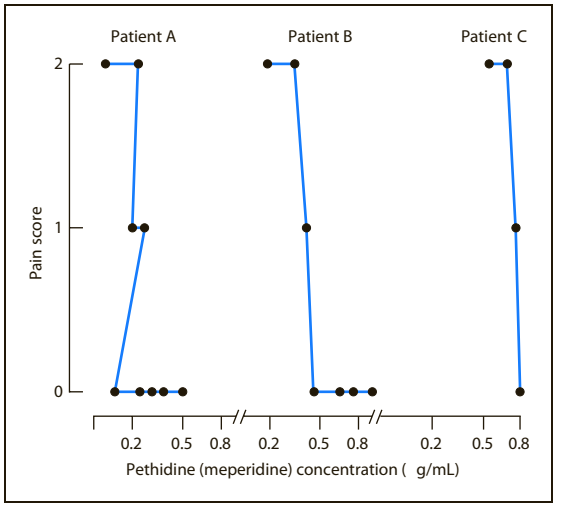

Figure 8.2 Blood meperidine concentration-response curves for three individual patients, illustrating a typical range in interpatient responses. (From Austin KL, Stapleton JV, Mather LE. Relationship between blood meperidine concentrations and analgesic response: a preliminary report. *Anesthesiology* 1980; 53: 460–66.)

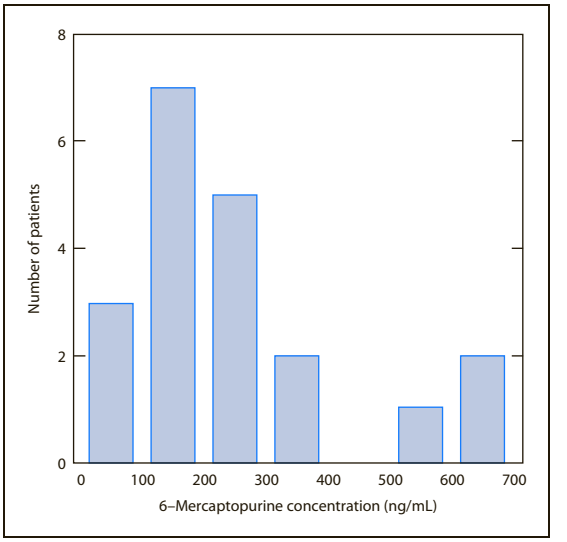

Figure 8.3 Distribution of peak 6-mercaptopurine concentrations achieved in a group of 20 patients receiving an oral dose of 1 mg/m^2. (Data from Sulh H *et al*. Pharmacokinetic determinants of 6-mercaptopurine myelotoxicity and therepeutic failure in children with acute lymphoblastic leukemia. *Clin Pharmacol Ther* 1986; 40: 604–609.)

(e.g., blood or one of its components). Figure 8.2[2] provides a good illustration of a drug whose pharmacological effect is particularly sensitive to changes in blood concentration. Numerous studies have been published that substantiate the critical nature of the concentration–effect relationship for a wide variety of drugs.

It is recognized now that drug therapy may be optimized by designing regimens that account for the concentration of a drug necessary to achieve a desired pharmacological response. However, there is often significant difficulty in achieving such target concentrations. In particular, it often is observed that if a fixed dose of a drug is administered to a group of individuals, the drug concentration measured in plasma can vary widely. For example, the peak concentration of 6-mercaptopurine achieved in a group of 20 patients who received a standard 1 mg/m^2 dose is shown in Fig. 8.3.[3] The concentrations ranged from 0 to 660 ng/mL. Taken together, this suggests that variability in drug concentration is a major source of variability in drug effect, and there may be a significant degree of variability among individuals in the drug concentrations produced by a given dose of drug.

A basic understanding of the factors that control drug concentration at the site of action is important for the optimal use of drugs. This is the area of study referred to as *pharmacokinetics*, which is the study of the time course of drug absorption, distribution, metabolism, and elimination.

Drug concentration versus time profile

Blood (or its components, plasma or serum) represents the most frequently sampled fluid used to characterize the pharmacokinetics of drugs. Drug concentration in the blood is the sum of several processes (Fig. 8.4).[4] Initially visual characterization of the processes controlling the concentration of drug in the blood can be made by constructing a drug concentration versus time profile (i.e., a plot of drug concentration in the blood versus time). As can be seen from Fig. 8.5, several useful pieces of information can be derived from such a profile. For example, the time at which the peak concentration occurs can be approximated and the peak concentration quantified. If the minimum concentration needed to maintain a desired effect is known, the onset and duration of effect also can be approximated. While useful information can be

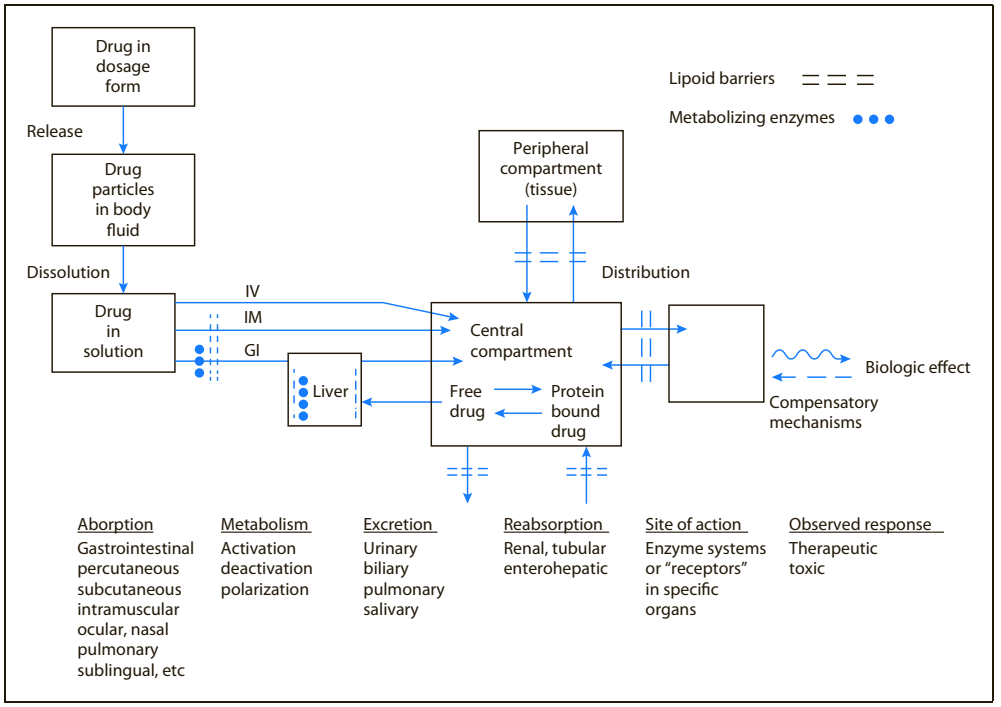

Figure 8.4 Diagram illustrating the factors that influence onset, duration, and intensity of drug effects. Note that the drug must dissolve before being absorbed and that it passes across many lipoid barriers and some metabolizing systems before reaching the site of action. (From Barr WH. Principles of biopharmaceutics. *Am J Pharm Educ* 1968; 32: 958–959.)

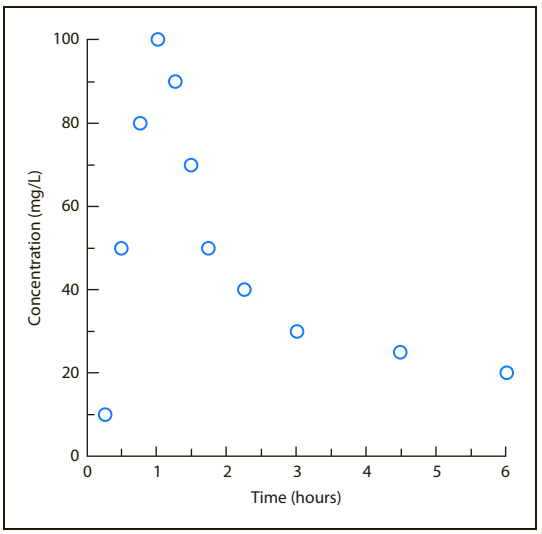

Figure 8.5 Hypothetical plot of drug-concentration data after oral administration of a drug.

drawn casually from a simple graph as depicted in Fig. 8.5, a more rigorous description of the pharmacokinetics of a drug is necessary to achieve the accuracy in dosage regimen design required for the safe and effective use of drugs. This higher degree of accuracy necessitates the development of mathematical models for describing the time course of absorption, distribution, metabolism, and elimination.

Pharmacokinetic models

One of the primary objectives of pharmacokinetic models is to develop a quantitative method to describe the relationship of drug concentration, or amount in the body, as a function of time. The complexity of the pharmacokinetic model will vary with the route of administration, the extent and duration of distribution into various body fluids and tissues, the processes of elimination, and the intended application of the pharmacokinetic model. Often, numerous potential mathematical models exist for a particular drug. In such cases, the simplest model that will adequately and accurately describe the pharmacokinetics of the drug is the model that should be chosen.

There are a wide variety of potential uses for pharmacokinetic models, which include:

1. Prediction of drug concentration in blood/plasma or tissue.
2. Calculation of a dosage regimen.
3. Quantitative assessment of the effect of disease on drug disposition.
4. Elucidation of the mechanism of disease-induced alterations in drug disposition.
5. Determination of the mechanism for drug–drug interactions.
6. Prediction of drug concentration versus effect relationships.

There are three primary types of pharmacokinetic models: compartmental, noncompartmental, and physiological.

Compartmental models describe the pharmacokinetics of drug disposition by grouping body tissues that are kinetically indistinguishable and describe the transfer of drug between body tissues in terms of rate constants.

Noncompartmental models describe the pharmacokinetics of drug disposition using time- and concentration-averaged parameters.

Physiological models attempt to describe drug disposition in terms of realistic physiological parameters, such as blood flow and tissue-partition coefficients.

Drug action and effect

A drug is an agent intended for use in the diagnosis, mitigation, treatment, cure, or prevention of disease in humans or other animals. One of the most remarkable qualities of drugs is the great diversity of their actions and effects on the body, which enables their selective use in the treatment of a wide range of conditions involving virtually every body organ, tissue, and cell. Some drugs selectively stimulate or depress the cardiac muscle, the central nervous system (CNS), or the gastrointestinal (GI) tract. Mydriatic drugs dilate the pupil of the eye, whereas miotic drugs constrict or decrease pupillary size. Some drugs can induce vomiting, whereas others prevent vomiting. Diuretic drugs increase the flow of urine, whereas other drugs decrease it. Laxatives evacuate the bowel; other drugs cause constipation. The diverse effects of drugs in the body include the treatment of infections, cancer, cardiovascular disease, asthma, glaucoma, Alzheimer disease, and many others. Drugs can aid in diagnosis, treatment, replenishment, prevention, as well as many other applications.

Drug discovery and development are complex phenomena that involve the collective contributions of many scientific specialists. After a new potential drug substance has undergone definitive chemical and physical characterization, the basic pharmacology, or the nature and mechanism of action of the drug on the biologic system, must be determined. The drug's effects, or multiple effects, as well as its selectivity, dose, potency and efficacy, dose–effect relationships, dose–intensity of effect relationships, dose–frequency of response relationships, and variations in response and responsiveness must be ascertained. Additional studies on how the new drug works investigate drug receptors and receptor theory, occupation and other theories, mechanisms of drug action, types of targets for drug action, receptor binding, receptor structure and function, voltage-sensitive channels, ligand-activated ion channels, G protein-coupled receptors, tyrosine kinase-linked receptors, intracellular receptors that control DNA transcription, enzyme inhibition, and receptor regulation.

The word *drug* imposes an action–effect context within which the properties of a substance are described. The description must include the pertinent properties of the recipient of the drug. Thus, when a drug is defined as an analgesic, it is implied that the recipient reacts to a noxious stimulus in a certain way, called *pain*. (Studies indicate that pain is not simply the *perception* of a certain kind of stimulus but rather, a *reaction* to the perception of a variety of kinds of stimuli or stimulus patterns.) Both because the pertinent properties are locked into the complex and somewhat imprecise biological context and because the types of possible response are many, descriptions of the properties of drugs tend to emphasize the qualitative features of the effects they elicit. Thus, a drug may be described as having analgesic, vasodepressor, convulsant, antibacterial, or other properties. However, the description of a drug does not end with the enumeration of the responses it may elicit. Certain intrinsic properties of the drug-recipient system can be described in quantitative terms and are essential to the full description of the drug and to the validation of the drug for specific uses. In the following section, Definitions and Concepts, certain general terms are

defined in qualitative language; the subsequent section lays the foundation for an appreciation of some of the quantitative aspects of pharmacodynamics.

Definitions and concepts

The vocabulary that is unique to the field of pharmacology is relatively small; the general vocabulary is that of the biological sciences and chemistry. Nevertheless, there are a few definitions that are important to the proper understanding of pharmacology. It is necessary to differentiate among *action*, *effect*, *selectivity*, *dose*, *potency*, and *efficacy*.

Action versus effect

The *effect* of a drug is an alteration of function of the structure or process upon which the drug acts. It is common to use the term *action* as a synonym for *effect*. However, action precedes effect. *Action* is the alteration of condition that brings about the effect.

The final effect of a drug may be far removed from its site of action. For example, the diuresis subsequent to the ingestion of ethanol does not result from an action on the kidney but, rather, from a depression of activity in the region of the hypothalamus, which regulates the release of antidiuretic hormone from the posterior pituitary gland. The alteration of hypothalamic function is, of course, also an effect of the drug, as is each subsequent change in the chain of events leading to diuresis. The action of ethanol was exerted only at the initial step, with each subsequent effect becoming then the action to a following step.

Multiple effects

No known drug is capable of exerting a single effect, although a number are known that appear to have a single mechanism of action. Multiple effects may derive from a single mechanism of action. For example, the inhibition of acetylcholinesterase by physostigmine will elicit an effect at every site where acetylcholine is produced, is potentially active, and is hydrolyzed by cholinesterase. Thus, physostigmine elicits a constellation of effects.

A drug also can cause multiple effects at several different sites by a single action at only one site, providing that the function initially altered at the site of action ramifies to control other functions at distant sites. Thus, a drug that suppresses steroid synthesis in the liver not only may lower serum cholesterol, impair nerve myelination and function, and alter the condition of the skin (as a consequence of cholesterol deficiency), but also may affect digestive functions (because of a deficiency in bile acids) and alter adrenocortical and sexual hormonal balance.

Although a single action can give rise to multiple effects, most drugs exert multiple actions. The various actions may be related, as for example, the sympathomimetic effects of phenylephrine that accrue to its structural similarity to norepinephrine and its ability to exert sympathetic responses, or the actions may be unrelated, as with the actions of morphine to interfere with the release of acetylcholine from certain autonomic nerves, block some actions of 5-hydroxytryptamine (serotonin), and release histamine. Many drugs bring about immunological (i.e., allergic or hypersensitivity) responses that bear no relation to the other pharmacodynamic actions of the drug.

Selectivity

Although most drugs have the potential to elicit multiple effects, one effect is generally more readily elicitable than another. This differential responsiveness is called *selectivity*. It usually is considered to be a property of the drug, but it is also a property of the constitution and biodynamics of the recipient subject or patient.

Selectivity may come about in any of several ways. The subcellular structure (receptor) with which a drug combines to initiate one response may have a higher affinity for the drug than that for some other action. Atropine, for example, has a much higher affinity for muscarinic receptors that subserve the function of sweating than it does for the nicotinic receptors that subserve voluntary neuromuscular transmission, so that suppression of sweating can be achieved with only a tiny fraction of the dose necessary to cause paralysis of the skeletal muscles. A drug may be distributed unevenly, so that it reaches a higher concentration at one site than throughout the tissues generally; for example, chloroquine is much more effective against hepatic than intestinal (colonic) amebiasis because it reaches a much higher concentration in the liver than in the wall of the colon. An affected function may be much more critical to, or have less reserve in, one organ than in another, so that a drug

will be predisposed to elicit an effect at the more critical site. Some inhibitors of dopa decarboxylase (also known as 5-hydroxytryptophan decarboxylase) depress the synthesis of histamine more than that of either norepinephrine or 5-hydroxytryptamine (serotonin), even though histidine decarboxylase is less sensitive to the drug, simply because histidine decarboxylase is the only step and, hence, is rate-limiting in the biosynthesis of histamine. Dopa decarboxylase does not become rate limiting in the synthesis of either norepinephrine or 5-hydroxytryptamine until the enzyme is nearly completely inhibited. Another example of the determination of selectivity by the critical balance of the affected function is that of the mercurial diuretic drugs. An inhibition of only 1% in the tubular resorption of glomerular filtrate usually will double urine flow, because 99% of the glomerular filtrate normally is resorbed. Aside from the question of the possible concentration of diuretics in the urine, a drug-induced reduction of 1% in sulfhydryl enzyme activity in tissues other than the kidney usually is not accompanied by an observable change in function. Selectivity also can be determined by the pattern of distribution of inactivating or activating enzymes among the tissues and by other factors.

Dose

Even the uninitiated person knows that the dose of a drug is the amount administered. However, the appropriate dose of a drug is not some unvarying quantity, a fact sometimes overlooked by pharmacists, official committees, and physicians. The practice of pharmacy is entrapped in a system of fixed-dose formulations, so that fine adjustments in dosage often are difficult to achieve. Fortunately, a rather wide latitude in dosages usually is allowable. It is obvious that the size of the recipient individual should have a bearing upon the dose, and the physician may elect to administer the drug on a body-weight or surface-area basis rather than as a fixed dose. Usually, however, a fixed dose is given to all adults, unless the adult is exceptionally large or small. The dose for infants and children often is determined by one of several formulas that take into account age or weight, depending on the age group of the child and the type of action exerted by the drug. Infants are relatively more sensitive to many drugs, often because systems involved in the inactivation and elimination of the drugs may not be developed fully in the infant.

The patient's nutritional status, his or her mental outlook, the presence of pain or discomfort, the severity of the condition being treated, the presence of secondary disease or pathology, and genetic factors as well as many other factors affect the dose of a drug necessary to achieve a given therapeutic response or to cause an untoward effect. Even two apparently well-matched normal persons may require widely different doses for the same intensity of effect. Furthermore, a drug is not always employed for the same effect and, therefore, is not always given in the same dose. For example, the dose of a progestin necessary for an oral contraceptive effect is considerably different from that necessary to prevent spontaneous abortion, and the dose of an estrogen used for the treatment of menopausal symptoms is much lower than that used for the treatment of prostatic carcinoma.

The wise physician knows that the dose of a drug is not a rigid quantity, but, rather, that which is necessary and can be tolerated, and he or she individualizes the regimen accordingly. The wise pharmacist also recognizes that official or manufacturer's recommended doses sometimes are quite narrowly defined and should serve only as a useful guide rather than as an absolute.

Potency and efficacy

The *potency* of a drug is the reciprocal of dose. Thus, it will have the units of persons/unit weight of drug or body weight/unit weight of drug, for example. Potency generally has little utility other than to provide a means of comparing the relative activities of drugs in a series; *relative potency*, relative to some prototypic member of the series, is a parameter commonly used among pharmacologists and in the pharmaceutical industry.

Whether a given drug is more potent than another has little bearing on its clinical usefulness, as long as the potency is not so low that the size of the dose is physically unmanageable or the cost of treatment is higher than with an equivalent drug. A drug that is less potent but more selective is the one to be preferred. Promotional arguments in favor of a more potent drug, therefore, are irrelevant to the important considerations that should govern the choice of a drug. However, drugs of the same class

sometimes differ in the maximum intensity of effect; that is some drugs of the class may be less efficacious than others, regardless of how large a dose is used.

Efficacy connotes the property of a drug to achieve the desired response, and *maximum efficacy* denotes the maximum achievable effect. Even huge doses of codeine often cannot achieve the relief from severe pain that relatively small doses of morphine can; thus, codeine is said to have a lower maximum efficacy than morphine. Efficacy is one of the primary determinants of which drug is chosen.

Drug absorption, distribution, metabolism, and excretion

Introduction

Drugs differ widely in their pharmacodynamic effects and clinical applications, as well as in penetration, absorption, and usual route of administration. They also differ in their distribution among the body tissues, and in disposition and mode of termination of action. Certain general principles that help explain the differences have both pharmaceutical and therapeutic implications. These principles facilitate an understanding of both the features that are common to a class of drugs and the differences among the members of that class.

To have the desired action, a drug must achieve absorption and transport to the appropriate tissue or organ, penetrate to the responding cell surface or subcellular structure, and elicit a response or alter ongoing processes. The drug may be distributed simultaneously or sequentially to a number of tissues, be bound or stored, be metabolized to inactive or active products, or be excreted. The basic entry, movement, and disposition of drugs and metabolites within the body are summarized in Fig. 8.6. Each of the processes or events depicted relates importantly to therapeutic and toxic effects of a drug and to the mode of administration, and drug design must take each into account. The extent to which all the components of absorption, distribution, metabolism (biotransformation), and elimination apply varies enormously with the drug or xenobiotic (the latter being a term widely used to refer to not only drugs but any chemical not part of the normal biochemistry and physiology of the body) and the dose (level of exposure), and to some extent is subject to interindividual variation, the latter often arising from genetic and disease state influences.

Pharmacokinetics is the science that treats the rate and extent of absorption, rates of distribution among

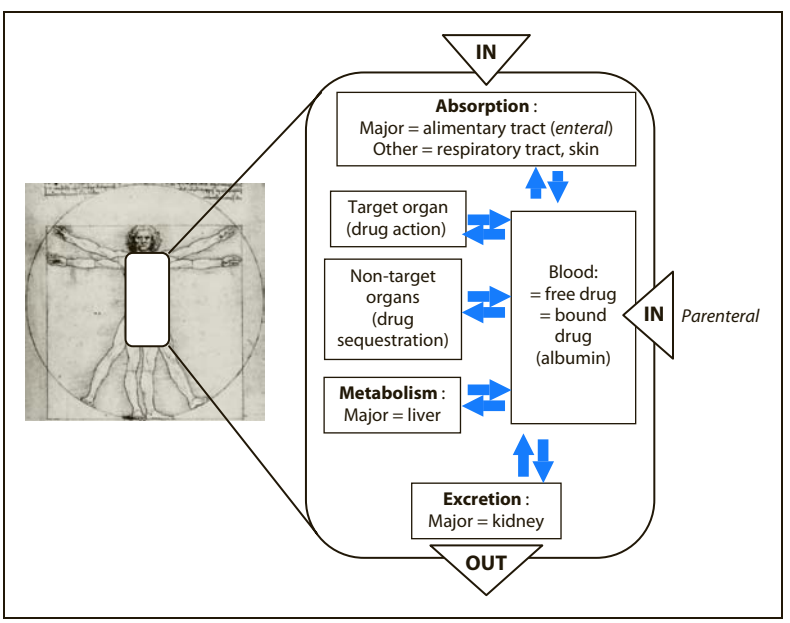

Figure 8.6 Interrelationship of the major components of drug entry, distribution, metabolism, and elimination within the body.

body compartments, rate of elimination, and related phenomena. Next we will consider the physiological bases of the processes.

Structure and properties of membranes

In almost all stages of absorption, distribution, metabolism (biotransformation), and elimination, a drug must pass through several to many biological membranes during the processes. Since membranes are traversed in all of these events, a brief description of biological membranes and membrane processes is in order, as well as the relationship of the physicochemical properties of a drug molecule to penetration and transport.

Numerous sophisticated techniques have established the nature of the plasma, mitochondrial, nuclear, and other cell membranes. The description of the plasma membrane that follows is much oversimplified, but it will suffice to provide a background for an understanding of drug penetration into and through membranes. The cell membrane has been characterized as a bimolecular layer of lipid material entrained between two parallel monomolecular layers of protein. However, rather than forming a continuous layer, the protein layer comprises "islands" sporadically scattered over the surfaces. For many proteins, much of the protein is below the surface and within the fatty bilayer. The lipid bilayer can be envisaged as a somewhat orderly, lamellar array of phospholipid molecules associated tail-to-tail, each tail being an alkyl chain or steroid group, and the heads being polar groups. The disorder that does exist is the result of the different degrees of saturation of the fatty acids and the interspersed cholesterol molecules that break up the close packing of the fatty acid tails. Cholesterol maintains the mechanical stability of cell membranes, is a determinant of membrane fluidity, and – with relevance to drug passage across membranes – decreases permeability to water-soluble molecules. Moreover, the lamellar portion is penetrated by large globular proteins with a highly hydrophobic interior (like the lipid layers), and by some fibrous proteins as well.

The plasma membrane is asymmetrical. The lipid composition varies from cell type to cell type and perhaps from site to site on the same membrane. There are, for example, differences between the membrane of the endoplasmic reticulum and the plasma membrane, even though the membranes are co-extensive. The membrane surface facing the cytoplasm is rich in phosphatidylethanolamine and phosphatidylserine, while the surface facing the outside is rich in phosphatidylcholine and sphingomyelin. Oligosaccharide chains linked to lipids (glycolipids), and oligo- and polysaccharide chains attahed to proteins (glycoproteins) are confined to non-cytosolic facing surfaces. Sugar moieties attached to the outer proteins are most often attached to the asparagine residue. These sugar moieties are important to both cellular and immunological recognition and adhesion, and they have other functions as well. Where membranes are double, the inner and outer layers differ considerably; the inner and outer membranes of mitochondria have strikingly different compositions and properties.

The cell membrane appears to be perforated by water-filled pores of various sizes, varying from about 4 to 10 Å, most of which are about 7 Å. Probably all major ion (water-filled) channels penetrate the large protein assemblies that traverse the membrane. Through these pores pass inorganic ions and small organic molecules. Among the common inorganic ions, because sodium ions are more hydrated than potassium and chloride ions, they are larger and do not pass as freely through the pores as do potassium and chloride. Ion (ion plus water) movement can be by diffusion down a chemical concentration gradient. However, movement of ions through the pores can be controlled by counterion transport, or expenditure of intracellular energy – adenosine triphosphate (ATP) hydrolysis – by so-called ABC transporters. Vascular endothelium appears to have pores at least as large as 40 Å, but these seem to be interstitial passages rather than transmembrane pores. Lipid molecules small enough to pass through the cell membrane pores may do so, but they have a higher probability of entering into the lipid layer (since pores constitute less than 1% of the cell surface upon which the drug molecule impinges); from there these molecules will equilibrate chemically with the interior of the cell. Other proteins may be confined to one or the other surface and not traverse the membrane. Often proteins on the inner surface protein are linked to intracellular structural proteins that contribute to cell shape.

Diffusion and transport

Transport is the movement of a drug from one place to another within the body. The drug may diffuse freely in uncombined form with a kinetic energy appropriate to its thermal environment, or it may move in combination with extracellular or cellular constituents, sometimes in connection with energy-yielding processes that allow the molecule or complex to overcome barriers to simple diffusion.

Simple nonionic diffusion and passive transport

Molecules in solution move in a purely random fashion, provided they are not charged and moving in an electrical gradient. Such random movement is called diffusion; if the molecule is uncharged, it is called nonionic diffusion. In a population of drug molecules, the probability that during unit time any drug molecule will move across a boundary is directly proportional to the number of molecules adjoining that boundary and, therefore, to the drug concentration. Except at dilutions so extreme that only a few molecules are present, the actual rate of movement (molecules per unit time) is directly proportional to the probability of movement and, therefore, to the concentration. Once molecules have passed through the boundary to the opposite side, their random motion may cause some to return and others to continue to move farther away from the boundary. The rate of return is likewise proportional to the concentration on the opposite side of the boundary. It follows that, although molecules are moving in both directions, there will be a net movement from the region of higher to that of lower concentration, and the net transfer will be proportional to the concentration differential. If the boundary is a membrane, which has both substance and dimension, the rate of movement is also directly proportional to the permeability and inversely proportional to the thickness. These factors combine into Fick's law of diffusion:

$$dQ/dt = \overline{D}A(C_1 - C_2)/x$$

where Q is the net quantity of drug transferred across the membrane, t is time, C_1 is the concentration on one side and C_2 that on the other, x is the thickness of the membrane, A is the area, and $\overline{D}$ is the diffusion coefficient, related to permeability. Since a biological membrane is heterogeneous, with pores of different sizes and probably with varying thickness and composition, both $\overline{D}$ and x probably vary from place to place. Nevertheless, some mean values can be assumed. It is customary to combine the membrane factors into a single constant, called a permeability constant or coefficient, P, so that $P = \overline{D}/x$, and A in the equation above has unit value. The rate of net transport (diffusion) across the membrane then becomes:

$$dQ/dt = P(C_1 - C_2)$$

As diffusion continues, C_1 approaches C_2, and the net rate, dQ/dt, approaches zero in exponential fashion, characteristic of a first-order process. Equilibrium is defined as that state in which $C_1 = C_2$. The equilibrium is, of course, dynamic, with equal numbers of molecules being transported in each direction during unit time. If water also is moving through the membrane, it may either facilitate the movement of drug or impede it, according to the relative directions of movement of water and drug; this effect of water movement is called solvent drag.

Ionic or electrochemical diffusion

If a drug is ionized, the transport properties are modified. The probability of penetrating the membrane is still a function of concentration, but it is also a function of the potential difference or electrical gradient across the membrane. A cationic drug molecule will be repelled from the positive charge on the outside of the membrane, and only those molecules with a high kinetic energy will pass through the ion barrier. If the cation is polyvalent, it may not penetrate at all.

Once inside the membrane, a cation will be simultaneously attracted to the negative charge on the intracellular surface of the membrane and repelled by the outer surface; it is said to be moving along the electrical gradient. If it is also moving from a higher toward a lower concentration, it is said to be moving along its electrochemical gradient, which is the sum of the influences of the electrical field and the concentration differential across the membrane.

Once inside the cell, cations will tend to be kept inside by the attractive negative charge on the interior of the cell, and the intracellular concentration of drug will increase until – by sheer numbers of accumulated drug particles – the rate of outward diffusion or mass escape equals that of inward transport. At this point

electrochemical equilibrium is said to have occurred. At electrochemical equilibrium at body temperature (37°C), ionized drug molecules will be distributed according to the Nernst equation:

$$\pm \log C_O/C_I = ZE/61$$

where C_O is the molar extracellular and C_I the intracellular concentration, Z is the number of charges per molecule, and E is the membrane potential in millivolts. Log C_O/C_I is positive when the molecule is negatively charged and negative when the molecule is positively charged.

Facilitated diffusion

Sometimes a substance moves more rapidly through a biological membrane than can be accounted for by the process of simple diffusion. This accelerated movement is termed facilitated diffusion. It is due to the presence of a special molecule within the membrane, called a carrier, with which the transported substance combines. There is considered to be greater permeability to the carrier–drug complex than to the drug alone, so that the transport rate is enhanced. After the complex has traversed the membrane, it dissociates. For the carrier process to be continuous, either the carrier must return to the original side of the membrane to be used again, or it must constantly be produced on one side and eliminated on the other. Many characteristics of facilitated diffusion, formerly attributed to ion carriers, can be explained by ion exchange. Facilitated diffusion only transports a molecule along its electrochemical gradient.

Active transport

Active transport can be defined as energy-dependent movement of a substance through a biological membrane against an electrochemical gradient. It is characterized as follows:

1. The substance is transported from a region of lower to one of higher electrochemical activity.
2. Metabolic poisons (that most often reduce ATP concentrations) interfere with transport.
3. The transport system shows a requirement for specific chemical structures.
4. Closely related chemicals are competitive for the transport system.
5. The transport rate approaches an asymptote (i.e., saturates) as concentration increases.

Characteristics 3, 4, and 5 are in common with those of carrier-mediated facilitated diffusion.

Many drugs are secreted by active transport from the renal tubules into urine, from liver cells into bile or blood, from intestinal cells into the lumen of the GI tract, or from the cerebrospinal fluid into blood, but the role of active transport of drugs in the distribution into most body compartments and tissues has been less extensively documented, although it is now an active area of research. Active transport is often required for the movement of drug metabolites, entities that generally have less lipid solubility than the parent drug, across cell membranes.

Pinocytosis and exocytosis

Many (perhaps all) cells are capable of a type of phagocytosis called pinocytosis. The cell membrane has been observed to invaginate into a sac-like structure containing extracellular materials and then pinch off the sac at the membrane, so that the sac remains as a vesicle or vacuole within the interior of the cell. Because metabolic activity is required and because an extracellular substance can be transported against an electrochemical gradient, pinocytosis shows some of the same characteristics as active transport. However, pinocytosis is relatively slow and inefficient compared with most active transport, except in GI absorption, where for some xenobiotics pinocytosis may be of some importance.

It is not known to what extent pinocytosis contributes to the transport of most drugs, but many macromolecules and even larger particles can be absorbed by the gut. Exocytosis is the reverse of pinocytosis. Granules, vacuoles, or other organelles within the cell move to the cell membrane, fuse with it, and extrude their contents into the interstitial space.

Physicochemical factors in penetration

Drugs and other substances may traverse the membrane primarily either through the pores, or by movement into the membrane lipids and subsequent diffusion from the membrane into the cytosol or other

fluid on the far side of the membrane. The physicochemical prerequisites differ according to which route is taken. To pass through the pores, the *diameter* of the molecule must be smaller than the pore, but the molecule can be longer than the pore diameter. The probability that a long, thin molecule will be suitably oriented, however, is low unless there is also bulk flow, and therefore transmembrane passage of such molecules is slow.

Water-soluble molecules with low lipid solubility are usually thought to pass through the membrane mainly via the pores. If there is a membrane carrier or active-transport system, a low solubility of the drug in membrane lipids is no impediment to penetration, because the drug–carrier complex is assumed to have an appropriate solubility, and energy from an active-transport system enables the drug to penetrate the energy barrier imposed by the lipids. Actually, the lipids are not an important energy barrier; rather, the barrier is the force of attraction of the solvent water for its dipolar-to-polar solute, so that it is difficult for the solute to leave the water and enter the lipid.

Drugs with a high solubility in the membrane lipids pass easily through the membrane. Even when their dimensions are small enough to permit passage through pores, lipid-soluble drugs primarily pass through the membrane lipids, not only because chemical partition favors the lipid phase but also because, as mentioned previously, the surface area occupied by pores is only a small fraction of the total membrane area.

Lipid solubility and partition coefficients

Over a century ago, the importance of lipid solubility in the penetration and absorption of drugs was being investigated. Eventually it was recognized that more important than lipid solubility was the lipid-to-water partition (or distribution) coefficient; in other words, a high lipid solubility does not favor penetration unless the water solubility is low enough so that the drug is not entrained in the aqueous phase. When the water solubility of a substance is so low that a significant concentration in water or extracellular fluid cannot be achieved, absorption may be negligible despite a favorable partition coefficient. Hence, such substances as mineral oil or petrolatum are virtually unabsorbed. The optimal partition coefficient for permeation of the skin appears to be lower than that for the permeation of the cell membrane, perhaps being as low as unity.

Dipolarity, polarity, and nonionic diffusion

The partition coefficient of a drug depends upon the polarity and the size of the molecule. Drugs with a high dipole moment, even though nonionized, have low lipid solubility and hence penetrate poorly. An example of a highly dipolar substance with a low partition coefficient, which does not penetrate into cells, is sulfisoxazole. Sulfadiazine is somewhat less dipolar, has a chloroform-to-water partition coefficient ten times that of sulfisoxazole, and readily penetrates cells. Ionization not only greatly diminishes lipid solubility but also may impede passage through charged membranes.

It is often stated that ionized molecules do not penetrate membranes, except for ions of small diameter. This is not necessarily true because of the presence of membrane carriers for some ions that effectively shield or neutralize the charge (formation of ion pairs). The renal tubular transport systems, which transport such obligate ions as tetraethylammonium, probably form ion pairs. Furthermore, if an ionized molecule has a large non-polar moiety such that appreciable lipid solubility is imparted to the molecule despite the charge, the drug may penetrate, though usually at a slow rate. Nevertheless, when a drug is a weak acid or base, the nonionized form, with a favorable partition coefficient, passes through a biological membrane so much more readily than the ionized form that for all practical purposes, only the nonionized form is said to pass through the membrane. This has become known as the principle of nonionic diffusion.

Absorption of drugs

Absorption is the process of movement of a drug from the site of application into the extracellular compartment of the body. Inasmuch as there is a great similarity among the various membranes through which a drug may pass to gain access to the extracellular fluid, it might be expected that the particular site of application (or route) would make little difference to the successful absorption of the drug. Actually it makes a great deal of difference; many factors, other than the structure and composition of the membrane, determine the ease with which a drug is absorbed.

Clinical pharmacokinetics and pharmacodynamics

Clinical pharmacokinetics is the discipline in which basic pharmacokinetic principles are applied to the development of rational dosage regimens. The concepts of pharmacokinetics are placed into perspective with the development of individualized drug dosage regimens. The clinical significance of drug absorption, distribution, and elimination and influence of disease states on these processes are emphasized. Examples are given of the ways pharmacokinetic principles can be applied in the calculation and adjustment of dosage regimens designed to fit the pharmacokinetic and pharmacodynamic properties of drugs and specific disease states that alter drug disposition. The principles of therapeutic drug monitoring and the rational use of this clinical science in the management of patients also are discussed.

The application of pharmacokinetic principles to patient care can aid the clinician in making rational drug use decisions. However, knowing the relationship between the time course of drug concentration and the pharmacologic effect is critical to the application of pharmacokinetic principles and the interpretation of plasma drug concentrations in the patient care setting.

As a general rule traditional pharmacokinetic research is an intensive study of a limited number of subjects resulting in very precise pharmacokinetic and pharmacodynamic parameter estimates. Clinical pharmacokinetics, on the other hand, is usually limited to very few and sometimes no plasma drug concentrations, requiring the clinician to make an educated guess about key elements of drug disposition and the drug use process. In the research setting it is common to obtain ten or more samples for drug concentration measurements within a single dosing interval. In the clinical setting it is uncommon to obtain more than two or three samples for a patient during a hospitalization or within a year for ambulatory care patients.

Therefore, understanding the usual manner in which drugs are absorbed, distributed, and eliminated, as well as the known factors that alter drug disposition and which of these elements is most likely to be altered in the individual patient, is key to the clinician's ability to effectively use pharmacokinetics. A basic knowledge of pharmacokinetics provides guidance to the clinician when selecting a drug product, dosing regimen, the anticipated onset of drug effect, and determining an appropriate sampling strategy if drug concentrations are to be obtained.

Principles of immunology

Physical barriers, such as the skin and mucosal membranes, represent the first line of protection against antigen and pathogen intrusion into the body. Once the foreign particle has transversed these barriers, a complex and coordinated response is activated in an effort to maintain tissue sterility and restore homeostasis. These activities are often compared to a military response towards a foreign incursion, in which the defensive response employs a diverse repertoire of assets to dispatch any threat. Similarly, the immune system is equipped with a vast array of humoral and cellular mechanisms, used to maintain physiological homeostasis.

Pharmacogenomics

Introduction

Pharmacogenomics is the science of optimizing pharmaceutical therapeutic outcomes for an individual based upon their genetic information. The term "pharmacogenomics" is often used synonymously with the more general phrase "personalized medicine". Personalized medicine, however, is a very broad model that includes environmental factors, enhanced detection of disease, and determining a person's predisposition to disease. Pharmacogenomics, or the genetic predetermination of reactions to pharmaceuticals, is therefore only one aspect of personalized medicine.

The goal of pharmacogenomics is to provide a genetic roadmap for both clinician and patient leading to the most appropriate medications for the treatment of disease. The ideal outcome is to optimize the benefits of a drug while minimizing its adverse effects. Responses to the therapeutic and adverse effects of a drug are highly variable. Every patient does not exhibit untoward adverse responses, nor do individuals who experience drug effects exhibit a response to the same degree. It is understood that a proportion

of adverse responses may be dose-related, but despite standardized drug dosing by body mass, age, sex, and health condition, there still remains large interindividual variation in drug response. Much, if not all, of this unpredictability is a product of the genetic profile of the patient. The science of pharmacogenomics, therefore, is one tool that is being used to reduce or eliminate the unpredictable nature of drug therapy. In doing so, drug treatments will result in fewer adverse events and decrease the overall costs of healthcare.

A key expectation of pharmacogenomics is to remove the trial-and-error method of finding the best drug treatment for a particular condition. Clinicians and their patients often try a variety of drugs and dosages, individually or in combination, to effect a desired therapeutic outcome. This method is both inefficient and ineffective. Considerable time is wasted searching for that one drug, or combination of drugs, that will produce the best result. Then when the drug is found, the most efficacious dose must be determined. The financial cost of this method is surely higher than knowing ahead of time, through genetic testing, what drugs and dosages would be most effective for an individual with a particular condition or disease.

Many pharmaceutical companies are sponsoring the development of companion diagnostics. These are diagnostic tests developed alongside of drugs in clinical trials to provide a means of screening patients who would be most responsive to the treatment and not experience potentially severe side-effects of these drugs. The use of pharmacogenomic testing in this manner, therefore, may reduce the overall cost of drug development by reducing the number of failed drugs. New formulations that show a lack of efficacy in the general population may be saved from the trash heap by identifying specific subpopulations that may be helped by a new drug.

Pharmacogenomics and the pharmacist

As pharmacists become more involved in medication therapy management services, the role of pharmacogenomics will be increasingly significant. As the medication experts of the medical team, pharmacists have a unique opportunity to improve patient care. How well a medication works for a particular patient is based on many factors – environment, sex, race, health of the patient, and other medications.[5] Pharmacogenomics data add a new factor to give a more complete picture of the patient. A pharmacist who knows how patients will metabolize certain medications can predict adverse effects and influence medication selection recommendations. As the field of pharmacogenomics grows, the pharmacist can play a vital role in individualized medicine. This role may be more nontraditional, such as a consultant; alternatively, community pharmacists might provide a service to their patients right at the pharmacy. These new roles may require additional training and education[5] but will lead to better patient outcomes.

History of pharmacogenomics

Clinical observations of inherited differences in the effects of drugs were first documented in the 1950s[6–18] and led to the early development of the field of *pharmacogenetics*. As a result of the successful sequencing of the entire human genome and the development of genome-wide analysis techniques, pharmacogenetics has been redefined by a broad spectrum of academia and industry, giving rise to *pharmacogenomics*. The goal of pharmacogenomics is to elucidate the inherited basis for interindividual differences in drug response, using genome-wide approaches to identify the genetic polymorphisms that determine an individual's response to specific medications. In addition to conventional targeted genetic studies to identify functional variants, the field includes such diverse areas as RNA-based microarray analysis and genome-wide DNA analysis to identify the major genetic sites (loci) associated with altered drug effects.

Because a key principle in the practice of pharmacotherapy is the optimization of drug treatment through the identification of those patient-specific variables that affect the likelihood of a clinical response or toxicity, this section will focus on the examination of the genetic basis of differences in drug response.

The human genome

The human genome project

In 1990 the Human Genome Project was officially initiated in the United States under the direction of the

National Institutes of Health and the US Department of Energy with a 15-year, $3 billion plan for completing the genome sequence of humans. This enormous multinational effort was undertaken by a number of public and private laboratories, known collectively as the International Human Genome Sequencing Consortium (IHGSC). The IHGSC first announced a draft sequence of the human genome in 2000, and by April of 2003, the entire 3.1 gigabases that make up the human genome were essentially complete.[9,10] In other words, more than 99% of what can be done with current technology was done, and virtually all of the bases were identified in their proper order. Political leaders from the United States, Britain, China, France, Germany, and Japan issued a joint proclamation honoring their scientists who worked on the project, hailing their work as one of the most significant scientific breakthroughs of modern times.

While much is now known about the structure of the human genome, many mysteries remain. It is known, for instance, that less than 2% of the human genome consists of sequences that actually encode proteins, while over 50% represents repetitive sequences of several types, whose function is less well understood.[9] Moreover, it is still not known precisely how many genes the human genome contains. Data indicate that the human genome includes approximately 30,000 to 35,000 genes – a number that is substantially smaller than was previously thought.[9] Only about half these genes have recognizable DNA-sequence patterns, or motifs, that suggest their possible function. Furthermore, while it was once dogma that one gene encodes one protein, it now appears that, through the mechanism of alternative splicing, more than 100,000 different proteins can be derived from these 30,000 to 35,000 genes.[10] In addition to alternative splicing, a number of "epigenetic" phenomena, such as methylation, phosphorylation, and histone modification, can alter the effect of a gene.[11–13] Furthermore, a complex array of molecular signals allows specific genes to be "turned on" (expressed) or "turned off" in specific tissues and at specific times. It is widely accepted that every human gene contains inherited genetic variants or mutations.[14] Mutations known to cause disease have been identified in approximately 1000 genes. However, it is likely that nearly all human genes are capable of causing disease or altering response to drug treatment if their function is altered significantly.

Because pharmacogenomics relies on the genetic basis of an individual in predicting drug variability, certain aspects of pharmacogenomics responses are inherited. Depending on the type of genetic variation (discussed under Types of Genetic Variations), certain responses would follow classical Mendelian models of inheritance. In fact, it has been proposed that genetics may account for 20 to 95% of variability in drug response and effects.[15] There are now several examples where interindividual differences in drug response have been traced to heritable genetic variations (genetic polymorphisms) in genes encoding drug-metabolizing enzymes, drug transporters, or drug targets.[16,17] While it is clearly important to identify environmental factors that influence the effect of medications, inherited determinants of drug response remain stable for an individual's lifetime and can affect agents across number of different drug classes; moreover, the effects can be profound.

Variation in the human genome

One characteristic of the human genome with medical and social relevance is that, on average, two unrelated persons share over 99.9% of their DNA sequences.[14] However, given that more than 3 billion base pairs constitute the human genome, this means that the DNA sequences of two unrelated individuals differ at millions of bases. Because a person's genotype represents the blending of parental genotypes, we are each thus heterozygous at about 3 million genetic loci. Many efforts are currently under way, in both the academic and commercial sectors, to catalogue these variants – commonly referred to as single-nucleotide polymorphisms (SNPs) – and to correlate these specific genotypic variations with specific phenotypic variations relevant to health.

The Single Nucleotide Polymorphism (SNP) Consortium was established in 1999 as a collaboration of several companies and institutions within the larger IHGSC to produce a public resource of genetic variation in the human genome. SNPs, as the name implies, are single-nucleotide changes in the DNA sequence that are present in the genome, and therefore represent inheritable genetic variations. More than 1.4 million SNPs were identified in the initial sequencing of the human genome,[14] with over 60,000 of

these in the regions encoding the proteins, and it is anticipated that 10 million common SNPs will ultimately be identified. Some of these SNPs have already been associated with significant changes in the metabolism or effects of medications, and are beginning to make their way into clinical medicine as important molecular diagnostic tools.[16–18] Because most drug effects are determined by the complex interplay of gene products that influence both the pharmacokinetics and pharmacodynamics of medications, pharmacogenomics is increasingly focused on polygenic determinants of drug effects, including inherited difference in drug targets (e.g., receptors) and drug disposition (e.g., metabolizing enzymes, transporters). The human genes involved in many pharmacogenetic traits have now been identified, their molecular mechanisms detailed, and their clinical importance more clearly defined. In some cases, SNP–phenotype correlations occur as a direct result of the influence of the SNP on health. However, more commonly, the SNP is merely a marker of biological diversity that happens to correlate with health because of its proximity to the genetic factor that is the actual cause of the clinical phenotype.[19] In this sense, the term "proximity" is only a rough measure of physical closeness. More specifically, proximity means that, as genetic material has passed through 5000 generations from our common ancestral pool, recombination between the SNP and the actual genetic factor has occurred only rarely. In genetic terminology, the SNP and the actual genetic factor are said to be in *linkage disequilibrium*.[20,21]

As an extension of the current efforts to catalogue individual SNPs and correlate them to phenotype, efforts are being made to map and use haplotypes.[19–21] Whereas a SNP represents a single-base variant, a haplotype represents a considerably longer sequence of nucleotides (averaging about 25,000 bases), that tend to be inherited together.[20–22] SNPs and haplotypes will be the key to the association studies (i.e., studies of affected persons and control subjects) necessary to identify the genetic factors in complex, common diseases, just as family studies have been important to the identification of the genes involved in monogenic conditions. Also, until whole-genome sequencing of individual patients becomes feasible clinically, the identification of SNPs and haplotypes will prove instrumental in efforts to use genomic medicine to individualize healthcare.

Types of genetic variations

There are several categories of genetic variation currently known to influence an individual's response to a drug. Three categories of genetic variation believed to impact pharmacogenomics that are sufficiently described in literature today are: point mutations in genes, or SNPs; copy number variation; and epigenomic variation. These three genetic-variation criteria are considered in addition to the known conditions classified as "genetic diseases" that include insertions or deletions of large portions of chromosomes or genes, or chromosomal duplication or chromosomal deletions.

Point mutations or *SNPs* both refer to a change in a single DNA base in the sequence. The difference between a point mutation and a SNP is based upon the frequency at which it is found in the population. If a point mutation is found at a frequency greater than or equal to 1% in the general population, it is called a SNP. When a DNA base change is found in less than 1% in the population, it is termed a point mutation. Depending on the location and substation of the point mutations or SNPs, they result in different effects. One type of result is a missense mutation, where a single DNA base change results in the encoding of a different amino acid. Because there is some redundancy of the three-base sequence codon for amino acids, some single DNA base changes do not result in the encoding of a different amino acid. These mutations that do not result in amino acid changes are called "silent mutations." Other single DNA base changes can result in more dramatic changes, such as the change from encoding a particular amino acid to a "stop" codon, which causes the termination of the protein instead of producing an amino acid. These types of mutations are called "nonsense mutations" and can produce proteins that have altered or no functionality. Another type of genetic change is the frameshift mutation, which changes the way the cell's transcription machinery reads the sequence of the gene downstream from the site of the mutation, often leading to a premature stop codon.

However, most variants in the human genome sequence have no apparent phenotypic effect, such as the silent mutations, which replace one base with

another yet still encode the same amino acid. Also, some mutations may not alter or affect the encoded protein if the altered codon substitutes an amino acid for another similar one that produces little to no change in the function of the protein. These are referred to as "conservative mutations." In contrast, "nonconservative mutations" replace an amino acid with a very different one and are more likely to affect the phenotype or functioning of the protein. Protein structure, or three-dimensional structure, is affected by its particular amino acid sequence. Three-dimensional structural changes can alter a protein receptor's recognition of a hormone or signaling ligand, whereas proteins with enzymatic function can be altered such that the rate at which it processes a substrate is impacted.

Although genetic mutations can result in altered protein function by a variety of means, the most common is loss of function. Loss-of-function mutations alter the phenotype of the affected individual by decreasing the quantity or the functional activity of a protein. Typically, loss-of-function mutations are the most easily identified as a result of their "all-or-none" phenotypic outcome. Therefore, examples of heritable genetic changes involving loss of function are plentiful. For instance, mutations in the glucose-6-phosphate dehydrogenase (*G6PD*) gene on the X chromosome decrease the functional activity of the enzyme, leading to acute hemolytic anemia if a male (who would have only one copy of the X chromosome) with the mutation is exposed to certain drugs, including sulfonamides, primaquine, and nitrofurantoins.[23] Furthermore, because genes involved in metabolism do not exist merely to handle pharmacological agents, variants that cause severe G6PD deficiency also lead to hemolytic anemia when affected males ingest fava beans (favism), because the enzyme is also important in the degradation of a toxic component of the beans.[24,25] Additional well-described examples of loss-of-function mutations in drug-metabolizing enzymes include cytochrome P450 2D6 (CYP2D6),[26,27] thiopurine methyltransferase (TPMT),[28,29] and dihydropyrimidine dehydrogenase (DPD); official name DYPD).[30,31] Alternatively, some mutations can result in a gain of function, whereby the protein can take on some new function or is simply more highly expressed. While fewer gain-of-function mutations have been identified, probably as a result of the subtlety of their phenotypic effects, some examples include mutations in the genes that cause such neurological disorders as Huntington disease and spinocerebellar ataxia, which appear to lead to neuropathological abnormalities by producing proteins with abnormally improved function.[32,33] Gain-of-function mutations are often dominantly inherited, because a single copy of the mutant gene is sufficient to alter function.

Although it was previously assumed that mutations in the approximately 98.5% of the genome that does not code for proteins do not affect the phenotype, several examples of noncoding mutations with important phenotypic implications have changed this perception. Indeed, while the vast majority of these "noncoding" mutations do not affect protein function, other "regulatory mutations" may ultimately prove as important in the variability of drug metabolism and etiology of common diseases as the coding-region variants. Such regulatory mutations act by altering the expression of a gene and therefore the amount of its protein product. For instance, a regulatory mutation could lead to the loss of expression of a gene, to unexpected expression in a tissue in which it is usually silent, or to a change in the time at which it is expressed. Examples of regulatory mutations associated with disease include those in the flanking region of the *FMR1* gene (causing fragile X syndrome),[34] a regulatory site of the type I collagen gene (increasing the risk of osteoporosis),[35] and an intronic regulatory site of the calpain-10 gene (increasing the risk of type 2 diabetes mellitus).[36] For the past several decades, pharmacogenomics has largely been focused on drug-metabolizing enzymes, in particular the genetic variation in the cytochrome P450 enzymes. Regulatory mutations with important implications for drug metabolism have been identified in the gene that encodes cytochrome P450 3A5.[37]

In summary, certain SNP changes can significantly impact the functional activity of drug-metabolizing enzymes (Fig. 8.7). When a single base pair change results in the coding change of a particular amino acid to an entirely different amino acid, this change alters the primary amino acid sequence and can potentially alter the secondary and tertiary or three-dimensional structure of an enzyme. A change in the three-dimensional protein structure of an enzyme can increase or decrease the binding affinity of a substrate

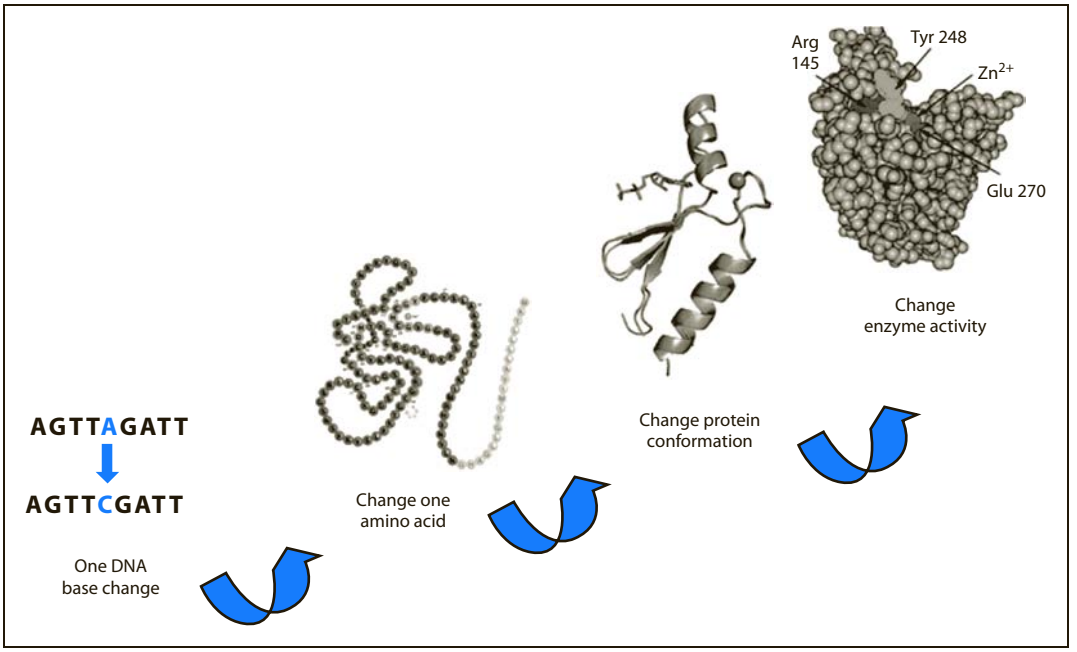

Figure 8.7 How one SNP can impact on an individual's response to drug therapy.

for that particular enzyme, which in turn can result in an increase or decrease in the enzymatic activity of that particular enzyme. If this change occurs in an enzyme responsible for drug metabolism, then one may see a resulting impact on that individual's response to a particular drug therapy.

Pharmacokinetics/ Pharmacodynamics in drug development

Drug development is a long, expensive process of discovery and preclinical development followed by clinical trials resulting in the submission of a package of data to a regulatory agency that will ultimately lead to licensure of that product for sale.

The goal of drug development is to find a dose of a drug for a specific indication that attains the desired therapeutic outcome while engendering a low probability of the patient experiencing a toxic event. Pharmacokinetics and pharmacodynamics can straightforwardly lead to attaining this goal. Indeed, in the past one to two decades there has been a marked increase in our understanding of the relationship between drug exposure and response. This is related to wider availability of the appropriate mathematical modeling methodologies. The application of these techniques in the timeline of drug development is presented in Fig. 8.8.

The clearest example of employing a pharmacokinetic/pharmacodynamic approach to drug development can be seen in the area of anti-infective agents. Part of the reason for this is that these drugs are unique in that we are not attempting to dock a molecule into a receptor in the human body. Rather, the target of drug action and the site to which we are attempting to bind the drug is a receptor in the pathogen of interest. This has several important consequences.

The first is toxicity. Anti-infective targets are chosen specifically so that they have little sequence homology to similar mammalian targets. A straightforward example is the topoisomerase enzymes seen in bacteria but also in man. The fluoroquinolone antimicrobials have a 100- to 1000-fold difference in the concentrations necessary for microbiological effect relative to activity for topoisomerase targets in man.[37] In contrast, there is often a narrow therapeutic index, for example, between normal human

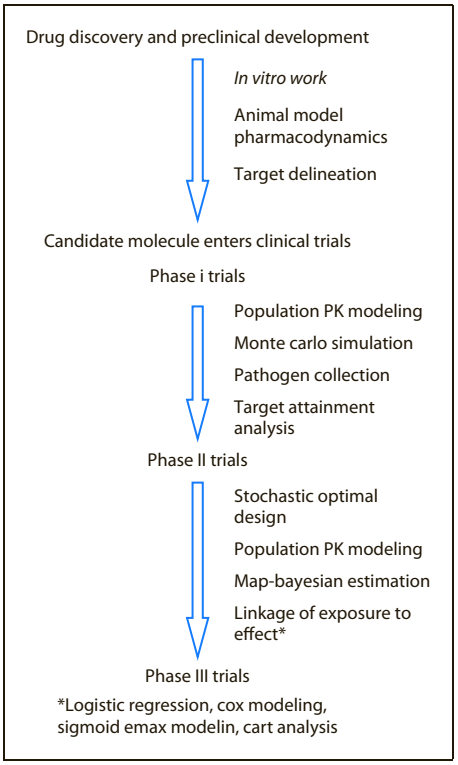

Figure 8.8 Use of pharmacodynamics in the drug development process.

cells and cancerous cells, meaning that oncologic chemotherapy is often (but not always) saddled with considerable toxicity.

The other important consequence is the ease with which pharmacodynamic relationships can be developed both preclinically as well as in clinical trials. The reason is that almost always (Hepatitis C is currently an exception to the rule) one can straightforwardly grow the pathogen of interest *in vitro* and determine a measure of drug exposure that will affect the growth of the pathogen in some standardized way. For example, for viruses, we can measure an EC_{50}, a drug concentration that will cause a 50% downturn in the number of rounds of replication per unit time. For bacteria, we can measure indices such as MICs or MBCs, that are defined as drug concentrations that will keep the bacteria from growing enough over an 18- to 24-hour period to cause turbidity in the growth medium (minimum inhibitory concentration) or to cause the number of bacteria to be reduced by 1000-fold over the 18 to 24 hour timeframe (minimum bactericidal concentration). This ability to measure the difficulty a drug will encounter inhibiting or killing different pathogens allows the drug exposure necessary to achieve different endpoints to be normalized across pathogens. In contrast, if one were to try to develop an antihypertensive agent, the true between-patient variability in the affinity with which a drug will bind to the receptor cannot currently be measured. Certainly, in the near future, the widespread use of phamacogenomic profiling, looking, for example, for specific single nucleotide polymorphisms (SNPs) or deletions will allow identification of patients likely to respond less well to therapy. Currently, however, this true between-patient variance in receptor affinity is completely unobserved variability.

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9

Pharmaceutical dosage forms: manufacturing and compounding

Powders

Introduction

Powder applications are expanding in a variety of highly developed fields, such as foods, cosmetics, chemicals, and many other fundamental fields, particularly in pharmaceuticals. The majority of active pharmaceutical ingredients (APIs) are administered as solid dosage forms, prepared by processing and formation of powders. A powder is defined as a dry, solid substance, consisting of a large number of finely divided particles (varying in size from 10 nm to 1000 μm), and typically obtained by crushing, grinding, or comminuting.[1] Powders have a large specific surface area and surface free energy, therefore, exhibiting some physical and chemical properties. Some of the properties related to pharmaceutics, such as particle size, shape, surface area, density, porosity, flowablility, will influence the forming, packing, and processing of a variety of dosage forms, such as granules, tablets, capsules, and suspensions. Additionally, the solubility and bioavailability of a drug formulation can be affected by some basic characteristics of powders as well. Besides acting as pharmaceutical excipients, such as diluents, disintegrating agents, and lubricants, powders can also present as a pharmaceutical dosage form. In short, powders are fundamental to pharmaceutics, which have a significant impact on the development, manufacture, quality control, and packing of a variety of dosage forms, including tablets, capsules, granules, suspensions, microcapsules, microspheres, and dry powder inhalers (DPIs).

Powders as a dosage form

When the term "powder" is referred to as a dosage form, it represents a formulation that is a mixture

of powdered drug and excipients. Powders are one of the most conventional dosage forms. Nowadays, with the rapid development of formulations containing highly potent compounds, the use of powders as a dosage form has declined. Most of the powders have been replaced by tablets and capsules. However, under certain circumstances, powders still have some advantages over solid dosage forms on the market. Advantages of powders include: chemically stable; relatively convenient, when able to provide a large dose of drugs, rather than capsules or tablets; and the dissolution rate of oral powders containing water soluble drugs is generally faster than that of tablets or capsules, in which disintegration of the tablet or the capsule shell is required prior to dissolution. Disadvantages of powders as a dosage form include: they are not convenient for patients to carry, compared to capsules or tablets; masking unpleasant tastes is difficult; potent drugs requiring low doses may not be appropriate; and irritating drugs, which can cause damage to the stomach, are not suitable. There are a variety of powdered dosage forms commercially available, such as bulk powders, divided powders, dusting powders, insufflations, and DPIs.

Bulk powders

Bulk powders refer to a mixture of all the materials, packed into a properly designed bulk container, such as a glass or plastic bottle. The major problem of bulk powders is the inaccuracy of dose. The dose of bulk powders can be affected by many factors, including the measuring device (spoon), storage humidity, degree of settling, and patient factors. For example, the dose of bulk powder may vary for patients using differently sized spoons, or even those using the same spoon according to their technique. In addition, drugs present in the bulk powders are better suited if they have a wider therapeutic window, a large dose, and pleasant taste. Effervescent powders are a special type of bulk powder. In addition to drugs and other excipients, effervescent powders contain an effervescent couple (i.e., sodium bicarbonate and citric acid), which reacts and effervesces when in contact with water. The effervescent dosage form is helpful to cover the unpleasant taste of salty or bitter drugs. In this section, bulk powders are described for internal use, including oral powders, as well as powders for injection. For drugs that are not stable when dissolved in an aqueous pharmaceutically acceptable diluent, such as water, sterile liquid can be added to sterile powders contained in ampules to form the solution just prior to use.

Divided powders

Divided powders are bulk powders in which the individual dose has been packed separately. The traditional packing of divided powders is in wrapped paper. However, many problems are involved in this, when the materials are volatile, hygroscopic, or deliquescent. Therefore modern packing methods have been developed to replace the use of paper wrapping, such as foil and plastic laminates. Effervescent powders can be packed into individual doses, because the plastic laminates can protect powders from moisture adsorption. The powdered product should always be protected from exposure to moisture.

Dusting powders

Dusting powders are designed for external use, acting as a therapeutic, lubricant, or protective. Dusting powders act locally and are intended to have no systemic absorption. Dusting powders are usually dispensed in a relatively fine state (micronized) to increase efficacy and decrease irritation. Dusting powders can be packed in glass or metal containers with a perforated lid to allow the powders to be dusted to the effective area. Excellent flowability is necessary for this dosage form. Pressure aerosols are another delivery form that can generate dusting powders. They are more expensive than the sifter-container, but several advantages are realized, such as convenient operation, and protection from moisture, air, and contamination.

Insufflations and Dry Powder Inhalers (DPIs)

Insufflations are fine powders of drugs, which are dosed into the nose, ear, or throat by the use of an insufflator. The use of conventional insufflators has declined, due to poor patient compliance and dose non-uniformity. Some newly developed devices have been introduced to replace the traditional insufflators. In these devices, drugs are usually dispensed with a carrier excipient, such as lactose, and placed into a hard gelatin capsule. When the device is operated, the capsule is broken and the fine powder is inhaled into the patient's body.[2]

Pulmonary delivery of dry powder formulations is a popular approach to deliver the drug to the lung locally, for the treatment of such diseases as asthma and chronic obstructive pulmonary disease (COPD). Dry powder inhalers are similar to the new insufflators previously discussed above.[3]

Solutions, emulsions, suspensions, and extracts

These dosage forms are prepared by employing pharmaceutically and therapeutically acceptable vehicles. The active ingredient(s) may be dissolved in aqueous media, an organic solvent, or a combination of the two, by suspending the drug (if it is insoluble) in an appropriate medium or by incorporating the active pharmaceutical ingredient into one of the phases of an oil and water emulsion.

These dosage forms are useful for a number of reasons. They can be formulated for different routes of administration: orally, introduction into body cavities, or external application. The dose can easily be adjusted by dilution, making the oral liquid form ready to be administered to children or people unable to swallow tablets or capsules. Extracts eliminate the need to isolate the drug in pure form, allow several ingredients to be administered from a single source (e.g., pancreatic extract), and permit the preliminary study of drugs from natural sources. Occasionally, solutions of drugs, such as potassium chloride, are used to minimize adverse effects in the gastrointestinal tract.

The preparation of these dosage forms involves several considerations on the part of the pharmacist: the purpose of the drug, internal or external use, solubility and concentration of the drug, selection of the liquid vehicle(s), physical and chemical stability of the drug and any excipients, preservation of the preparation, and use of appropriate excipients, such as buffers, solubility enhancers, suspending agents, emulsifying agents, viscosity controlling agents, colors, and flavors. Oral preparations require consideration be given to improving patient compliance by making an acceptable product; consequently, color, odor, and taste must be considered. The viscosity of a product must also be considered, so it has the proper palatability for an oral preparation and has the appropriate suspending properties, if it is an emulsion or suspension. The theory of solutions involves solubility, ionization, pH control through the use of buffers, and solubilization. Due to the complexity of some manufactured products, compounding may be carried out with the aid of linear programming models to obtain the optimal product. Sterility requirement information on the preparation and characteristics of liquid preparations that are intended for parenteral and ophthalmic use is given in the Sterilization section.

Much has been written about the biopharmaceutical properties of solid dosage forms. Many researchers begin their absorption studies of drugs administered in solution to assess the bioavailability relative to tablets and capsules. Absorption occurs when drugs are in a dissolved state; thus, it is frequently observed that the bioavailability of oral dosage forms decreases in the following order: aqueous solution > aqueous suspension > tablet or capsule. Formulation may influence the bioavailability and pharmacokinetics of drugs in solution, including drug concentration, volume of liquid administered, pH, ionic strength, buffer capacity, surface tension, specific gravity, viscosity, and excipients. Emulsions and suspensions are more complex systems; consequently, the bioavailability and pharmacokinetics of these systems may be affected by additional formulation factors, such as surfactants, type of viscosity agent, particle size and particle-size distribution, polymorphism, and solubility of drug in the oil phase.

Liquid preparations may be dispensed in one of three ways: (1) in its original container, (2) repackaging a bulk product at the time a prescription is presented by the patient, or (3) compounding the solution, suspension, or emulsion in the dispensary. Compounding may involve nothing more than mixing marketed products in the manner indicated on the prescription or, in specific instances, may require the incorporation of active ingredients and excipients in a logical and pharmaceutically acceptable manner into aqueous or organic solvents that will form the bulk of the product.

The pharmacist, in the first instance, depends on the pharmaceutical manufacturer to produce a product that is safe, efficacious, elegant, and stable until its expiration date, when stored at conditions described on its label. Manufacturers guarantee efficacy of their products, but, in some instances, consumer preference

is variable. For example, cough syrups marketed by two different manufacturers may contain the same active ingredient(s), and the relative merits of the two products may appear interchangeable. In such instances, the commercial advantage may be based on factors such as flavor, color, aroma, mouth feel, and packaging.

Solvents for liquid pharmaceutical preparations

The pharmacist's knowledge of the physical and chemical characteristics of a given drug dictates the selection of the appropriate solvent for a particular formulation. In addition to solubility, solvent selection is also based on clarity, toxicity, viscosity, compatibility with excipients, chemical inertness, palatability, odor, color, and economy. In most cases, especially solutions for oral, ophthalmic, or parenteral administration, water is the preferred solvent, because it meets the majority of the above criteria better than other available solvents. Often, an auxiliary solvent is also employed to augment the solvent action of water or to contribute to a product's chemical or physical stability. Alcohol, glycerin, and propylene glycol have been frequently used for these purposes.

Solvents such as acetone and isopropyl alcohol are too toxic for use in oral pharmaceutical preparations, but they are useful as solvents in organic chemistry and in the preparatory stages of drug development. For purposes such as this, certain solvents are officially recognized in the compendia. A number of fixed oils, such as corn oil, cottonseed oil, peanut oil, and sesame oil, serve useful solvent functions, particularly in the preparation of oleaginous injections, and are recognized in the compendia for this purpose.

Water

The major ingredient in most of the dosage forms described herein is water. It is used both as a vehicle and as a solvent for the desired flavoring or medicinal ingredients. Its tastelessness, freedom from irritating qualities, and lack of pharmacological activity make it ideal for such purposes. There is, however, a tendency to assume its purity is constant and it can be stored, handled, and used with a minimum of care. Although it is true that municipal supplies must comply with Environmental Protection Agency (EPA) regulations (or comparable regulations in other countries), drinking water must be purified before it can be used in pharmaceuticals. Water quality can have a significant impact on the stability of pharmaceutical dosage forms.[4] In manufacturing environments, the design of purified water systems must meet standards outlined in the *United States Pharmacopeia* (USP) and be validated.[5–8]

Five of the eight solvent waters described in the USP are used in the preparation of parenterals, irrigations, or inhalations. Purified Water must be used for all other pharmaceutical operations, dosage forms, and, as needed, in all USP tests and assays. It must meet rigid specifications for chemical purity. Purified Water is obtained by deionization, distillation, ion-exchange, reverse osmosis, filtration, or other suitable procedures. For parenteral administration, Water for Injection, Bacteriostatic Water for Injection, or Sterile Water for Injection must be used. Sterile Water may be sterile at the time of production but may lose this characteristic, if stored improperly.

The major impurities in water are calcium, iron, magnesium, manganese, silica, and sodium. These cations are combined with the bicarbonate, sulfate, or chloride anions. Hard waters are those that contain calcium and magnesium cations. Bicarbonates are the major impurity in alkaline waters. Deionization processes do not necessarily produce Purified Water that will comply with EPA requirements for drinking water. Resin columns retain phosphates and organic debris. Either alone or in combination, these substances can act as growth media for microorganisms. Observations have shown that deionized water containing 90 organisms/mL contained 106 organisms/mL after 24-hour storage. Ultraviolet radiant energy (240 to 280 nm), heat, or filtration can be used to limit the growth of, kill, or remove microorganisms in water. The latter method employs membrane filters and can be used to remove bacteria from heat-labile materials.

The phenomenon of osmosis involves the passage of water from a dilute solution across a semi-permeable membrane to a more concentrated solution. Flow of water can be stopped by applying pressure to the concentrated solution equal to the osmotic pressure. The flow of water can be reversed by applying a pressure greater than the osmotic pressure. The process of reverse osmosis uses

the latter principle; by applying pressure greater than the osmotic pressure to the concentrated solution (e.g., tap water), pure water may be obtained. Organic molecules are rejected on the basis of a sieve mechanism related to their size and shape. Small organic molecules, with a molecular weight smaller than approximately 200, will pass through the membrane material. Because there are few organic molecules with a molecular weight of less than 200 in the municipal water supply, reverse osmosis is sufficient for the removal of organic material. The pore sizes of the selectively permeable reverse-osmosis membranes are between 0.5 and 10 nm. Viruses and bacteria larger than 10 nm are rejected, if no imperfections exist in the membrane. The membranes may and do develop openings that permit the passage of microorganisms. Due to the semi-static conditions, bacteria can grow both upstream and downstream of the membrane.

Alcohols

Next to water, alcohol is the most commonly used solvent in pharmacy for many organic compounds. When mixed with water, a hydroalcoholic mixture is formed capable of dissolving both alcohol-soluble and water-soluble substances, a feature especially useful for extraction and purification of active constituents from crude drugs and synthetic procedures. Alcohol, USP, is 94.9% to 96.0% by volume, at 15.56°C of C_2H_5OH, and Dehydrated Alcohol, USP, contains not less than 99.5% C_2H_5OH by volume. Dehydrated alcohol is utilized when an essentially water-free alcohol is necessary. Alcohol is widely used for its miscibility with water and its ability to dissolve many water-insoluble ingredients, including drug substances, flavors, and antimicrobial preservatives. Alcohol is used in liquid products as an antimicrobial preservative or in conjunction with parabens, benzoates, sorbates, and other agents. Diluted Alcohol, NF, is prepared by mixing equal volumes of Alcohol, USP, and Purified Water, USP. Due to contraction upon mixing, the final volume of such mixtures is not the sum of the individual volumes of the two components, but is about 3% less.

The United States Food and Drug Administration (FDA) has expressed concern regarding undesired pharmacologic and potentially toxic effects of alcohol when ingested by children. For this reason, manufacturers of over-the-counter (OTC) oral drug products have been asked to restrict, if possible, the use of alcohol and include appropriate warnings in the labeling. For OTC oral products intended for children under 6 years of age, the recommended alcohol content limit is 0.5%; for products intended for children 6 to 12 years of age, the recommended limit is 5%; and for products recommended for children older than 12 years of age and for adults, the recommended limit is 10%.

Rubbing Alcohol, USP, must be manufactured in accordance with the requirements of the US Treasury Department, Bureau of Alcohol, Tobacco, and Firearms, Formula 23-H (8 parts by volume of acetone, 1.5 parts by volume of methyl isobutyl ketone, and 100 parts by volume of ethyl alcohol). It contains not less than 68.5% and not more than 71.5% by volume of dehydrated alcohol, the remainder consisting of water and the denaturants with or without color additives and perfume oils. Rubbing Alcohol contains in each 100 mL not less than 355 mg of sucrose octaacetate or not less than 1.40 mg of denatonium benzoate. The preparation may be colored with one or more color additives listed by the FDA for use in drugs, and a suitable stabilizer may be added. The use of this denaturant mixture makes the separation of ethyl alcohol from the denaturants a virtually impossible task with ordinary distillation apparatus. This discourages the illegal removal and use of the alcoholic content of Rubbing Alcohol as a beverage. The product is volatile and extremely flammable and should be stored in tight containers remote from ignition sources. It is used externally as a soothing rub for bedridden patients, a germicide for instruments, and a skin cleanser prior to injection.

Isopropyl Rubbing Alcohol is about 70% by volume isopropyl alcohol, the remainder consisting of water with or without color additives, stabilizers, and perfume oils. It is used exclusively as a vehicle in topical products and applications. This preparation and a commercially available 91% isopropyl alcohol solution are commonly employed to disinfect needles and syringes for hypodermic injections of insulin and for disinfecting the skin.

Glycerin is a clear, syrupy liquid with a sweet taste and is miscible with water and alcohol. Glycerin is used in a wide variety of pharmaceutical formulations, including oral, otic, ophthalmic, topical, and

parenteral preparations. In topical pharmaceutical formulations and cosmetics, glycerin is used primarily for its humectant and emollient properties. In parenteral formulations, glycerin is used mainly as a solvent. In oral solutions, glycerin is used as a solvent, sweetening agent, antimicrobial preservative, and viscosity-increasing agent.

Propylene glycol has become widely used as a solvent, extractant, and preservative in a variety of liquid pharmaceutical formulations, including parenterals. Propylene glycol is a viscous liquid and is miscible with water and alcohol. It is a useful solvent with a wide range of applications and is often used in place of glycerin. As an antiseptic, it is similar to ethanol, and against molds it is similar to glycerin and only slightly less effective than ethanol. Propylene glycol is also used as a carrier for emulsifiers and as a vehicle for flavors, as opposed to ethanol, due to its lack of volatility.

Stability considerations

The stability of the active ingredient in the final product is a primary concern to the formulator, the pharmacist, and the patient. In general, drug substances are less stable in aqueous media than solid dosage forms, and it is important to properly stabilize and preserve solutions, suspensions, and emulsions that contain water. Acid–base reactions, acid or base catalysis, oxidation, and reduction can occur in these products. Reactions and interactions (adsorption) can arise from ingredient–ingredient interactions or container–product interactions. For pH sensitive compounds, any of these interactions may alter the pH and cause precipitation.

Vitamins, essential oils, and almost all fats and oils can be oxidized. Formulators use the word "autoxidation," when the ingredient(s) reacts with oxygen but without drastic external interference. Such reactions can be initiated by heat, light, including ultraviolet radiant energy, peroxides, or other labile compounds or heavy metals, such as copper or iron. This initiation step results in the formation of a free radical that then reacts with oxygen. The free radical is regenerated and reacts with more oxygen (propagation). The reactions are terminated when the free radicals react with one another.

The effect of trace metals can be minimized using chelating agents such as citric acid or EDTA. Antioxidants may retard or delay oxidation by rapidly reacting with free radicals as they are formed (quenching). Common antioxidants include propyl, octyl, and dodecyl esters of gallic acid, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), and the tocopherols or vitamin E. Connors and coworkers provide a detailed approach for the prevention of oxidative degradation of pharmaceuticals.[9] Table 9.1 lists common antioxidants and chelating agents used in pharmaceutical preparations.

The USP states that, if a product must be repackaged, the container specified by the compendium must be used. For example, a suitable opaque plastic container should be used, if a light-resistant container is specified. If a product is diluted, or where two products are mixed, the pharmacist should use his or her knowledge to guard against incompatibility

Table 9.1 Common antioxidants and chelating agents used in liquid pharmaceutical dosage forms

Antioxidants	Alpha tocopherol Ascorbic acid Acorbyl palmitate Butylated hydroxyanisole Butylated hydroxytoluene Monothioglycerol Potassium metabisulfite Propionic acid Propyl gallate Sodium ascorbate Sodium bisulfite Sodium metabisulfite Sodium sulfite
Chelating Agents	Citric acid monohydrate Disodium edetate Dipotassium edetate Edetic acid Fumaric acid Malic acid Phosphoric acid Sodium edetate Tartaric acid Trisodium edetate

and instability. Oral antibiotic preparations constituted into liquid form should never be mixed with other products. If the chemical stability of extemporaneously prepared liquid preparations is unknown, their use should be minimized and every care taken to ensure product characteristics will not change while used by the patient.

Due to the number of excipients and additives in these preparations, it is recommended that all the ingredients be listed on the container to reduce the risks that confront hypersensitive patients when these products are administered. Finally, the pharmacist should inform the patient regarding the appropriate use of the product, the proper storage conditions, and the time after which it should be discarded.

Preservatives

In addition to stabilization of pharmaceutical preparations against chemical and physical degradation, liquid and semisolid preparations must be protected against microbial contamination. Nearly all products described in this section contain water and, thus, with certain exceptions, such as aqueous acids, will support microbial growth. Aqueous solutions, syrups, emulsions, and suspensions often provide excellent growth media for micro-organisms, such as molds, yeast, and bacteria (typically *Pseudomonas, E.coli, Salmonella* and *Staphylococcus*).

Kurup and Wan describe many preparations that are not preserved adequately and are not able to resist microbial contamination.[10] Products such as ophthalmic and injectable preparations are sterilized by autoclaving (20 minutes at 15 pounds of pressure at 120°C, followed by dry heat at 180°C for 1 hour) or filtration. However, many require the presence of an antimicrobial preservative to maintain aseptic conditions throughout their stated shelf-life.[11] Certain hydroalcoholic and alcoholic preparations do not require addition of a chemical preservative if the alcohol content is sufficient to prevent microbial growth: an alcohol content of 15% by weight in acid solutions and 18% by weight in alkaline solutions is sufficient to prevent microbial growth. Most alcohol containing preparations, such as elixirs, spirits, and tinctures, are self-preserving and do not require preservation. Indeed, the formulator should challenge any new preparation by procedures described in the General Tests and Assays, parts <51> and <61> of the USP, and other methods reported in the literature.[12–15]

When a preservative is required, its selection is based on several considerations, in particular, the site of use, whether internal, external, or ophthalmic.[16] Several researchers have described various interactions that must be considered when preservatives are selected.[17,18] The major criteria that should be considered in selecting a preservative are as follows: its physicochemical properties, such as solubility and dissociation constant, and it should be effective against a wide spectrum of microorganisms, stable for its shelf-life, nontoxic, nonsensitizing, compatible with the ingredients in the dosage form, inexpensive, and relatively free of taste and odor.

The chosen preservative should be sufficiently stable and soluble to achieve adequate concentration to provide protection. This choice is more critical in two- and three-phase emulsion systems in which the preservative may be more soluble in the oil phase than in the aqueous phase.[15,19] The pH of the preparation must be considered to ensure the preservative does not dissociate, rendering it ineffective, or degrade by acid- or base-catalyzed hydrolysis. The undissociated moiety or molecular form of a preservative possesses preservative capacity because the ionized form is unable to penetrate microorganisms. The preservative must be compatible with the formulation ingredients and the product container and closure. Finally, the preservative must not impact the safety or comfort of the patient when administered. For instance, preservatives used in ophthalmic preparations must be non-irritating. Chlorobutanol, benzalkonium chloride, and phenylmercuric nitrate are commonly used in these applications.

Although few microorganisms are viable below a pH of 3 or above a pH of 9, most aqueous pharmaceutical preparations are manufactured within the favorable pH range. Acidic preservatives, such as benzoic acid, boric acid, and sorbic acid, are less dissociated and more effective in acidic formulations. Similarly, alkaline preservatives are less effective in acidic or neutral conditions and more effective in alkaline formulations. The scientific literature is rife with examples of incompatibilities between preservatives and other pharmaceutical adjuncts.[20–22] Commonly used macromolecules, including cellulose derivatives, polyethylene glycol, and tragacanth gum, have been

reported to cause preservative failure, due to binding and adsorption.[23,24]

The mode of action by which preservatives interfere with microbial growth, multiplication, and metabolism occurs through one of several mechanisms. Preservatives often alter cell membrane permeability, causing leakage of cell constituents (partial lysis), complete lysis and cytoplasmic leakage, and/or coagulation of cytoplasmic constituents (protein precipitation). Other preservatives inhibit cellular metabolism by interference with enzyme systems or cell wall synthesis, oxidation of cellular constituents, or hydrolysis.

Table 9.2 lists preservatives commonly used in pharmaceutical products with typical concentration levels. Preservatives may be grouped into a number of classes, depending upon their molecular structure. These basic groups are discussed below.

Alcohols

Ethanol is useful as a preservative; when it is used as a solvent, however, it does need a relatively high concentration (somewhat greater than 15%) to be effective. Too high a concentration may result in incompatibilities in suspension and emulsion systems. Propylene glycol also is used as a solvent in oral solutions and topical preparations, and it can function as a preservative in the range 15 to 30%. It is not volatile like ethanol and is used frequently not only in solutions, but also in suspensions and emulsions. Chlorobutanol and phenylethyl alcohol are other alcohols used in lower concentrations (approximately 1%) as preservatives.

Acids

Benzoic acid has a low solubility in water (about 0.34% at 25°C) but the apparent aqueous solubility of benzoic acid may be enhanced by the addition of citric acid or sodium acetate to the solution. The concentration range used for inhibitory action varies from 0.1% to 0.5%. Activity depends on the pH of the medium, because only the undissociated acid has antimicrobial properties. Optimum activity occurs at pH values below 4.5; at values above pH 5, benzoic acid is almost inactive.[25] It has been reported that antimicrobial activity of benzoic acid is enhanced by the addition of the basic protein protamine.[26] Sorbic acid also has a low solubility in water, 0.3% at 30°C. Suitable concentrations for preservative action are in the range 0.05% to 2%. Its preservative action is due to the nonionized form; consequently, it is only effective in acid media. The optimum antibacterial activity is obtained at pH 4.5, and practically no activity is observed above pH 6. Sorbic acid is subject to oxidation, particularly in the presence of light and in aqueous solutions. Activity against bacteria can be variable, due to its limited stability. Thus, sorbic acid is frequently used in combination with other antimicrobial preservatives or glycols in which synergistic effects occur.

Esters

Parabens are esters of *p*-hydroxybenzoic acid and include the methyl, ethyl, propyl, and butyl derivatives. The water solubility of the parabens decreases as the molecular weight increases from 0.25% for the methyl ester to 0.02% for the butyl ester. These compounds are used widely in pharmaceutical products, stable over a pH range of 4 to 8, and have a broad spectrum of antimicrobial activity, although they are most effective against yeasts and molds. Antimicrobial activity increases as the chain length of the alkyl moiety is increased, but aqueous solubility decreases; therefore, a mixture of parabens is frequently used to provide effective preservation. Preservative efficacy is also improved by the addition of propylene glycol (2% to 5%) or by using parabens in combination with other antimicrobial agents, such as imidurea. Activity is reduced in the presence of nonionic surface active agents, due to binding. In alkaline solutions, ionization takes place, and this reduces their activity; in addition, hydrolytic decomposition of the ester group occurs with a loss of activity.

Quaternary ammonium compounds

Benzalkonium chloride is a mixture consisting principally of the homologs $C_{12}H_{25}$ and $C_{14}H_{29}$. This preservative is used at a relatively low concentration (0.002% to 0.02%) depending on the nature of the pharmaceutical product. This class of compounds has an optimal activity over the pH range 4 to 10 and is quite stable at room temperature. Due to the cationic nature of this type of preservative, it is incompatible with many anionic compounds and can bind to nonionic surfactants. It is used in preparations for external use or those solutions that come

Table 9.2 Common preservatives used in liquid pharmaceutical dosage forms and their typical concentration levels

Antimicrobial preservatives	Typical usage level (% w/w)	Antifungal preservatives	Typical usage level (% w/w)
Benzalkonium Chloride	0.002–0.02%	Butyl Paraben	0.1–0.4%
Benzethonium Chloride	0.01–0.02%	Methyl Paraben	0.1–0.25%
Benzyl Alcohol	3.0%	Ethyl Paraben	0.1–0.25%
Bronopol	0.01–0.1%	Propyl Paraben	0.1–0.25%
Cetrimide	0.005%	Benzoic Acid	0.1–0.5%
Cetylpyridinium chloride	0.0005–0.0007%	Potassium sorbate	0.1–0.2%
Chlorhexidine	0.002–0.5%	Sodium Benzoate	0.1–0.2%
Chlorobutanol	0.5%	Sodium Propionate	5–10%
Chlorocresol	0.2%	Sorbic Acid	0.05–0.2%
Chloroxylenol	0.1–0.8%		
Cresol	0.15–0.3%		
Ethyl Alcohol	15–20%		
Glycerin	20–30%		
Hexetidine	0.1%		
Imidurea	0.03–0.5%		
Phenol	0.1–0.5%		
Phenoxyethanol	0.5–1.0%		
Phenylethyl Alcohol	0.25–0.5%		
Phenylmercuric Nitrate	0.002–0.01%		
Propylene Glycol	15–30%		
Thimerosal	0.1%		

in contact with mucous membranes. In ophthalmic preparations, benzalkonium chloride is widely used at a concentration of 0.01% to 0.02% w/w. Often, it is used in combination with other preservatives or excipients, particularly 0.1% w/v disodium edetate, to enhance its antimicrobial activity against strains of *Pseudomonas*. A concentration of 0.002% to 0.02% is used in nasal and otic formulations, sometimes in combination with 0.002% to 0.005% thimerosal. Benzalkonium chloride 0.01% w/v is also employed as a preservative in small-volume parenteral products.

Clearly, when the pharmacist dispenses or compounds liquid preparations, responsibility is assumed, along with the manufacturer, for the maintenance of product stability. General chapter <1191> of the USP describes stability considerations for dispensing, which should be studied in detail.[12] Stock should be rotated and replaced, if expiration dates on the label so indicate. Products should be stored in the manner indicated on the manufacturer's label or in the compendium. Further, products should be checked for evidence of instability. With respect to solutions, elixirs, and syrups, major signs of instability are color change, precipitation, and evidence of microbial or chemical gas formation. Emulsions may cream, but, if they break (i.e., there is a separation of an oil phase), the product is considered unstable. Sedimentation and caking are primary indications of instability in suspensions. The presence of large particles may mean excessive crystal growth has occurred (Ostwald ripening).

Sterilization processes and sterility assurance

Microorganisms represent a potential threat to human health in various settings. The presence of some microorganisms in foods, pharmaceuticals and even the environment can cause illness and even death. Louis Pasteur established the link between microbes and disease, and his seminal work influenced Joseph Lister to use phenol to reduce contamination risk during invasive surgery in the late 1800s.[27] This knowledge led to the introduction of multiple measures to mitigate the risks associated with microbial contamination and led to the development of sterilization methods, sanitization practices, and other microbial control measures intended to assure product and procedural safety.

In the pharmaceutical and medical device industries, sterile products are produced using two primary methods: terminal sterilization or aseptic processing. Where products are manufactured with aseptic processing followed by terminal sterilization, there is little difference in the manner in which either process is controlled compared to when they are performed individually.

In addition to the therapeutic goal of all medical products there is a safety requirement, a major component of which in the context of sterile pharmaceuticals and medical devices is "sterility". Sterility, which has been defined as the absence of life (or inability to reproduce), is an absolute concept. Items are "sterile," or they are not; there is no middle ground. However, at the present time, there are no nondestructive means to demonstrate sterility. Instead we define processes to attain that goal, subject the materials to these processes, and then estimate the results. For the lethal sterilization processes, whether terminal or in-process, the "sterility" expectation is fulfilled by demonstrating a minimum Probability of a Non-Sterile Unit (PNSU) of not more than one positive unit in 1 000 0000 units or 1×10^{-6}.[28,29] It must be understood that the microorganism of concern in any process is the bioburden present prior to treatment. In actual practice this target is often exceeded by a substantial margin as the industry is inherently conservative about such a critical quality attribute. The focus of the treatment is on the removal/destruction of any bioburden microorganisms that might be present on/in the materials prior to the process. Where liquids are sterilized by filtration, the filters utilized are shown capable of removing a minimum of seven logs of a challenge microorganism specifically cultured for its small size and potential penetration of the filter. In aseptic processing, which relies on prior sterilization of the materials, equipment, and other items, the goal is to prevent the recontamination of those items in the assembly process. Aseptic process simulations are used to demonstrate contamination rates of not more than one unit in 5000 units. The various estimations of performance from these processes are established during the validation efforts with the assumption that routine operations deliver comparable (or superior) results. In most instances everyday manufacturing performance is well in excess of the targeted and demonstrated minimum levels established by the validation efforts. Nevertheless, the level of sterility present after any of these processes is never known with any degree of precision.

Sterilization and aseptic processing are essential practices for healthcare product manufacture and many healthcare services. The execution of these processes in an appropriate manner is essential for patient safety. Products that are sterile but non-stable, due to excessive conditions during sterilization, are unusable. Products that are stable but unsafe as a

result of inadequately robust aseptic processing are equally inappropriate. Achieving suitably safe and stable products for administration as parenterals, ophthalmics, or by inhalation requires careful consideration of many factors, including the method of sterilization, its effects on the materials, and how those materials are handled post-sterilization.

Parenteral preparations

Parenteral (Gk, *para enteron*, beside the intestine) dosage forms differ from all other drug dosage forms, because they are injected directly into body tissue through the primary protective system of the human body, the skin, and mucous membranes. They must be exceptionally pure and free from physical, chemical, and biological contaminants. These requirements place a heavy responsibility on the pharmaceutical industry to practice current good manufacturing practices (cGMPs) in the manufacture of parenteral dosage forms and on pharmacists and other healthcare professionals to practice good aseptic practices (GAPs) in dispensing parenteral dosage forms for administration to patients.

Certain pharmaceutical agents, particularly peptides, proteins, and many chemotherapeutic agents, can only be given parenterally, because they are inactivated in the gastrointestinal tract when given by mouth. Parenterally-administered drugs are relatively unstable and generally highly potent drugs that require strict control of administration to the patient. Due to the advent of biotechnology, parenteral products have grown in number and usage around the world. Parenteral drugs are formulated as solutions, suspensions, emulsions, liposomes, microspheres, nanosystems, and powders to be reconstituted as solutions.

Overview of unique characteristics of parenteral dosage forms

Parenteral products are unique from any other type of pharmaceutical dosage form for the following reasons:

- All produces must be sterile.
- All products must be free from pyrogenic (endotoxin) contamination.
- Injectable solutions must be free from visible particulate matter. This includes reconstituted sterile powders.
- Products should be isotonic, although strictness of isotonicity depends on the route of administration. Products administered into the cerebrospinal fluid must be isotonic. Ophthalmic products, although not parenteral, must also be isotonic. Products to be administered by bolus injection by routes other than intravenous (IV) should be isotonic, or at least very close to isotonicity. IV infusions must be isotonic.
- All products must be stable, not only chemically and physically like all other dosage forms, but also "stable" microbiologically (i.e., sterility, freedom from pyrogenic and visible particulate contamination must be maintained throughout the shelf-life of the product).
- Products must be compatible, if applicable, with IV diluents, delivery systems, and other drug products co-administered.

General manufacturing process

The preparation of a parenteral product may encompass four general areas:

1. Procurement and accumulation of all components in a warehouse area, until released to manufacturing;
2. Processing the dosage form in appropriately designed and operated facilities;
3. Packaging and labeling in a quarantine area, to ensure integrity and completion of the product; and
4. Controlling the quality of the product throughout the process.

Procurement encompasses selecting and testing according to specifications of the raw-material ingredients and the containers and closures for the primary and secondary packages. Microbiological purity, in the form of bioburden and endotoxin levels, has become standard requirements for raw materials.

Processing includes cleaning containers and equipment to validated specifications, compounding the solution (or other dosage form), filtering the solution, sanitizing or sterilizing the containers and equipment,

filling measured quantities of product into the sterile containers, stoppering (either completely or partially for products to be freeze-dried), freeze-drying, terminal sterilization (if possible), and final sealing of the final primary container.

Packaging normally consists of the labeling and cartoning of filled and sealed primary containers. Control of quality begins with the incoming supplies, being sure that specifications are met. Careful control of labels is vitally important, as errors in labeling can be dangerous for the consumer. Each step of the process involves checks and tests to ensure the required specifications at the respective step are being met. Labeling and final packaging operations are becoming more automated.

The quality control unit is responsible for reviewing the batch history and performing the release testing required to clear the product for shipment to users. A common FDA citation for potential violation of cGMP is the lack of oversight by the quality control unit in batch testing and review and approval of results.

Components

Components of parenteral products include the active ingredient, formulation additives, vehicle(s), and primary container and closure. Establishing specifications to ensure the quality of each of these components of an injection is essential. Secondary packaging is relevant more to marketing considerations, although some drug products might rely on secondary packaging for stability considerations, such as added protection from light exposure for light-sensitive drugs and antimicrobial preservatives.

The most stringent chemical-purity requirements will normally be encountered with aqueous solutions, particularly if the product is sterilized at an elevated temperature where reaction rates will be accelerated greatly. Dry preparations pose relatively few reaction problems but may require definitive physical specifications for ingredients that must have certain solution or dispersion characteristics when a vehicle is added.

Containers and closures are in prolonged, intimate contact with the product and may release substances into, or remove ingredients from, the product. Rubber closures are especially problematic (sorption, leachables, air and moisture transmission properties), if not properly evaluated for compatibility with the final product. Assessment and selection of containers and closures are essential for final product formulation, to ensure the product retains its purity, potency, and quality during the intimate contact with the container throughout its shelf-life. Administration devices (e.g., syringes, tubing, transfer sets) that come in contact with the product should be assessed and selected with the same care as are containers and closures, even though the contact period is usually brief.

Pharmaceutical compounding: USP <797> sterile preparations

Medications that are compounded and injected into humans or other animals must be sterile and free from contaminants and pyrogen. Mortality and morbidity from contaminants being injected into the blood-stream require that personnel involved in intravenous compounding follow more stringent guidelines when compounding sterile preparations. In 2004, the USP/NF published standards of practice for compounding sterile preparations. The chapter, referred to as USP <797>, was developed in part as a result of patient injuries and deaths that had occurred secondary to problems with medication delivery and sterile compounding.[30] Publication of USP <797> is meant to increase practitioners' understanding of how sterile preparations must be prepared in order to achieve safe, accurate, quality sterile compounds for patient use.[31] The chapter was updated in 2008 to clarify risk levels, primary engineering controls (PECs), personnel training and evaluation, verification of compounding accuracy, finished preparation checks and tests, storage and beyond use dating, maintenance of sterility and purity of dispensed and distributed sterile preparations, and suggested standard operating procedures.[31] The 2008 USP <797> also introduced new topics and made some significant changes in the areas of immediate use sterile preparations, single use and multiple dose vials, hazardous compounding including radiopharmaceuticals and allergen extracts, environmental quality control, personnel training and competency evaluation.[31] Since its publication in 2008, the International Journal of Pharmaceutical Compounding and the American Society of Health Systems Pharmacy

(ASHP) have published numerous articles to help practitioners implement chapter USP <797> into all aspects of sterile compounding.[30–52] The objective of the USP <797> chapter is to "describe conditions and practices to prevent harm, including death, to patients that could result from (1) microbial contamination (nonsterility), (2) excessive bacterial endotoxins, (3) variability in the intended strength of correct ingredients that exceeds either monograph limits for official articles [sic] or 10% for nonofficial articles, (4) unintended chemical and physical contaminants, and (5) ingredients of inappropriate quality in compounded sterile preparations (CSPs)." [31] While many pharmacies have become compliant, others cite costs and lack of scientific justification to support these changes.[32,33] Most hospitals and facilities have gradually implemented the standards from the original recommendations in 2004, and are now taking steps towards becoming compliant with the 2008 revisions.[32,33]

In order to facilitate implementation of the standards, Baxter Healthcare Corporation and ASHP developed a discussion guide that suggests among other things, that a gap analysis be completed. A gap analysis in this context is used to identify areas in need of improvement in sterile compounding facilities.[30] USP <797> requirements should be compared to the current practices of compounding personnel and environmental standards of the compounding facility to determine where "gaps" exist. Successful completion of a gap analysis and subsequent revisions to address the identified gaps may result in a direct positive impact on the delivery of quality patient care and may be used to demonstrate compliance with the standards to regulatory authorities.[34]

In an effort to control the purity and sterility of intravenous medications, the USP/NF developed rules and recommendations termed USP Chapter <797>. These rules and recommendations apply to all injected medications whether made by pharmacy, nursing, medicine, dental, or and any other healthcare provider. The costs associated with implementation have created some controversy. However, a majority of institutions have come into compliance with the 2004 standards, and are now in the process of implementing the 2008 standards. The risks associated with injectable medications are high when standards are not followed. Quality patient care must be the number one priority. Developing quality assurance programs and following standard operating procedures are necessary to maintain continuous quality care to patients.

Ophthalmic preparations

Introduction[53]

Ophthalmic preparations are specialized dosage forms designed to be instilled onto the external surface of the eye (topical), administered inside the eye (intraocular) or adjacent to it (periocular, e.g., juxtascleral or subtenon), or used in conjunction with an ophthalmic device. The last includes preparations used in conjunction with surgical implantation (such as an intraocular lens) and dry eye formulations compatible with a punctal appliance (e.g., a punctal plug), and extends to a variety of solutions used in the maintenance of contact lenses. The preparations may have any of several purposes (e.g., therapeutic, prophylactic, or palliative for topically administered agents) but include mechanical, chemical, and biochemical actions of agents used in the care of ocular appliances and tissue prophylaxis during or following surgery. Because of the dangers associated with the administration or repetitive administration of intraocular and periocular preparations, their suitability is restricted to therapeutic applications or surgical adjuncts.

The versatility of dosage forms of ophthalmic preparations allows the clinician to choose the form most suitable for the function desired. Therapeutically active formulations can be designed to provide extended action for convenience or for reduction in risk of repetitive administration, improved bioavailability of the agent, or improved delivery to a targeted tissue. The residence of an ocular preparation can range from the few seconds needed for tears to clear an irritating substance; to hours for a gel, a gel-forming solution, or an ointment; to months or years for an intraocular or periocular dosage form. A preparation may be strictly therapeutic or may serve in prophylaxis. The latter includes surgical adjuncts to maintain the health of fragile cells, and postsurgical or posttrauma preparations designed to prevent or reduce the likelihood of infection. Another form of prophylaxis, one for a device, is the antisoiling function provided by some contact lens solutions.

Ophthalmic preparations are similar to parenteral dosage forms in their requirement for sterility as well as considerations for osmotic pressure (tonicity), preservation, tissue compatibility, the avoidance of pyrogens in intraocular dosage forms, particulate matter, and suitable packaging.

Topical therapeutic dosage forms have customarily been restricted to solutions, suspensions, and ointments. But with advances in materials science, the range of ophthalmic dosage forms has expanded significantly to include gels, either preformed or spontaneous gels responsive to the ocular environment, and ocular inserts, both forms reducing dosage frequency. These are most often multidose products, containing suitable preservative(s) to meet compendial preservative effectiveness test (e.g., *US Pharmacopeia* (USP),[54] European *Pharmacopoeia*,[55] or *Japanese Pharmacopoeia*[56]) requirements. Now, however, single-dose units (also referred to as unit-dose products) that are preservative-free preparations have become available, generally packaged in 0.25 mL to up to 0.8 mL form-fill-seal plastic containers. These unit-dose containers are designed to be discarded after a single use or after a single day's use if the container has a reclosable feature and the product is so labeled.

Injections and implants have been developed for intraocular drug delivery. Irrigating solutions and viscoelastic gels are available specifically for adjunctive use in ophthalmic surgery. Specialized formulations are now available for use in the care of contact lenses. The designs of these preparations, meeting all of the requirements for safety, efficacy, component compatibility, tissue acceptability, storage, shipping, and shelf- life, are beyond the scope of this review. Nonetheless, a description of the requirements and the designs for some of these formulations should be illustrative and didactic.

From a historical perspective, preparations intended for treatment of eye disorders can be traced to the writings of the Egyptians, Greeks, and Romans. In the Middle Ages, *collyria* were referred to as materials that were dissolved in water, milk, or egg white and used as eyedrops. One such collyrium contained the mydriatic substance belladonna to dilate the pupils of milady's eyes for cosmetic purposes.

From the time of belladonna collyria, ophthalmic technology progressed at a pharmaceutical snail's pace until after World War II. Before World War II and into the 1950s, ophthalmic preparations were mostly compounded by the pharmacist for immediate use. Not until 1953 was there a legal requirement by the FDA that all manufactured ophthalmic solutions be sterile. The range of medicinal agents to treat eye disorders was limited, as was the state of eye surgery and vision correction, which was limited to eyeglasses. In the past 50 years, a modern pharmaceutical industry specializing in ophthalmic preparations has developed to support the advances in diagnosis and treatment of eye diseases, in eye surgery, and in contact lens design and use. Because of the variety of ophthalmic products readily available commercially, the pharmacist now is rarely required to compound a patient's ophthalmic prescription. More important, however, is that the pharmacist appreciate even subtle differences in formulations that may impact efficacy, comfort, compatibility, or suitability of a preparation for particular patients.

Currently and in the future, in addition to the advances in dosage-form technology, drug molecules will be designed and optimized specifically for ophthalmic application. New therapies may become available for preventing blindness caused by degenerative disease – including age-related macular degeneration (AMD), macular edema, and diabetic retinopathy. Biotechnological products may also become available to treat causes of multifactorial eye disorders like glaucoma. Such specialized therapeutic agents also will require carefully designed and compatible dosage forms.

Types of ophthalmic dosage forms

Ophthalmic products include prescription and OTC drugs, products for the care of contact lenses, and products used in conjunction with ocular surgery. This section will focus on the pharmaceutical aspects of the various ophthalmic dosage forms encompassed by these types of products. The therapeutic uses of individual products can be found in several reference books along with the individual product's labeling.[57,58]

Ophthalmic solutions

These are by far the most common dosage forms for delivering drugs to the eye. By definition, ingredients are completely soluble such that dose uniformity is

not an issue, and there is little physical interference with vision. The principal disadvantage of solutions is their relatively brief contact time with the drug and the absorbing tissues of the external eye. Contact time can be increased by the inclusion of viscosity-imparting agents; however, their use is limited to relatively low viscosities so as to allow dispensing of the eyedrop from the container or eyedropper and to minimize excessive blurring of vision. A residue can be produced on the eyelashes and around the eye when any excess of a viscous solution spills out of the eye and dries. The residue usually can be removed easily by careful wiping with a moist towel to the closed eye.

Gel-forming solutions

Ophthalmic solutions (usually water-based), which contain a polymer system that is a low-viscosity liquid in the container but gels on contact with the tear fluid, have increased contact time and can provide increased drug absorption and prolonged duration of therapeutic effect. The liquid-to-gel phase transition can be triggered by a change in temperature, pH, ionic strength, or presence of tear proteins, depending on the particular polymer system employed. Timolol maleate gel-forming solutions formulated with specific patented gellan or xanthan gums have clinically demonstrated prolonged duration of intraocular pressure (IOP) lowering, such that their dosing frequency can be reduced from twice to once a day.[59,60]

Powders for solutions

Drugs that have very limited stability in aqueous solution can sometimes be prepared as sterile powders for reconstitution by the pharmacist before dispensing to the patient. The sterile powder should be aseptically reconstituted with the accompanying sterile diluent that has been optimized for dissolution, preservation, and stability. The pharmacist must convey to the patient any special storage instructions, including the expiration date.

Ophthalmic suspensions

Suspensions are dispersions of finely divided, relatively insoluble drug substances in an aqueous vehicle containing suitable suspending and dispersing agents. The vehicle is, among other things, a saturated solution of the drug substance. Because of a tendency of particles to be retained in the cul-de-sac, the contact time and duration of action of a suspension could theoretically exceed that of a solution. The drug is absorbed from solution, and the solution concentration is replenished from retained particles. Each of these actions is a function of particle size, with solubility rate being favored by smaller size and retention favored by a larger size; thus, optimum activity should result from an optimum particle size.

For aqueous suspensions the parameters of intrinsic solubility and dissolution rate must be considered. The intrinsic solubility determines the amount of drug actually in solution and available for immediate absorption upon instillation of the dose. As the intrinsic solubility of the drug increases, the concentration of the drug in the saturated solution surrounding the suspended drug particle also increases. For this reason, any comparison of different drugs in suspension systems should include their relative intrinsic solubilities. The observed differences in their biological activities may be ascribed wholly or in part to the differences in this physical parameter. As the drug penetrates the cornea and the initial saturated solution becomes depleted, the particles must dissolve to provide a further supply of the drug. The requirement here is that the particles must undergo significant dissolution within the residence time of the dose in the eye if any benefit is to be gained from their presence in the dosing system.

For a drug whose dissolution rate is rapid, the dissolution requirement may present few problems, but for a slowly soluble substance the dissolution rate becomes critical. If the dissolution rate is not sufficiently rapid to supply significant additional dissolved drug, there is the possibility that the slowly soluble substance in suspension provides no more drug to the aqueous humor than does a more dilute suspension or a saturated solution of the substance in a similar vehicle. Obviously, the particle size of the suspended drug affects the surface area available for dissolution. Particle size also plays an important part in the irritation potential of the dosing system. This consideration is important, because irritation produces excessive tearing and rapid drainage of the instilled dose, as discussed earlier. It has been recommended that particles be smaller than 10 μm to minimize irritation to the eye. It should be kept in mind, however, that in any suspension system the effects of prolonged

storage and changes in storage temperature might cause the smallest particles to dissolve and the largest particles to become larger.

The pharmacist should be aware of two potential difficulties inherent in suspension dosage forms. In the first instance, dosage uniformity nearly always requires brisk shaking to distribute the suspended drug. Adequate shaking is a function not only of the suitability of the suspension formulation but also – and most importantly – patient compliance. Studies have demonstrated that a significant number of patients may not shake the container at all; others may contribute a few trivial shakes. The pharmacist should use a "Shake Well" label and counsel the patient whenever an ophthalmic suspension is dispensed. An improved ophthalmic suspension has been developed for insoluble drugs such as steroids, which tend to cake upon settling.[61] The improved suspension controls the flocculation of the drug particles such that they remain substantially resuspended for months and provides for easy resuspension of any settled particles. Nonetheless, the pharmacist also should be aware of the possibility of crystal growth over time. This potential stability problem is especially problematic for drug substances whose solubility is significantly dependent on temperature. The majority of suspension products have a "Do Not Freeze" warning on the label, because they are likely to agglomerate on freezing and will not be resuspended by simple shaking.

A second and infrequently occurring characteristic of suspensions is the phenomenon of polymorphism, or the ability of a substance to exist in several different crystalline forms. A change in crystal structure may occur during storage, resulting in an increase (or decrease) in crystal size and alteration in the suspension characteristics, causing solubility changes reflected in increased or decreased bioavailability. Manufacturers of commercial suspensions take these possibilities into account in the development and testing of the final formulation and the labeled storage conditions.

In some cases a water-soluble drug has been converted to an insoluble form and formulated as a suspension to improve the drug's stability, compatibility, bioavailability, or patient tolerance. The insoluble forms of steroids such as prednisolone and dexamethasone have better ocular bioavailability and are considered more potent anti-inflammatories for topical ocular use. A resin-bound form of the beta-blocker betaxolol has been formulated as a suspension and is prepared *in situ* using a carbomer polymer.[62] The novel suspension formulation improves both comfort and ocular bioavailability of betaxolol, the 0.25% suspension therapeutically equivalent to a 0.5% solution.

Ophthalmic ointments

Ophthalmic ointments are primarily anhydrous and contain mineral oil and white petrolatum as the base ingredients, the proportions of which can be varied to adjust consistency and the melting temperature. Dosage variability probably is greater than with solutions (though probably no greater than that with suspensions). Ointments will interfere with vision, and their use is usually limited to bedtime instillation. They remain popular as a pediatric dosage form and for postoperative use. The anhydrous nature of the base enables its use as a carrier for moisture-sensitive drugs. The petrolatum base can be made more miscible with aqueous components by the addition of liquid lanolins.

Ointments do offer the advantage of longer contact time and greater total drug bioavailability, albeit with slower onset and time to peak absorption. The relationship describing the availability of finely divided solids dispersed in an ointment base was given by Higuchi,[63] where the amount of solid (drug) released in unit time is a function of concentration, solubility in the ointment base, and diffusivity of the drug in the base.

Ophthalmic emulsions

An emulsion dosage form offers the advantage of the ability to deliver a poorly water-soluble drug in a solubilized form as an eyedrop. The drug is dissolved in a nonaqueous vehicle, such as castor oil, and emulsified with water, using a nonionic surfactant and, if needed, an emulsion stabilizer. An emulsion with water as the external phase can be less irritating and better tolerated by the patient than use of a purely nonaqueous vehicle. Such an emulsion is used to deliver cyclosporine topically for the treatment of chronic dry eye conditions.[64]

Ophthalmic gels

Gel-forming polymers, such as carbomer, have been used to develop aqueous, semisolid dosage forms,

which are packaged and administered the same as ointments. The viscous gels have significantly increased topical residence time and can increase drug bioavailability and decrease dosage frequency, compared to solutions. Although they contain a large proportion of water, they can still cause blurring of vision. A carbomer gel of pilocarpine administered at bedtime has been shown to prolong the IOP-lowering effect in patients for up to 24 hours.[65]

Ocular inserts

Ocular inserts have been developed in which the drug is delivered on the basis of diffusional mechanisms. Such a solid dosage form delivers an ophthalmic drug at a near-constant known rate, minimizing side effects by avoiding excessive absorption peaks. The delivery of pilocarpine by such an insert was commercialized in 1975 (Ocusert Pilo) by Alza Corporation. The Ocusert is designed to be placed in the lower cul-de-sac to provide a weekly dose of pilocarpine, at which time the system is removed and replaced by a new one. The near zero-order rate delivery is based on the selection of a noneroding copolymer membrane enclosing the drug reservoir.[66]

Ocular inserts are plagued with some of the same manipulative disadvantages as conventional eyedrops. The insert must be placed in the eye in a manner similar to the insertion of a contact lens. Additionally, the insert must be removed from the eye when exhausted of its drug content. Such manipulations can be difficult for the elderly patient. Nonetheless, such therapeutic inserts represent a notable commercialized scientific achievement in pharmaceutical sciences. The Ocusert Pilo product is no longer marketed, because the drug has largely been replaced in glaucoma therapy by topical beta-blockers.

Ocular inserts that gradually erode in the tear fluid have been studied but not commercially developed as ocular drug delivery systems.[67] In theory, an erodible insert would be advantageous, because it would not require removal at the end of its therapeutic cycle, would provide precise unit dosing, and, if anhydrous, would not require a preservative. It may also increase ocular bioavailability and reduce the therapeutic dosage and possible systemic effects. The chief disadvantages may be related to patient use issues, control of erosion and drug release rates, and sterilization.

An erodible insert is available (Lacrisert) for treatment of dry eye. It is molded in the shape of a rod from a hydroxypropyl cellulose polymer, which is the active ingredient. When inserted into the lower cul-de-sac, the polymer imbibes tear fluid and forms a gel-like mass that gradually erodes while thickening the tear film over a period of several hours. The unit-dose insert is anhydrous, and no preservative is required, which is beneficial for some sensitive patients.

Ophthalmic preparation characteristics

Clarity

Ophthalmic solutions, by definition, contain no undissolved ingredients and are essentially free from foreign particles. Filtration can enhance clarity in some cases. It is essential that the filtration equipment be clean and well rinsed to avoid introduction of particulate matter into the solution by equipment designed to remove it. Operations performed in clean surroundings, the use of laminar-flow hoods, and proper nonshedding garments will contribute collectively to the preparation of clear solutions essentially free from foreign particles. In many instances the same filtration step can produce both clarity and sterility. If viscosity-imparting polymers are used, a polish-filtering step may be necessary before the final filtration.

Both container and closure must be thoroughly clean, sterile, and non-shedding, so that neither one introduces particulate matter to the solution during prolonged contact for the duration of the shelf-life. Normally this is established by thorough stability testing, which also will indicate whether insoluble particles (by-products of drug degradation) have been generated. Solution formulations may also contain viscosity-imparting polymers that can diminish clarity. In these situations it may be important to both define the visual clarity of the product and monitor its stability. The *European Pharmacopoeia* describes visual clarity and recommends standards that can be used for clarity specifications.[55]

Stability

The stability of a drug in an ophthalmic product depends on a number of factors, including the chemical nature of the drug substance, whether it is in solution or suspension, product pH, method of preparation (particularly temperature exposure), solution

additives, and type of packaging. A pharmaceutical manufacturer strives for a shelf-life measured in years at controlled room-temperature conditions, whereas the compounding pharmacist often is uncertain about the shelf-life of his or her preparation and thus provides relatively small quantities at one time, assigns a shelf-life in terms of days or weeks, and may specify refrigerated storage as a further precaution. The attainment of optimum stability often requires some compromises in the formulation, packaging, and preparation of the final product.

The product's pH is often the stability-controlling factor for many drugs. Drugs such as pilocarpine and physostigmine are both active and comfortable in the eye at a pH of 6.8; however, at this pH, chemical stability (or instability) can be measured in days or months. Either drug will lose a substantial amount of chemical stability in less than a year. On the other hand, at a pH of 5.0, both drugs are stable for a period of several years. (With regard to eye comfort at acidic pH, see the later discussion under Buffer and pH.)

In addition to optimal pH, if oxygen sensitivity is a factor, adequate stability may require inclusion of an antioxidant or special packaging. Plastic packaging, such as the low-density polyethylene containers (e.g., the DropTainer from Alcon) that are convenient for patient use, may prove detrimental to stability by permitting oxygen permeation, resulting in oxidative decomposition of the drug substance. Development of an epinephrine solution with 2 to 3 years' stability in a plastic package requires the use of a pH of about 3.0 for protection from oxidation, whereas an epinephrine borate solution formulated at a pH of about 7.0, which is more comfortable to the patient, requires an antioxidant system and the use of glass packaging. The prodrug of epinephrine, dipivefrin, significantly increases ocular bioavailability and is effective at one-tenth the concentration of epinephrine. The structure of the chemical derivative protects the active epinephrine portion from oxidation, so that it can be packaged in plastic. However, the a labile ester linkage introduced in the prodrug requires that it be formulated at a pH of about 3.0 to minimize hydrolysis; even with this precaution, the shelf-life of dipivefrin stored at room temperature can be extended to no longer than 18 months.

Pharmaceutical manufacturers conduct comprehensive stability programs to assure the assigned expiration dating for each product. In addition to monitoring the standard chemical and physical stability of the pharmaceutical, they test the stability of the preservative by chemical means or by actual challenge of its efficacy with appropriate test organisms. Sterility is not a stability parameter *per se*, but each container-closure system can be tested by microbial challenge to assure integrity of the package against environmental contamination before opening.

Some of the newer classes of ophthalmic drugs, like prostaglandins, are very hydrophobic and have very low concentrations. For example, in the product Xalatan, latanoprost is present at 0.005%, and in the product Travatan, travoprost is present at 0.004%. Active agents at such low concentrations present a challenge for formulators, because the loss of even small amounts of drug (e.g., from adsorption losses to packaging) can become significant. Pharmacia's Xalatan requires refrigerated storage, and as indicated earlier, temperature cycling also can reduce the concentration of active drug. It is important that the pharmacist knows the properties of the drug substance, in order to maintain product quality throughout the shelf-life of the product.

Buffer and pH

Ideally, ophthalmic preparations should be formulated at a pH equivalent to the tear fluid value of 7.4. Practically, formulators seldom achieve this. Most active ingredients used in ophthalmology are salts of weak bases and are most stable at an acid pH. This property generally holds for suspensions of insoluble corticosteroids.

Optimum pH adjustment generally requires a compromise on the part of the formulator, who should select not only a pH that is optimal for stability but a buffer system that has adequate capacity to maintain pH within the stability range for the duration of the product shelf-life. Buffer capacity is the key in this situation.

It generally is accepted that a low (acid) pH *per se* necessarily will not cause stinging or discomfort on instillation. If the overall pH of the tears, after instillation, reverts rapidly to pH 7.4, discomfort is minimal. On the other hand, if the buffer capacity is sufficient to resist adjustment by tear fluid and the overall eye pH remains acid for an appreciable period of time, then stinging and discomfort may result. Consequently,

buffer capacity should be adequate for stability but minimized, so far as possible, to allow only momentary disruption of the overall pH of the tear fluid. Special care in formulating intraocular products is required regarding their pH and buffer capacity. The corneal endothelium can tolerate much less deviation from physiological conditions, compared to the external corneal epithelium.[68]

Tonicity

Tonicity refers to the osmotic pressure exerted by salts in aqueous solution. An ophthalmic solution is isotonic with another solution when the magnitudes of the colligative properties of the solutions are equal. An ophthalmic solution is considered isotonic when its tonicity is equal to that of a 0.9% sodium chloride solution (290 mOsm). However, the osmotic pressure of the aqueous intraocular fluid is slightly higher than that of normal tears, measuring about 305 mOsm.

In actuality the *external* eye is much more tolerant of tonicity variations than was at one time suggested and usually can tolerate solutions equivalent to a range of 0.5% to 1.8% percent sodium chloride. Given a choice, one will find that isotonicity is desirable and is particularly important in intraocular solutions.[69] However, in certain cases a nonisotonic topical product is desirable. Tear fluid in some cases of dry eye (keratoconjunctivitis sicca) is reported to be hypertonic, and a hypotonic artificial-tear product is used to counteract this condition. Hypertonic ophthalmic products are used to relieve corneal edema, and solutions and ointments containing 2% or 5% sodium chloride are available for this use.

The tonicity of ophthalmic (and parenteral) solutions has been the subject of intensive investigation over the years. These studies have resulted in the accumulation and publication of a large number of sodium chloride equivalents that are useful in calculating tonicity values.

Viscosity

Ophthalmic solution and suspension eyedrops may contain viscosity-imparting polymers to thicken the tear film and increase corneal contact time (i.e., reduce the rate of tear fluid drainage). For suspensions, the increased viscosity also retards the settlng of particles between uses and at the same time maintains their suspension for uniform dosing. However, added viscosity may impede initial resuspension, particularly in a suspension that has a tendency to cake during storage. The hydrophilic polymers most often used for these purposes are methylcellulose, hydroxypropyl methylcellulose, hydroxyethyl cellulose, and polyvinyl alcohol – at concentrations that produce viscosities in the range of about 5 to 100 centipoise. These polymers also themselves appear as the active ingredients in artificial-tear solutions for dry eye therapy because of their lubrication and moisturizing properties. Viscosity agents can have several disadvantages, in that they sometimes produce blurring of vision and can leave a residue on the eyelids. These effects are most often seen at the higher end of the viscosity range. The added viscosity can make filtration more difficult, particularly for the small pore-size filters used to sterilize solutions.

Newer ophthalmic dosage forms, such as gel-forming solutions and semisolid aqueous gels with their increased viscosity and gel elasticity, significantly improve drug bioavailability and duration of effect. With these advances, the frequency of dosing can be reduced and patient compliance improved. These newer dosage forms incorporate novel polymer systems with special rheological properties to enhance their effect. Their complex rheology and intricate dependence on environment, however, increase the complexity of the sterile manufacturing process.

Additives

Most ophthalmic dosage forms contain additives or pharmaceutical excipients as inactive ingredients. Because of the need for tissue compatibility in ophthalmics, particularly in intraocular products, however, the use of additives is perhaps less common.

The most common inactive ingredient is the product's vehicle. For topical dosage forms, Purified Water USP is used. Because of the requirement for nonpyrogenicity, Water for Injection USP is used for intraocular products. While a mineral oil and petrolatum combination is the vehicle used for ophthalmic ointments, nonaqueous liquids are rarely used in topical eyedrops because of their potential for ocular irritation and poor patient tolerance. Some mineral and vegetable oils have served as vehicles for very moisture-sensitive or poorly water-soluble drugs. Use of the purest grade of oil, such as that used for parenteral products, is a requirement.

Multiple-dose topical ophthalmic products commonly contain microbiological preservatives. Other commonly used additives in topical eye products are ingredients to adjust pH and tonicity, and to buffer pH, in addition to the viscosity agents previously discussed. Ingredients to adjust pH and tonicity and to buffer pH are essentially the same as those used in parenteral products. Less commonly used additives are antioxidants, such as sodium bisulfite, ascorbic acid, and acetylcysteine.

Topical eye products sometimes incorporate surfactants to disperse insoluble ingredients or to aid in solubilization. Formulators use them in the smallest concentration possible to achieve the desired function, because they can be irritating to sensitive ocular tissues. Nonionic surfactants are preferable, because they are generally less irritating than ionic surfactants. Polysorbate 80 is the surfactant used to prepare an ophthalmic emulsion. Polyoxyl 40 stearate and polyethylene glycol function to solubilize a drug in an anhydrous ointment so that it can be filter-sterilized. Formulators often add surfactants to stabilize more hydrophobic drugs, for example, preventing loss to adsorption on the container walls. For example, the nonionic surfactant like polyoxyl 40 hydrogenated castor oil (HCO-40) stabilizes travoprost, a prostaglandin derivative.[70] Similarly, Cremophor EL stabilizes diclofenac in the Voltaren formulation marketed by Novartis.

The FDA has published a list of all inactive ingredients used in approved drug products on its website at http://www.fda.gov/cder. The list includes dosage forms and concentration ranges.

Summary

There has been considerable progress in ophthalmic pharmaceutics and in lens care products during the last decade. Very substantial advances have occurred in designing vehicles and packaging for highly potent active ingredients presented at very low concentrations; in increasing ophthalmic bioavailability and controlling factors influencing ophthalmic drug absorption; in the design of implants and means of delivering them for providing therapeutic agents to the retina and other deep ophthalmic tissues; and in devising robust yet delicately balanced multipurpose solutions for contact lens wearers. Continuing advances in the general field of ophthalmic pharmaceutics and pharmacokinetics can be expected to assist in maintaining and improving ocular health.

Medicated topicals

The application of medicinal substances to the skin and its appendages (e.g., nails) or various body orifices is a concept as old as humanity. The papyrus records of ancient Egypt describe a variety of such medications for external use. Galen described the use in Roman times of a forerunner to today's vanishing creams.

Medications are applied in a variety of forms reflecting the ingenuity and scientific imagination of pharmacists through the centuries. New modes of drug delivery have been developed to remedy the shortcomings of earlier vehicles or, more recently, to optimize drug delivery. Conversely, some external medications have fallen into disuse because of changes in the practice of medicine.

Medications are applied to the skin or its appendages or inserted into body orifices in liquid, semisolid, or solid form.

Oral solid dosage forms

Medicinal substances are most frequently administered orally, by means of solid dosage forms, such as tablets and capsules. Large scale production methods used for their manufacture, as is described in this section, require the incorporation of other materials, in addition to the active ingredients. These additives are usually included in the formulation to facilitate handling, enhance the physical appearance, improve stability, and aid in the delivery of the medicament to the bloodstream after administration. These materials, as well as the employed production methods, have been shown to potentially influence the absorption and/or bioavailability of the drugs.[71] In addition, the physicochemical characteristics of the drug substances may influence the physiological bioavailability from solid dosage forms.[72]

Tablets

According to the USP, tablets are solid dosage forms, containing medicinal substances with or without

suitable diluents. They may be classed, according to the method of manufacture, as compressed tablets or molded tablets. The vast majority of all tablets manufactured today are made by compression, and compressed tablets are the most widely used dosage form. Compressed tablets are prepared by the application of high pressures, utilizing steel punches and dies, to powders or granulations. Recently, punching of laminated sheets, electronic deposition methods, and three-dimensional printing methods have been used to make tablets. Tablets have been in widespread use since the latter part of the nineteenth century, and their popularity continues. The term "compressed tablet" is believed to have been first used by John Wyeth and Brother, Inc. of Philadelphia. During this same period, molded tablets were introduced for use as hypodermic tablets, for the extemporaneous preparation of solutions for injection. Tablets remain popular as a dosage form, due to the advantages afforded both to the manufacturer (e.g., simplicity and economy of preparation, stability, and convenience in packaging, shipping, and dispensing) and to the patient (e.g., accuracy of dosage, compactness, portability, blandness of taste, and ease of administration). Although the basic mechanical approach for most tablet manufacture has remained the same, tablet technology has undergone great improvement and experimentation. Efforts are continually made to understand more clearly the physical characteristics of powder compaction and the factors affecting the availability of the drug substance from the dosage form after oral administration. Tableting equipment continues to improve as regards both production speed and the uniformity of tablets. Recent advances in tablet technology have been reviewed.[73,74]

Although tablets are frequently discoid in shape, they also may be round, oval, oblong, cylindrical, or triangular. Other geometric shapes, such as diamonds, pentagons, and hexagons have also been used. They may differ greatly in size and weight, depending on the amount of drug substance present and the intended method of administration. Most commercial tablets can be divided into two general classes: whether they are made by compression or molding. Compressed tablets are prepared by large-scale production methods, whereas molded tablets involve small-scale operations. The various tablet types and abbreviations used in referring to them are listed here.

Compressed Tablet (CT)

Compressed tablets are formed by compression and, in their simplest form, contain no special coating. They are made from powdered, crystalline, or granular materials, alone or in combination with binders, disintegrants, controlled-release polymers, lubricants, diluents, and, in many cases, colorants. The vast majority of tablets commercialized today are compressed tablets, either in an uncoated or coated state.

Sugar-Coated Tablets (SCT)

Sugar-coated tablets are compressed tablets surrounded by a sugar coating. Such coatings may be colored and are beneficial in covering up drug substances possessing objectionable tastes or odors and in protecting materials sensitive to oxidation. These coatings were once quite common, but lost commercial appeal due to the high cost of process validation. Recently, they have made a comeback, due to patient popularity and technical advances.

Film-Coated Tablets (FCT)

Film-coated tablets are compressed tablets covered with a thin layer or film of a water-soluble material. A number of polymeric substances with film-forming properties may be used. Film coating imparts the same general characteristics as sugar coating with the added advantage of the greatly reduced time required for the coating operation. Advances in material science and polymer chemistry have made these coatings the first-choice of formulators.

Enteric-Coated Tablets (ECT)

Enteric-coated tablets are compressed tablets coated with substances that resist solution in gastric fluid but disintegrate in the intestine. Enteric coatings can be used for tablets containing drug substances inactivated or destroyed in the stomach, for those that irritate the mucosa, or as a means of delayed release of the medication.

Multiple Compressed Tablets (MCT)

Multi-compressed tablets are compressed tablets made by more than one compression cycle. This process is best used when separation of active ingredients is needed for stability purposes or if the mixing process is inadequate to guarantee uniform distribution of two or more active ingredients.

Layered tablets

Layered tablets are prepared by compressing additional tablet granulation on a previously compressed granulation. The operation may be repeated to produce multilayered tablets of two or more layers.

Press-coated tablets

Press-coated tablets, also referred to as dry-coated tablets, are prepared by feeding previously compressed tablets into a special tableting machine and compressing another granulation layer around the preformed tablets. They have all the advantages of compressed tablets (i.e., slotting, monogramming, speed of disintegration), while retaining the attributes of sugar-coated tablets in masking the taste of the drug substance in the core tablets. An example of a press-coated tablet press is the Manesty Drycota. Press-coated tablets can also be used to separate incompatible drug substances; in addition, they can provide a means of giving an enteric coating to the core tablets. Both types of multi-compressed tablets have been widely used in the design of prolonged-action dosage forms.

Controlled-Release Tablets (CRT)

Compressed tablets can be formulated to release the drug slowly over a prolonged period of time. Hence, these dosage forms have been referred to as "prolonged-release" or "sustained-release" dosage forms as well. These tablets, as well as capsule versions, can be categorized into three types: (1) those that respond to some physiological condition to release the drug, such as enteric coatings; (2) those that release the drug in a relatively steady, controlled manner; and (3) those that combine combinations of mechanisms to release pulses of drug, such as repeat-action tablets. Other names for these types of tablets are; Extended Release, Sustained Release, Prolonged Release, Delayed Release, and, in the case of pulsatile tablets, Repeat Action, Pulsatile Release, or Pulse Release.

Tablets for Solution (CTS)

Compressed tablets used for preparing solutions or imparting given characteristics to solutions must be labeled to indicate they are not to be swallowed. Examples of these tablets are Halazone Tablets for Solution and Potassium Permanganate Tablets for Solution.

Effervescent tablets

In addition to the drug substance, effervescent tablets contain sodium bicarbonate and an organic acid, such as tartaric or citric. In the presence of water, these additives react, liberating carbon dioxide that acts as a disintegrator and produces effervescence. Except for small quantities of lubricants present, effervescent tablets are soluble.

Compressed suppositories or inserts

Occasionally, vaginal suppositories, such as Metronidazole tablets, are prepared by compression. Tablets for this use usually contain lactose as the diluent. In this case, as well as for any tablet intended for administration by means other than swallowing, the label must indicate the manner in which it is to be used.

Buccal and sublingual tablets

Buccal and sublingual tablets are small, flat, oval tablets. Tablets intended for buccal administration by inserting into the buccal pouch (the space between the lip and gum in the mouth) may dissolve or erode slowly; therefore, they are formulated and compressed with sufficient pressure to give a hard tablet. Progesterone tablets may be administered in this way. Some newer approaches have employed materials that act as bioadhesives to increase absorption of the drug. Other approaches use tablets that melt at body temperatures. The matrix of the tablet is solidified, while the drug is in solution. After melting, the drug is automatically in solution and available for absorption, thus eliminating dissolution as a rate-limiting step in the absorption of poorly soluble compounds. Sublingual tablets, such as those containing nitroglycerin, isoproterenol hydrochloride, or erythrityl tetranitrate, are placed under the tongue. Sublingual tablets dissolve rapidly, and the drug substances are absorbed readily by this form of administration.

Molded Tablets or Tablet Triturates (TT)

Tablet triturates are usually made from moist material, using a triturate mold that gives them the shape of cut sections of a cylinder. Such tablets must be completely and rapidly soluble. The problem arising from compression of these tablets is the failure to find a lubricant that is completely water-soluble.

Dispensing Tablets (DT)

Dispensing tablets provide a convenient quantity of potent drug that can be incorporated readily into powders and liquids, thus circumventing the necessity to weigh small quantities. These tablets are supplied primarily as a convenience for extemporaneous compounding and should never be dispensed as a dosage form.

Hypodermic Tablets (BT)

Hypodermic tablets are soft, readily soluble tablets and were originally used for the preparation of solutions to be injected. Since stable parenteral solutions are now available for most drug substances, there is no justification for the use of hypodermic tablets for injection. Their use in this manner should be discouraged, since the resulting solutions are not sterile. Large quantities of these tablets continue to be made, but for oral administration. No hypodermic tablets have ever been recognized by the official compendia.

Capsules

Capsules are solid dosage forms in which the drug substance is enclosed in either a hard or soft, soluble container or shell of a suitable form of gelatin. The soft gelatin capsule was invented by F.A.B. Mothes, a French pharmacist, in 1833. During the following year, A. DuBlanc obtained a patent for his soft gelatin capsules. In 1848, J. Murdock patented the two-piece hard gelatin capsule. Although development work has been done on the preparation of capsules from methylcellulose, starch, and calcium alginate, gelatin, due to its unique properties, remains the primary composition material for the manufacture of capsules. The gelatin used in the manufacture of capsules is obtained from collagenous material by hydrolysis. There are two types of gelatin, Type A, derived mainly from pork skins by acid processing, and Type B, obtained from bones and animal skins by alkaline processing. Blends are used to obtain gelatin solutions with the viscosity and bloom strength characteristics desirable for capsule manufacture.

The encapsulation of medicinal agents remains a popular method for administering drugs. Capsules are tasteless, easily administered, and easily filled either extemporaneously or in large quantities commercially. In prescription practice, the use of hard gelatin capsules permits a choice in prescribing a single drug or a combination of drugs at the exact dosage level considered best for the individual patient. This flexibility is an advantage over tablets. Some patients find it easier to swallow capsules than tablets, therefore preferring to take this form when possible. This preference has prompted pharmaceutical manufacturers to market products in capsule form, even though the products have already been produced in tablet form. Although the industry prepares approximately 75% of its solid dosage forms as compressed tablets, 23% as hard gelatin capsules, and 2% as soft elastic capsules, market surveys indicated a consumer preference of 44.2% for soft elastic capsules, 39.6% for tablets, and 19.4% for hard gelatin capsules.[75]

Coating of pharmaceutical dosage forms

Introduction

Any introduction to tablet coating must be prefaced by an important question – *Why coat tablets?* – since coatings are often applied to dosage forms that are already functionally complete. That said, a broad range of pharmaceutical oral solid dosage forms are coated, for a plethora of reasons that include

1. Protecting the drug from its surrounding environment (particularly air, moisture, and light) in order to improve stability.
2. Masking unpleasant taste and odor.
3. Making it easier for the patient to swallow the product.
4. Improving product identity, from the manufacturing plant, through intermediaries, and to both healthcare workers and patients.
5. Facilitating handling, particularly in high-speed packaging/filling lines, and automated counters in pharmacies, where the coating minimizes cross-contamination due to dust elimination.
6. Improving product appearance, particularly where there are noticeable visible differences in tablet core ingredients from batch to batch.
7. Reducing the risk of interaction between incompatible components. This would be achieved by

using coated forms of one or more of the offending ingredients (particularly active compounds).

8. Improving product robustness because coated products generally are more resistant to mishandling (abrasion, attrition, etc.).
9. Modifying drug release, as in repeat-action, delayed release (enteric coated) and sustained-release products.

Evolution of the coating process

Coating of medicinal products is a concept steeped in history. Rhazes (850–932 AD) used the mucilage of psyllium seeds to coat pills that had an offending taste. Subsequently, Avicenna[76] was reported to have used gold and silver for pill coating. Since those early times, a wide range of materials have been used in tablet coating. White[77] mentioned the use of finely divided talc in what was at one time popularly known as pearl coating, while Kremers and Urdang[78] described the introduction of the gelatin coating of pills by Garot in 1838.

An interesting reference[79] reports the use of waxes to coat poison tablets. These waxes, being insoluble in all parts of the gastrointestinal tract, were intended to prevent accidental poisoning (the contents could be "activated" by breaking the tablet open prior to administration).

While earlier coated products were produced by individuals working in pharmacies, particularly when extemporaneous compounding was the common practice, that responsibility now has been assumed by the pharmaceutical industry. Early attempts to apply coatings to pills yielded variable results and usually required the handling of individual pills. Such pills would have been mounted on a needle or held with a pair of forceps and literally dipped into the coating fluid, a procedure that would have to be repeated more than once to ensure that the pill was coated completely. Subsequently, the pills were held at the end of a suction tube, dipped, and then the process repeated for the other side of the pill. Not surprisingly, these techniques often failed to produce a uniformly coated product.[80]

Initially, the first sugar-coated pills seen in the United States were imported from France in about 1842;[80] while Warner, a Philadelphia pharmacist, became among the first indigenous manufacturers in 1856.[81]

Pharmaceutical pan-coating processes were initially based on those used in the candy industry, where techniques were highly evolved, even in the Middle Ages. Candy coating processes typically used coating pans made of copper because drying was accomplished by applying an external heat source directly to the outside of the coating pan. Current pharmaceutical coating processes use coating pans, of a broad range of designs, made from stainless steel, where drying of the product being coated is achieved by means of a supply of heated air, and moisture, and dust-laden air is removed from the vicinity of the pan by means of an air-extraction system.

Conventional pharmaceutical pan-coating processes, employed essentially for sugar coating, remained unchanged for the first half of the twentieth century. However, since then there have been significant advances made in coating-process technology, mainly as a result of a steady evolution in pan design and associated ancillary equipment, primarily control systems.

Until the early 1950s, pharmaceutical coating was dominated by the sugar coating of tablets. However, at that time, a new form of technology (called film coating) was developed. Recognizing the potential limitations of the sugar-coating process, the pioneers of film coating created significant improvements by employing coating formulations based on polymers dissolved in highly volatile organic solvents, with the result that coating processes that took days to carry out could now be completed in only a few hours.

While the use of organic solvents circumvented the problems associated with the poor drying capabilities of conventional equipment available at the time, this approach had its disadvantages; these organic solvents were highly flammable, potentially toxic, and presented significant handling and environmental problems.

Fortunately advances in equipment design, including the introduction of fluid-bed coating processes and those using side-vented coating pans, have resulted in the gradual emergence of coating processes where drying efficiencies have been maximized. The result has been the emergence of aqueous coating processes as the preferred means, with a few exceptions, of coating pharmaceutical products.[82]

While advances in equipment design have resulted in film coating becoming the dominant process for

coating pharmaceutical oral solid dosage forms, these improvements in equipment design have also benefited the sugar-coating process, creating fully automated processes that can produce a batch in less than one day.

Oral modified-release drug delivery systems

Introduction

In recent years, the scope of drug delivery technologies has expanded significantly, irrespective of the route of administration, as a result of an advanced understanding of disease, science, and safety associated with pharmaceuticals. The overall purpose of drug delivery systems, however, has remained constant: to provide a therapeutically effective amount of drug to the appropriate site in the body for a desired duration of action. The site at which a drug is delivered (drug targeting) and the rate at which the drug is released (profile) have to be carefully considered during dosage form design and product development. Site-specific drug delivery has been one of the key focus areas for pharmaceutical formulation scientists for many decades. The main purpose of site-specific drug delivery systems is to improve the efficacy and safety of drugs. Pharmaceutical scientists have also focused on the development of formulations that deliver drugs at a desired-release rate, the duration of which may span from very fast (a few seconds) to very slow and controlled (days, weeks, and months). Combining site-specific aspects of drug delivery with controlled-release rates is highly desirable for patient treatment.

With better understanding of gastrointestinal tract anatomy, physiological barriers to drug absorption, and the need for different release profiles for different disease conditions, more efficient and advanced drug delivery systems have been developed. In recent years, the purposes of such modified-release drug delivery technologies have evolved to optimize drug performance and enhance patient tolerance (reduce in side-effects). These technologies have not only had a significant impact on the success of developing and commercializing new chemical entities, but the reformulation of marketed drug products for better patient acceptance has allowed pharmaceutical companies to extend the patent life of their products. As a result of the market success and thus opportunities for enhanced drug delivery systems, considerable efforts have been expended on developing appropriate polymeric carriers and sophisticated processing and manufacturing machineries. A tremendous amount of research has been directed toward the development of robust modified-release (MR) oral dosage forms. These efforts have followed the science-based and risk-managed process of drug product development, supported by quality-by-design (QbD) principles. This section describes various MR technologies used for drug delivery to the oral cavity (oral route of administration) as well as formulation approaches and manufacturing considerations.

Rationale and definitions of oral modified-release technologies

The oral route for delivering medications has been the preferred route for most drugs due to patient acceptance, ease of administration, accurate dosing, cost-effective manufacturing methods, and generally the improved shelf-life of the product. For conventional oral dosage forms, the drug (API) is rapidly released after administration and subsequently absorbed into the body from the gastrointestinal tract. The concentration of drug in the blood peaks shortly after administration as the drug absorption process dominates, then decreases over time as metabolism and/or excretion processes dominate. Conventional immediate-release (IR) dosage forms, however, do not maintain the plasma levels of the drug within the therapeutic range for an extended period of time and thus a short duration of action may be observed. For many drugs and therapeutic indications, multiple dosing of IR formulations provides satisfactory clinical performance with an appropriate balance of efficacy and safety. For example, multidose therapy may be tolerated for short-term treatment, but is not desirable for treating chronic conditions. To reduce dosing frequency and eliminate the fluctuations in blood concentration associated with conventional delivery, extended-release (ER) systems have been and continue to be developed, where the drug is slowly released over an extended timeframe. Delayed-release (DR) technologies exhibit a lag time in drug release (no drug released immediately) to target the drug to a specific site in the body. Both ER and DR systems are

broadly referred to as modified-release (MR) dosage forms. The common goal for the development of any MR formulation is to enhance the drug's therapeutic benefits, minimize side-effects, and improve the overall management of the disease. These technologies may be combined with conventional IR delivery or combined with other MR technologies

Summary

Advancements in the science and technology of oral modified-release drug delivery systems have resulted in the commercial availability of a number of products. More importantly, these improved delivery systems are impacting the health of patients worldwide. The development and commercialization of modified-release products is no longer considered just a life-cycle management strategy for the manufacturer. Formulation scientists will continue to investigate and develop novel drug delivery platforms to improve the overall effectiveness of drug therapies.

Aerosols

Definitions

The term aerosol is used to denote various systems ranging from those of a colloidal nature to systems consisting of pressurized packages. Aerosols have been defined as colloidal systems consisting of very finely subdivided liquid or solid particles, dispersed in and surrounded by a gas. Originally, the term aerosol referred to liquid or solid particles having a specific size range, but this concept has fallen into disuse.

The present-day definition refers to those products that depend upon the power of a liquefied or compressed gas to dispense the active ingredient(s) in a finely dispersed spray, foam, or semisolid. Pump systems that also dispense the active ingredient(s) in the form of a finely dispersed mist (although of greater particle size) often are classified as aerosols. These pump systems generally are used to dispense medication intranasally.

In 1978, the use of certain chlorofluorocarbons (CFCs) was curtailed by the FDA, EPA, and CPSC. These restrictions applied to the use of Propellants 11, 12, and 114 (CFCs) for use in all aerosol products. Exemptions were granted to MDIs and a few other essential uses. Because of these restrictions, new valve systems and dispensing systems, which allowed greater use of liquefied hydrocarbons and compressed gases, were developed for non MDIs. Individual drugs which have been successfully converted to hydrofluoroalkane propellants have had the CFC products phased out.

Aerosol delivery systems

Inhalation therapy has been used for many years, and there has been a resurgence of interest in delivery of drugs by this route of administration. The number of new drug entities delivered by the inhalation route has increased over the past five to ten years. This type of therapy also has been applied to delivery of drugs through the nasal mucosa, as well as through the oral cavity for buccal absorption. Originally, this type of therapy was used primarily to administer drugs directly to the respiratory system (treatment of asthma); inhalation therapy is now being used for drugs to be delivered to the bloodstream and finally to the desired site of action. Proteins (insulin), steroids, cardiac agents, immunizing agents, etc., are being developed for delivery in this manner. Drugs administered via the respiratory system (inhalation therapy) can be delivered either orally or nasally. Further, these products can be developed as a

- nebulizer/atomizer
- dry powder inhaler
- nasal inhaler
- metered-dose aerosol inhaler.

Drugs delivered via a nebulizer/atomizer are generally formulated as sterile aqueous solutions (or suspensions) and are inhaled by the patient through an atomizer, nebulizer, or other similar devices.

Dry powders have been used for inhalation therapy for over 75 years. The active ingredients were packaged in capsules, representing a single dose of drug. The capsule was punctured, and a small amount of powder fell into a chamber while the patient inhaled. The procedure was repeated until all of the powder was inhaled. While these dry powders were somewhat popular during the early 1940s to 1950s, they fell into disuse with the introduction of the aerosol metered-dose inhaler (MDI), which became

available around 1955. This first generation MDI was formulated with chlorofluorocarbons (CFC), was compact and portable, and contained epinephrine hydrochloride or albuterol as the active ingredient. These MDIs quickly became the dosage form of choice for inhalation therapy, especially for the treatment of asthmatics. The dry powder inhalers, powders containing about 25–30 to 60 doses of active ingredient, were developed and became commercially available from 2000 to 2003. Several dry powder inhalers currently available include salmeterol, fluticasone, and budesonide. Mometasone dry powder inhaler is available in Europe. These dry powder inhalers do not contain a propellant. These consist of active, very potent drugs that are dispensed from a specially designed package. An accurate amount of drug as a dry powder is released from a small unit dose package while the patient inhales deeply. The dry powder will then travel to the lungs along with the inspired air. Carrier molecules, such as lactose, are often used to reduce agglomeration of the small drug particles as well as facilitate fluidization during the inhalation process.

The nasal metering drug delivery system produces an aqueous spray, consisting of active ingredient and excipients. The drugs used can act locally within the nasal mucosa or systemically by passing through the nasal mucosa and enter the general circulation system. This occurs via numerous capillary vessels present in the mucosa. These nasal sprays can also be formulated similarly to MDIs, using propellants and a nasal actuator. The development of the MDI in the mid-1950s made possible a convenient dosage form for the delivery of medication to the respiratory system. Atomizers and nebulizers were cumbersome to use and in many instances did not offer convenience of use, so that administration of drugs by atomizers/nebulizers was generally left to hospital or at-home use. While many improvements were made to these nebulizers and atomizers, they lacked convenience of use, especially as to their portability and use outside of a hospital and/or home setting.

MDIs consist of a pressurized container filled with solutions or suspensions of active drug in a mixture of solvents, dispersing agents, and liquefied gas propellants, and a metered-dose valve. The pressurized container is placed within an oral adapter (mouthpiece), and when the unit is dispensed, an exact amount of drug is expelled in the proper particle size distribution to achieve maximum deposition of drug into the lungs. The aerosol dosage form (MDI) has become the dosage form of choice for delivery of drugs to the lungs.

Topical aerosol products are becoming more popular because they are easy to administer and have a better feel than ointments and creams. Topical pharmaceutical aerosols can be formulated as a spray, foam, and semisolid. They can be used to deliver therapeutic agents topically (to the skin surface), rectally, and vaginally. They consist of a liquid, emulsion, or semisolid concentrate and liquefied gas or compressed gas propellant. Many therapeutically active ingredients have been administered or applied to the body by means of the aerosol dosage form. This dosage form has been used orally to dispense a variety of agents, such as budesonide, salmeterol xinafoate, fluticasone propionate, fenoterol, epinephrine hydrochloride, albuterol, albuterol sulfate, metaproterenol sulfate, cromolyn sodium, flunisolide hemihydrate, ipratropium bromide, beclomethasone dipropionate, and triamcinolone acetonide.

Advantages

One of the main reasons for the rapid and widespread acceptance of the MDI dosage form for the administration of therapeutically active agents is that it affords many distinct advantages to the user. These advantages have been described by various investigators and, for MDIs, include the following:

- Rapid onset of action
- Circumvention of the first-pass effect and avoidance of degradation in the gastrointestinal tract
- Lower dosage that will minimize adverse reactions, especially in the case of steroid therapy, in which most of the steroid reaches the respiratory tract and less is swallowed
- Dose titration to individual needs and ideal for prn (when required) medication
- Alternative route when therapeutic agent may interact chemically or physically with other medicinals needed concurrently
- Viable alternative when the drug entity exhibits erratic pharmacokinetics upon oral or parenteral administration
- Container and valve closure are tamperproof.

The pressure package is convenient and easy to use. Medication is dispensed in a ready-to-use form at the push of a button. There is generally no need for further handling of the medication. Since the medication is sealed in a tamperproof pressure container, there is no danger of contamination of the product with foreign materials, and at the same time, the contents can be protected from the deleterious effects of both air and moisture. Easily decomposed drugs, such as epinephrine, lend themselves to this type of package, for oxygen is excluded from the headspace.

Sterility is always an important consideration with certain pharmaceutical and medicinal preparations. While initial sterility is generally no problem to the manufacturer, there is concern for the maintenance of the sterility of the package during use, for example, with ophthalmic preparations. When necessary, the aerosol package can be prepared under aseptic conditions, and sterility can be maintained throughout the life of the product. For those products requiring regulation of dosage, a metering valve can be used. An accurately measured dose of therapeutically active drug can be administered quickly and, in the case of drugs for inhalation, buccal, or nasal application, in the proper particle-size range.

There are many advantages to the administration of medicinal agents by inhalation, buccally and nasally. Response to drugs administered by inhalation, buccally and nasally, is prompt, often very specific and with minimal side-effects, faster in onset of activity than drugs given orally and, with most drugs, approaching intravenous therapy in rapidity of action. Drugs that normally are decomposed in the gastrointestinal tract can be administered safely by inhalation, buccally and nasally. The use of the self-pressurized aerosol package makes this type of therapy simple, convenient, and acceptable, compared with the use of atomizers and nebulizers, which are bulky and require cleaning.

Biotechnology and drugs

The past 40 years have witnessed the emergence, development, and maturation of biotechnology in medicine and pharmaceuticals. Previously rare, or even unattainable, pharmaceuticals can now be produced in useful quantities by harnessing the power of molecular biology. Interestingly, the term *biotechnology* was first coined in 1919 by the Hungarian engineer Károly (Karl) Ereky to describe how products could be produced from raw materials with the aid of living organisms as agriculture began to join forces with industry following World War I.[83] Hence, biotechnology is not a new concept. Humans have been manipulating living organisms over the millennia to solve problems and improve the quality of life. But today, especially in the context of science and health, the term biotechnology is used interchangeably with "genetic engineering." The concept of DNA manipulation is central to most modern references to biotechnology.

The practical realization of this technology has followed from our ability to now detect, decode, isolate, produce, and characterize the various proteins that coordinate the numerous functions essential to human life and health. Processes that precede or are causative in pathophysiology can not only be identified but also now manipulated in an attempt to restore normal function. This relatively new methodology involves the synergism of discoveries in recombinant DNA methodology, genetic engineering, immunology, genomics, proteomics, and bioinformatics, with advances in automation and data analysis to create a cogent, high-technology industry. Overall, biotechnology has led to the creation of new products for home and industry, improvement of agricultural yields, diagnosis of genetic disorders, and the enhancement of our medical arsenal against disease. The publications in February 2001 of the virtually complete sequence of the human genome[84,85] are certainly accelerating the application of these technologies. While the close of the past millennium has clearly witnessed the benefits resulting from the proliferation of biotechnology-derived products, new questions have arisen regarding issues of ethics and pharmacoeconomics. Nonetheless, it is clear that the benefits of biotechnology already have far outweighed the drawbacks.

Background

Now that biotechnology-derived pharmaceuticals have become commonplace in healthcare, pharmacy practitioners should have a detailed knowledge of the manufacture and use of these newer agents.[86,87] As a

backdrop to understanding modern biotechnology, it will be instructive to review some of the basic biological milestones that precede it. Table 9.3 provides a compilation of milestones in biotechnology, especially for their connections with pharmaceutical sciences. It is clear that technology is proceeding at a rate that is already threatening to bypass our ability to manage the ethical dilemmas presented by these advances. Fortunately, visionaries such as Nobel laureate James Watson have used their positions to encourage the proper and ethical use of genetic information and technology. As the initial director of the publically funded Human Genome Project, Watson announced a plan to set aside 3% of the project budget devoted to Ethical, Legal, and Social Implications (ELSI) research, a decision he subsequently deemed, "probably the smartest thing I did."[88]

Nature has for some 3.5 billion years been conducting what we may call natural genetic experiments. These include mutation (random heredity alteration), crossing-over (breakage and exchange of corresponding segments of homologous chromosomes), and recombination at meiosis (fertilization). These processes all have contributed to the current diversity of life on this planet. In addition, it is well known that humans have been manipulating genetic characteristics of different species for over 10,000 years through inbreeding and cross-breeding experiments. To cite a few examples, one can point to the modern robust strains of wheat or corn, which are a far cry from their puny ancestors. Similarly, the varied breeds of dogs, cats, poultry, and cattle may be mentioned. These manipulative efforts continue, and in less than a lifetime, the development of larger and sweeter oranges, seedless watermelons, and flamboyant ornamental plants has occurred. Also familiar are such hybridizations as the tangelo (crossing the tangerine and the grapefruit) and the mule (crossing a donkey and a horse).

All cell structures and functions begin with proteins, and the code for building the proteins is found in deoxyribonucleic acid (DNA). This is why the discovery of the double-helix structure of DNA by Watson and Crick in 1953 fundamentally began the unraveling of the mystery of cell processes. (The 50th anniversary of publication of their model was celebrated in 2003, with some exceptional retrospective documentation published in print and on the Internet by Cold Spring Harbor Laboratory and the journals, *Science* and *Nature*). DNA, the genetic blueprint of an organism, is made up of building blocks known as nucleotides (molecules containing a sugar, nitrogen-containing purine or pyrimidine bases, and a phosphate group) that are connected in a very long ladder-like structure. When this rubber-like twisted-ladder structure is coiled tightly, it is referred to as a two-stranded, or double, helix.

There are four different nucleotides (containing the bases adenine, cytosine, guanine, and thymidine) with a total of about 3 billion nucleotide units in the human genome, tightly packed into chromosomes. These include the genetic code for a large number of genes, originally estimated at 100,000 in the human but downgraded to roughly 25,000 as a result of the Human Genome Project, a surprisingly low number compared with other species. Each of these genes controls the synthesis of a protein made up of a long strand of anywhere from 50 to 3000 amino acids. Nirenberg and Matthei, in 1961, and others later, elucidated how the nucleotide sequence of a gene regulates the particular sequence in which the 20 different amino acids will be united to produce a particular protein. A single codon is made up of units of three adjacent nucleotides; each codon specifies one amino acid. The arrangement of codons in the DNA, following transcription into messenger RNA (mRNA), determines the sequence of amino acids that will form a particular protein. The detailed understanding of how these genes and their proteins govern basic cellular processes is the underpinning of molecular biology and biotechnology.

Because each of the major organs of the body (brain, liver, blood, etc.) has a specified set of tasks to perform, certain specific sets of genes in each organ (collection of specialized cells) must be activated and deactivated, that is, turned *on* and *off* as needed. Following the directions laid down by the genetic code of DNA and mediated by mRNA, each cell type continuously produces a unique and characteristic array of proteins. Each cell type maintains a complement of transcriptional activating and repressing proteins whose actions balance to create the specific gene expression profile of a particular tissue. Moreover, epigenetic processes such as gene methylation and histone acetylation status also contribute to tissue-specific gene expression. Expressed proteins are then

Table 9.3 Milestones in Biotechnology. The recent explosion of growth in the development and application of biotechnology may be traced to a number of successive, discrete, milestone discoveries and events.

Discoveries and events	Time, scientists, and companies
1. X-ray diffraction data and proposed double-helix model for the 3-dimensional structure of DNA	RE Franklin and MH Wilkins; JD Watson and FH Crick, 1953
2. Site-specific recognition and cleavage of DNA by restriction endonucleases	W Arber, 1962; M Meselson and R Yuan, 1968; HO Smith, 1970; D Nathans, 1971
3. Determination of the genetic code	M Nirenberg, S Ochoa, and P Leder, 1966; HG Khorana, 1966
4. Identification of DNA ligase	M Gellert, 1967
5. Identification of RNA-directed DNA polymerase (reverse transcriptase)	HM Temin and S Mizutani, 1970; D Baltimore, 1970
6. DNA cloning techniques	HW Boyer, S Cohen, and P Berg, 1971–1972
7. Formal discussions on emerging DNA technologies	Gordon Conference on Nucleic Acids, June 1973
8. Self-imposed standards for rDNA research	Asilomar Conference, Feb 1975
9. Hybridoma created	C Milstein and G Kohler, 1975
10. Recombinant Advisory Committee (RAC) issues guidelines	Recombinant Advisory Committee, 1976
11. DNA sequence technologies	F Sanger, 1977; W Gilbert, 1977
12. US Supreme Court ruled that microorganisms are patentable	General Electric superbug, 1980
13. US approval of first diagnostic kit using mAb technology, anti-C3d BioClone	Ortho Diagnostics, 1981
14. US approval of first ethical pharmaceutical produced by using rDNA technologies, Humulin (human insulin)	Genentech and Eli Lilly and Co, 1982
15. Expression of a foreign gene in plants: bacterial antibiotic resistance gene expressed in tobacco plants	Monsanto Co, Washington University, and Max Planck Institute, 1982
16. FDA approval of first monoclonal murine antibody drug, Orthoclone OKT3, for reversal of acute kidney transplant rejection	Ortho Biotech, 1986
17. The polymerase chain reaction (PCR) methodology enables targeted amplification of DNA sequences	KB Mullis; Cetus Corp., 1983; use of thermostable DNA polymerase, 1988
18. FDA approval of first recombinant vaccine for hepatitis B virus	Chiron Corp., 1986
19. US Patent and Trademarks Office issues first patent for genetically engineered mammal, transgenic mouse	P Leder and Harvard University, 1988
20. Formal launch of Human Genome Project	USA, 1990

(continued overleaf)

Table 9.3 *(continued)*

Discoveries and events	Time, scientists, and companies
21. First human patient received gene therapy for adenosine deaminase deficiency	WF Anderson, 1990
22. Dolly the sheep becomes the first cloned mammal	I Wilmut, 1997
23. RNA interference's gene silencing activity in nematode worm *C. elegans*	A Fire and C Mello, 1998
24. FDA approval of the first rationally designed and target specific cancer chemotherapy drug, Gleevec, to treat certain types of leukemia	Novartis, 2001
25. Simultaneous publication of human genome sequence by Human Genome Project and Celera Genomics	Human Genome Project and Celera Genomics, 2001
26. Approval of the first gene therapy drug worldwide, Adenovirus-based delivery of p53 tumor suppressor	Gendicine, in China, 2003
27. EMEA approval of the first biosimilar drug, Omnitrope (recombinant human growth hormone)	Sandoz, 2006
28. US district court in New York rejected the breast cancer gene patents	US district court in New York, 2010

secreted into the extracellular milieu, while many are used within the cell itself. The number of possible biosynthetic permutations is very high if one considers that a typical protein can be made up of some 500 amino acids and, further, that every one of these sites may be occupied by any one of 20 different amino acids. It is likely that over the long periods of evolution of each organism, given the vast array of possible combinations of these amino acids, a multitude of unique proteins with all sorts of optimized functions have developed.

The concept that genetic information flows from DNA to RNA to proteins has become a fundamental milestone of modern biology. Thus, with the discovery of reverse transcriptase (from an RNA virus) by Temin and Baltimore, in 1970, which could convert its own genomic RNA into double-stranded RNA, a second milestone was reached. Molecular biology relies heavily on this enzyme to convert mRNA into DNA for gene cloning, library construction, and gene sequencing and detecting. Examples of cellular catalysts, or enzymes, include those that are involved in the digestion of food and others that produce the chemical building blocks of cell life, such as sugars and lipids, hormones for organism regulation, fuel for energy production, and important molecules such as DNA.

Proteins also make up the cell cytoskeleton providing an organized, three-dimensional structure. They permit directed transport and movement of molecules throughout the cell. They are embedded in the outer cell membrane and pump nutrients and ions across the membranes. They serve as receptor sites for hormones that finitely adjust the functions of the cell according to changing bodily needs. Another group of proteins regulates gene activities by binding to DNA and activating or repressing gene transcription. Still other proteins, and their smaller fragments (peptides), are secreted by cells as neurotransmitters or hormones like insulin. Some serve as carrier molecules, like hemoglobin, the body's oxygen carrier.

As is well recognized, these hormones and various related peptide molecules hold enormous power, and because they can act on numerous specific cell surface receptors, they can influence virtually all bodily functions from the nervous system to the immune system. It is obvious that their selectivity, potency, and often-desired evanescent effects on selective target cells make them enormously attractive candidates

as a new generation of drugs in the *magic bullet* concept of Paul Ehrlich. Further, when administered parenterally, hormones have the potential to reach target receptors on the surface of cells, without the need to penetrate membranes. Not unlike the normal bodily processes, they can bind to cell surface receptors and activate the cell's particular function. An example of one such approach is seen with the anticancer drug interferon-alpha, which can stimulate some immune cells to attempt to overcome cancerous cell growth.

The body's specific defense response to invading organisms is due to the immune system. Normally, phagocytes called to a site of inflammation induced by pathogens mount a generalized attack response. Indiscriminately, they engulf cellular debris as well as anything recognized as foreign. Occasionally, however, this is not enough, and illness ensues. At this point, several more focused counterattacks proceed by the three types of white blood cells known as macrophages, T lymphocytes, and B lymphocytes. The key features of the immune system are specificity (the ability to focus on specific pathogens) and memory (the ability to recognize and respond rapidly to previously encountered infections). About 1% of the blood cells are white blood cells. The ones that are central to the immune responses are the following:

B Cells – Lymphocytes that produce antibodies (antibody-mediated immune response).

Macrophages – Phagocytic cells that alert helper T cells to the presence of pathogens.

Helper T Cells – *Master switches* of the immune system that stimulate the rapid division of both killer T cells and B cells.

Suppressor T Cells – Lymphocytes with regulatory functions; i.e., they slow down or prevent immune responses.

Killer T Cells and Natural Killer (NK) Cells – Lymphocytes that directly destroy body cells that already have been infected by pathogens (or cancer cells).

Memory Cells – A group of the T cell and B cell population that was produced during the primary encounter with a pathogen but was not used in the battle. These circulate through the body ready to respond rapidly to later attacks by the same organisms.

As a further refinement in the understanding of the immune system, several key weapons are involved in the process. These include the antibodies, which are circulating freely or membrane-bound receptor molecules that bind specific foreign invaders and thereby tag them for destruction by the complement system or phagocytes. There are the perforin proteins, which are secreted by certain T cells and kill their cellular targets by punching holes in them. Finally, there are the lymphokines and interleukins, which are secretions by which white blood cells communicate with each other. Thus, the immune system has two fighting branches with specificity, and often both are employed against infections and antigens in general. The T cells dominate one part of the system, and when they are activated, it is referred to as a *cell-mediated* response. The B cells dominate the other branch, and events associated with their activation are referred to as *antibody-mediated* response.

Before the broad application of whole genome sequencing, expressed sequence tags (ESTs) of complementary DNA provided shortcuts to uncover a large number of new genes. Similarly, *lighthouses* have been developed along the chromosomes to guide the way for sequencing dim restriction maps. DNA research, using the polymerase chain reaction (PCR), has become a powerful tool in forensic and research applications. Based on the principle of PCR, real-time polymerase chain reaction (RT-PCR) or quantitative real time polymerase chain reaction (Q-PCR) has been developed and applied as another powerful technology to detect or quantify one or multiple gene targets precisely and simultaneously. Non-specific fluorescent dyes or sequence-specific DNA probes can be used as indicators. In the clinic, RT-PCR provides rapid and accurate diagnoses.[89]

New publications have described how modern metabolic engineering has brought intermediary metabolism back to life through techniques involving enhancing copies of a gene at a rate-controlling point, adding a gene to remove a poisonous product, or adding several genes to introduce a new pathway into an organism that stops short of the desired product. This metabolic engineering has had numerous practical results in addition to helping develop new theories. DNA technology has been applied to metabolic pathways so that branch point control problems can be solved. Even the insertion of similar

enzymes from different species into the studied organism has introduced new flexibility and better metabolic characteristics into the older organism.

The recent developments of the vaccinia virus mean that it now can serve as a molecular vehicle for carrying foreign genes into other organisms. As a means for research, this recombinant vaccinia vector has served as a vehicle for producing live vaccines that would otherwise be difficult to produce. Monoclonal antibodies have also been used successfully in diagnosis and therapy. The first monoclonal antibody drug for humans, OKT3, was approved by the FDA in 1986 for treatment of acute renal allograph rejection. Antibody power has been enhanced by attachment of a biological toxin such as ricin, a cytotoxin such as calicheamycin, or a radioisotope such as an alpha emitter. The latter can be used to damage tissue adjacent to that with which the antibody interacts. These are all good examples of combined basic research followed by rapid practical application.

Moral and ethical questions

On the matter of moral and ethical questions of biotechnology applications in medicine, numerous articles appear periodically[90–92] to debate the issue. Francis Collins, Director of the National Human Genome Research Institute (NHGRI) has written, "It is estimated that all of us carry dozens of glitches in our DNA – so establishing principles of fair use of this information is important for all of us."

There are many questions, such as the following:

- Does genetic testing constitute invasion of privacy?
- Will there be an increase in abortions that discriminate against the *genetically unfit?*
- Should those destined to be stricken with a fatal genetic disease be informed of their fate, especially if there is no remedy available?
- Will these decisions become mandated legally and ultimately demean humans or create a new underclass of the genetically less-fortunate?
- Should gene therapy be used only for treating disease or also for *improving* an individual's genetic legacy?

Currently, most protections on the use of genetic information are regulated at the state level, resulting in uneven application across the population. Senators Jeffords and Daschle have outlined their respective views on the passage of federal laws that protect the collection and use of genetic information, particularly relating to employment and health insurance.[93] The Human Genome Project's ELSI program (Ethical, Legal, and Social Implications of Human Genetics Research) is now charged with addressing issues that appear as daunting as the sequencing of the genome itself. The benefits of biotechnology in disease prevention and treatment are numerous, and the decoding of the human genome will continue to produce new opportunities to improve our quality of life. But as with all technological advances, safeguards are required to prevent discriminatory and unethical use of this new information.

Pharmaceutical packaging

A container closure system must be designed to protect the drug during actual conditions of storage, shipment, and use, and be able to deliver the correct amount of product at the time of use. It must not interact with the product over its shelf-life to the extent that it renders the drug ineffective or unacceptable for use. As defined in the USP, "a container, including the closure, does not interact physically or chemically with the pharmaceutical preparation in any manner to alter the strength, quality, or purity beyond the official requirements under ordinary or customary condition of handling, shipment, storage, sale or use."[94]

The general requirements for containers for foods, including dietary supplements, drugs, cosmetics, and medical devices, are provided in the Food Drug and Cosmetic Act as amended.[95] The regulations are provided in *Code of Federal Regulations* Title 21. The FDA Center for Food Safety and Nutrition (CFSAN) is responsible for the regulations that apply to foods and dietary supplements. The Center for Drug Evaluation (CDER) and the USP/NF are responsible for the regulations that apply to drug packaging. The Center for Biologics Evaluation and Research (CBER) and USP are responsible for the regulations that apply to biologics. The Center for Veterinary Medicine (CVM) relies on CDER and USP/NF for its packaging requirements. The Center for Devices and Radiological Health (CDRH) uses 21 CFR Subchapter

H – Medical Devices, ISO, and ASTM International standards. If a liquid medication dispenser is purchased by a pharmacist, independently of the drug, it is regulated by CDRH. If it is sold with the drug, it is regulated by CDER. If an injection syringe is sold by itself, it is regulated by CDRH, and if it contains a drug (prefilled syringe) it is regulated by CDER.

The standards for drug packaging in USP/NF include General Notices, General Chapters <87>, <88> Biological Reactivity Testing, <381> Elastomeric Closures for Injection, <660> Containers-Glass, <661> Containers-Plastic, <670> Auxiliary Packaging Components, <671> Containers-Performance Testing, and <698> Deliverable Volume. In addition to these requirements, one must be cognizant of the EPA requirements for monomer content in Polyvinyl Chloride (PVC), waste disposal policies, CONEG (Coalition of Northeastern Governors), and Toxics in Packaging Clearing House (TPCH) requirements. For certain drugs, such as most tablets and capsules, the regulations of the Poison Prevention Packaging Act (PPPA) apply. There are also regulations in 21 CFR §201.25 Barcoding, which require barcoding the National Drug Code (NDC) number on the drug labels, including blisters. On May 2, 2011, the ASTM issued a new standard for Water Vapor Permeation titled D7709 – Standard Test Methods for Measuring Water Vapor Transmission Rate (WVTR) of Pharmaceutical Bottles and Blisters.[96] Although these standards are current at the time of publication, it is important to note that the standards in USP and ASTM are evolving, and it is important to refer to the current versions of these standards, which are reviewed and revised routinely. In addition to the law, regulations, ASTM and USP standards, FDA CDER provides guidance in the amount and type of testing required for drug containers.[97]

The amount of effort required to develop or select the appropriate container system is based on a risk assessment considering the route of administration, class of drug product, therapeutic range, and the chemical and physical stability of the drug substance, drug product matrix, packaging components, and the conditions of storage and use. The route of administration determines the degree of testing necessary to determine the acceptability of a container. In some cases, a component, such as a delivery system, will function at one temperature but not another. Therefore, all evaluations must include storage and use temperatures and packaging conditions. The following is a list of dosage forms from highest to lowest risk for use by patients: injectables, implants, inhalation drugs, ophthalmics and otics, oral liquids, oral solids, and transdermals and topical liquids. The concerns about containers have been fostered by actual events of either interaction or the failure to perform. Some examples of those instances are as follows:

- Migration of nitrosamines from rubber;
- Degradation of components from sterilization;
- Reactions to latex allergens in natural rubber;
- Concentration of drug in pouches and polyethylene vials, due to excessive water loss;
- Migration of inks, adhesives, and chemicals in paper into inhalation solutions;
- Migration of vanillin for labels and cartons into inhalation solutions;
- Migration of chemicals from heat seals, plastics, and foils into drugs;
- Presences of vinyl monomer in polyvinyl chloride (toxic);
- Ions and glass in injection solutions;
- Migration of drug to plastic or coating glass;
- Migration of preservatives;
- Migration of plastic additives to drugs;
- Migration of environmental estrogens to drugs;
- Cross-linking of gelatin capsule shells from furfural in Rayon Coil;
- Interaction of residual bleach and dyes in Cotton Coil;
- Failure of a delivery system to deliver the correct dose;
- Low potency or dissolution properties from excess moisture permeation; and
- Degradation from light.

Container designs and materials have evolved to meet new demands and more sophisticated requirements. Due to a tightening of limits on drug product impurities, degradants, and migrants, the selection of containers has become more complicated. Pharmaceutical companies must conduct compendial tests on the containers[98] and compatibility tests[99] on the containers with the actual product, using validated methods. The test methods used by the drug companies to test

for impurities and migrants are specific to the pharmaceutical formulation and the packaging material.

Container components must also perform, as needed, to protect the products from physical change, loss of contents, and exposure to moisture, oxygen, and light. To develop the appropriate container closure system, the scientist must know the critical attributes of the specific drug product and chemical and physical properties of the container options. The importance of selecting the appropriate materials of composition cannot be underestimated. This critical step is often not considered until problematic issues arise. It is essential to consider, first, the container's requirements, and then select materials that fulfill those needs. To determine the appropriate container closure system, one should consider the following:

- Preformulation information on the drug substance (sensitivity to heat, oxygen, humidity, light, glass, metals, pH, reactivity with plastics, metals, or types of glass);
- The nature of the dosage form (solid oral, liquids – aqueous, alcohol, oil, suspensions, inhalation powders, creams, ointments, biodegradable polymers, implants, transdermals, etc.);
- Drug product information (open pan studies on impact of humidity, light, heat, pH, and compatibility studies with the components);
- Container material qualification (CAS number, 21 CFR qualification, USP qualification, etc.);
- Container/product compatibility;
- Impact of the packaging operation on the drug product;
- Ruggedness of the container system under actual conditions of packaging, shipping, storage and use;
- Performance; and
- Cosmetic features.

The drug manufacturer has access to all of the data listed, and the information is reviewed by the FDA in support of their submission. Container manufacturers file Type III Drug Master Files (DMFs) with the FDA, so the information can be reviewed in conjunction with the drug application and FDA can determine if the container is compatible and the information is sufficient for approval of the drug product. The challenge for the repackager, pharmacist, or pharmacy compounder is selecting the appropriate container, when the drug manufacturer does not provide repackaging instructions and the container supplier does not provide chemical or performance information. In these cases, the most conservative approach may be the best approach.

Selecting materials that CDER already approved for use for similar products reduces the risk of component failure. Certain chemicals have become associated with concern regarding their safety and appropriateness of use in packaging drug products. These include, but are not limited to, nitrosamines, butylated hydroxytoluene (BHT), certain carbon blacks, and some antistatic agents. It is best to eliminate these concerns by selecting components manufactured without these chemicals. If possible, the packager should know which 21 CFR references, Food Contact Numbers, and USP or EU requirements the component or material meets. It is advisable to choose materials available commercially. Medical grade materials are preferred, but are often more expensive. The classification of medical grade does not mean the materials are of a particular composition; it means the supplier complies with a change control program. Although selecting medical grade materials is preferable, the materials should, at least, come from a reliable source and be cGMP manufactured. One should know the details of the suppliers change control program. When suppliers are not willing to report changes to the packager or pharmacist or control their changes, the quality of every lot is in question and may require full extensive testing, particularly if it is used to package a high-risk product.

Pharmaceutical excipients

The practice of pharmacy is an ever-evolving profession. A non-scientific survey of community pharmacies has revealed that extemporaneous compounding of prescriptions increasingly occurs. Whether this is a result of the physician not writing for compounded medicines or the pharmacy not being interested in preparing such medicines is a topic for discussion elsewhere. It is, however, undoubtedly driven by the pharmaceutical industry, addressing many disease treatment and prevention efforts by commercially manufacturing products for mass distribution by the healthcare system in the United States.

The FDA has levied large fines on manufacturers who have failed to comply with cGMPs. Several companies have been forced to operate under what is known as a "Consent Decree," due to significant deficiencies in cGMPs. Additionally, the FDA's approval of new products is trending downward, this being a result of companies focusing research and development activities on the next "blockbuster" compound and the FDA frequently issuing "not approvable" letters, requiring the sponsor company to conduct additional studies. At the community level, more independent pharmacies are closing their doors or selling their patient lists to national or regional chains. Hospital settings are seeing a greater degree of mergers, so economics are more favorable, and an influx of patients using the facility as a clinic, rather than an acute care provider.

In addition to the profession of pharmacy, pharmacy education has undergone changes in the United States since the previous edition of the *Remington* was published. The PharmD degree has been the entry-level degree for anyone intending to practice pharmacy for well over a decade. Many practicing pharmacists pursue certification in subspecialties, such as diabetes or cancer. The focus of pharmacy education has become even more clinically oriented on outcomes and patient interactions. This focus comes at the expense of basic pharmaceutics, and in some instances, due to course loads, electives, such as industrial pharmacy courses, are not considered by students. The pharmaceutical industry used to be able to hire graduates with pharmacy degrees for positions in production, quality control, and dosage-form development, due to the breadth of understanding the graduate had of pharmaceutical processes. Unfortunately, gaining this knowledge as a PharmD has become increasingly difficult, unless the student pursues an advanced degree in industrial pharmacy or pharmaceutics. However, many schools of pharmacy have introduced new degree programs focusing on the pharmaceutical sciences. These programs provide a foundation in the sciences that the industry requires of new hires: preformulation, analytical chemistry, formulation development, and manufacturing science. It is imperative that pharmacists in all practice settings know it is their obligation to understand what is used to prepare a medication, whether by commercial means or by extemporaneously compounding it in a practice setting.

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10

Fundamentals of pharmacy practice

Application of ethical principles to practice dilemmas

The growing sophistication and complexity of contemporary healthcare practice presents many ethical challenges including: protecting privacy and confidentiality in an environment of easily accessible information and perplexing regulations, maternal–fetal conflicts, cost containment and downsizing of professional staff, threats to the rights of human subjects in research, genetic engineering and screening, and delivery of treatment and services in a highly fragmented system, to name only some of the more problematic issues. As pharmacy practice becomes more complex and increasingly patient-oriented, pharmacists have to deal with the aforementioned broader ethical issues shared by all health professionals and those unique to or more commonly encountered in pharmacy practice. New and difficult questions face pharmacists. How does one reduce or eradicate the under-treatment of pain? Should pharmacists participate in the practice of capital punishment by lethal injection?[1] Whose responsibility is it to manage an impaired colleague? What are acceptable boundaries to avoid inappropriate interactions with industry?[2] Do pharmacists have the right to refuse to fill a legal prescription on the grounds of conscience?[3] How should scarce drug resources be rationed? How will changes in state and federal laws and new court decisions impact the delivery and quality of pharmaceutical care?

"Because ethical dilemmas are commonplace in pharmacy practice, pharmacists must develop a working knowledge of formal and systematic ethical analysis, as well as learn to distinguish ethical issues from social, psychological, political, and legal issues."[4] Moreover, the difficulty of the ethical issues mentioned thus far suggests that a collaborative approach to resolving them would be preferable to individuals struggling alone. Pharmacists must be able to work with others on the healthcare team to find a justifiable resolution. To collaborate with others and work effectively, there must be a systematic approach to working through an ethical dilemma. Applied ethics is defined as well as its application to pharmacy practice with emphasis on the use of normative models of ethical decision-making to resolve practice dilemmas. A process for ethical decision-making is explained and applied to clinical cases that refer to issues encountered on an individual, institutional, and societal level. Resources to help in the resolution of ethical dilemmas are also noted.

Applied ethics and healthcare

The contemporary application of the ideas and concepts of ethics to issues in healthcare began in the late 1960s with questions about the allocation of the new technologies such as hemodialysis and vital organ transplantation, and the protection of human research subjects. "General normative ethics attempts to answer the question, 'which general moral norms for the guidance and evaluation of conduct should we accept, and why?'"[5] When theories or norms derived from normative ethical inquiries are used to examine moral problems in professions, the term applied or practical ethics is used. The term "applied" ethics in this case is applied to practical ethical questions in pharmacy practice. To arrive at a clearer understanding of ethics in general, it helps to have a baseline knowledge of key terms. Three terms underlie all the discussion in this section: (1) ethics, (2) values, and (3) dilemmas.

Ethics

Ethics is a careful, systematic inquiry into the nature of morality, guidelines, or standards that give meaning and direction to the human community. Simply put, ethics is the study of good and evil, of right and wrong. But, ethics is much more than that. Ethics is concerned with the duties and obligations one has to others and to him- or herself. Ethics is also concerned with the rights of individuals and how those rights are recognized and respected. The systematic nature of ethics helps illuminate what one ought to do, who one should be as a human being, and what and whom one should nurture and sustain in life.

Values

Values are an important part of ethics. One uses values to help explain how and why things are important to us. "Values are not to be confused with concrete goods. They are ideas, images, and notions. Values attract us. One aspires after the good they articulate. One expects to find our own good in relation to what they offer."[6] When one looks at the goodness or badness of an action, one must also look at the values attached to the action. Values are the internal motivators for our actions. Evidence of values is observed in human behavior. True values elicit deeply held positive or negative attachments. Basic values and a value system are developed in childhood and result from such influencing factors as family, teachers, friends, religious traditions, and culture. People of different religious faiths or of no faith ascribe to many values and principles one acts upon on a daily basis. Values also have their roots in professions. Some traditional values of the pharmacy profession are compassion, faithfulness, and fairness. With the introduction of pharmaceutical care as a standard for pharmacy practice, the values of patience, responsiveness, and kindness have been added to the list of traditional values.[7]

Usually, values remain unchanged after one reaches adulthood unless they are challenged by great spiritual or emotional distress. Values can also change when it becomes apparent that an old value system doesn't work anymore. Whatever their origin or evolution, the resulting personal and professional values can profoundly affect the ethical decisions that pharmacists make.

Dilemmas

An individual has a dilemma when, wanting to make a good choice he or she realizes that no matter what

is done, a choice will result in loss or harm. Simply put, a dilemma is choosing among equally unappealing alternatives. "A difficult problem becomes a 'dilemma' when one is quite sure that one will be making a big mistake regardless of what path one chooses. It is instructive to consider moral dilemmas in this context. The anxiety one experiences as one faces each unpalatable alternative informs us about the nature of moral dilemmas. It seems that any decision one makes will violate one or another value which one holds dear."[8] In particular, moral dilemmas in pharmacy can arise in several ways. They can arise when the right thing to do, such as telling the truth, conflicts with obligations like loyalty to a peer or protecting the patient from harm. They can also arise when what is best for the patient runs counter to patient self-determination or one's own well-being, that is, one's health, obligations to family or one's employer, and so on. To resolve a dilemma effectively, one must have a method for reviewing the facts, generating alternatives, and choosing the "best" alternative given the circumstances of the dilemma.

Ethical codes

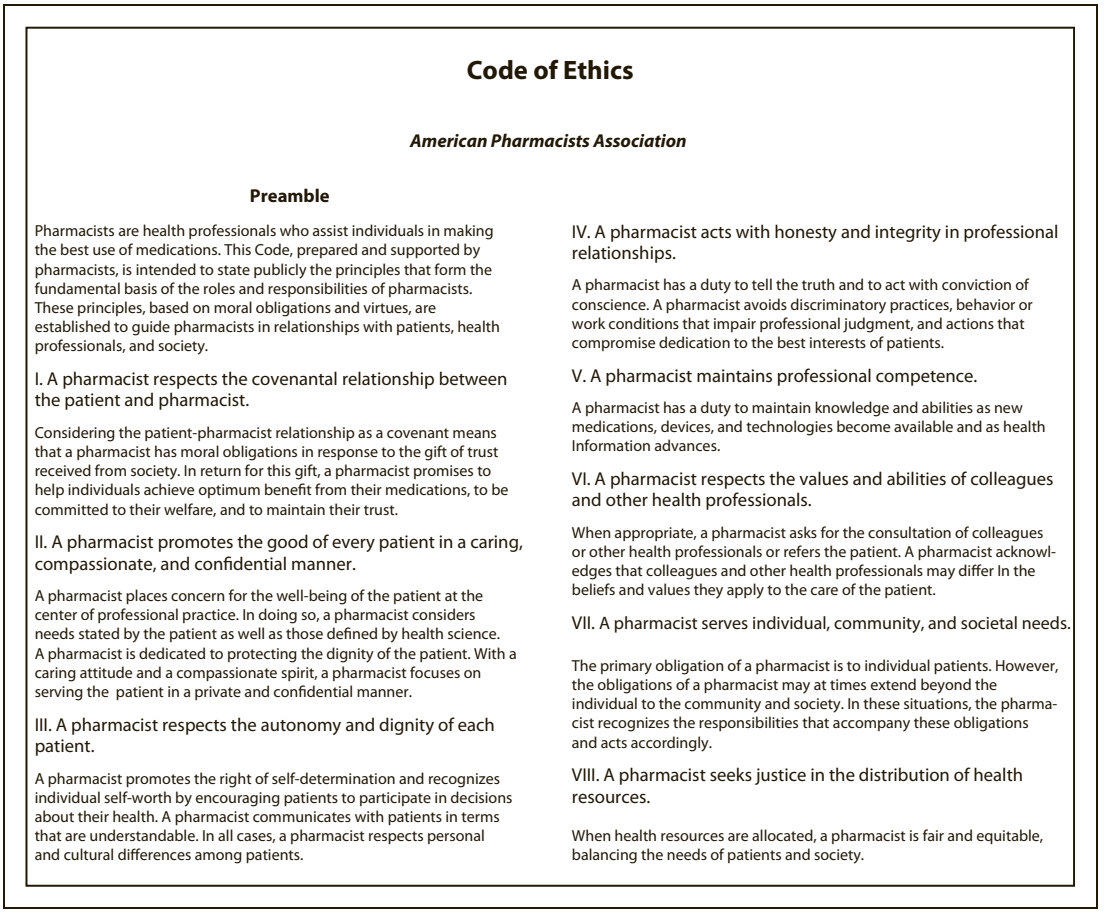
Ethical principles and rules that apply to medical practice and research have long served as the basis for a system or code of ethical conduct. Ethical codes provide healthcare professionals with ethical principles and standards by which to guide their practice. However, ethical principles and codes cannot provide healthcare professionals with answers to every ethical question that may arise in the course of their practice. Ethical questions in healthcare involve decision-making that is usually situation-specific. The purpose of such principles and codes is not to provide practitioners with right and wrong answers but to offer them a framework to use when faced with ethical questions. The Code of Ethics of the American Pharmacists Association (APhA) is the only code of ethics that specifically guides the practice of pharmacy (Fig. 10.1). The current version of the code was adopted in 1994 and includes eight ethical principles to guide ethical decision-making by pharmacists. "It espouses both an ethic of respect for patient autonomy and pharmacist responsibility for outcomes of care in the context of a covenantal pharmacist–patient Relationship."[9]

Although codes of ethics are helpful, they are not without their flaws. For example, there may be conflicts between personal values or one's own code of ethics and the professional code. There can also be conflicts between the professional code and the code of the institution in which one works. In such cases, which code takes priority? On the other hand, a code might be silent on a particular ethical issue and provide no guidance to members of the profession as to how they should respond. The principles in a code of ethics are not self-justifying; that is, just because the code of ethics prescribes certain conduct doesn't make it ethically correct. The thoughtful pharmacist should ask, "Why should I follow this tenet of the Code of Ethics of the APhA?" Finally, codes appeal to our desire to have things simplified. We like clear answers to complicated questions and muddy situations. As mentioned previously, codes are written in general terms. Because of this, there are gaps between actual ethical issues in pharmacy practice and what is included in the Code.

Technology and automation

The American Heritage Dictionary defines a system as, "A group of interacting, interrelated, or interdependent elements forming a complex whole; a condition of harmonious, orderly interaction."[10] Systems are so important to the profession that they are major contributors to the efficiency and effectiveness of a pharmacy operation, as well as the underlying factor involved in medication errors. Providing contemporary pharmacy services involves such a sufficiently complex process that it most certainly necessitates a systems approach. Pharmacy is, of course, a subsystem of a larger, comprehensive healthcare system. In this section the authors will focus on a systems approach in utilizing technology to support the practice of pharmacy and describe the complex interactions that occur in a pharmacy practice between people, data, and technologies. These interactions focus primarily on the welfare of patients and are performed by pharmacists and their associates, who share a common vision because they are involved in the pursuit of rendering appropriate pharmaceutical care.[11]

It is impossible to imagine any scenario for the future of pharmacy that does not involve the use of many forms of technology and automation. This assumption holds true regardless of the practice setting selected. Consider that technology has two



Code of Ethics

American Pharmacists Association

Preamble

Pharmacists are health professionals who assist individuals in making the best use of medications. This Code, prepared and supported by pharmacists, is intended to state publicly the principles that form the fundamental basis of the roles and responsibilities of pharmacists. These principles, based on moral obligations and virtues, are established to guide pharmacists in relationships with patients, health professionals, and society.

I. A pharmacist respects the covenantal relationship between the patient and pharmacist.

Considering the patient-pharmacist relationship as a covenant means that a pharmacist has moral obligations in response to the gift of trust received from society. In return for this gift, a pharmacist promises to help individuals achieve optimum benefit from their medications, to be committed to their welfare, and to maintain their trust.

II. A pharmacist promotes the good of every patient in a caring, compassionate, and confidential manner.

A pharmacist places concern for the well-being of the patient at the center of professional practice. In doing so, a pharmacist considers needs stated by the patient as well as those defined by health science. A pharmacist is dedicated to protecting the dignity of the patient. With a caring attitude and a compassionate spirit, a pharmacist focuses on serving the patient in a private and confidential manner.

III. A pharmacist respects the autonomy and dignity of each patient.

A pharmacist promotes the right of self-determination and recognizes individual self-worth by encouraging patients to participate in decisions about their health. A pharmacist communicates with patients in terms that are understandable. In all cases, a pharmacist respects personal and cultural differences among patients.

IV. A pharmacist acts with honesty and integrity in professional relationships.

A pharmacist has a duty to tell the truth and to act with conviction of conscience. A pharmacist avoids discriminatory practices, behavior or work conditions that impair professional judgment, and actions that compromise dedication to the best interests of patients.

V. A pharmacist maintains professional competence.

A pharmacist has a duty to maintain knowledge and abilities as new medications, devices, and technologies become available and as health Information advances.

VI. A pharmacist respects the values and abilities of colleagues and other health professionals.

When appropriate, a pharmacist asks for the consultation of colleagues or other health professionals or refers the patient. A pharmacist acknowledges that colleagues and other health professionals may differ In the beliefs and values they apply to the care of the patient.

VII. A pharmacist serves individual, community, and societal needs.

The primary obligation of a pharmacist is to individual patients. However, the obligations of a pharmacist may at times extend beyond the individual to the community and society. In these situations, the pharmacist recognizes the responsibilities that accompany these obligations and acts accordingly.

VIII. A pharmacist seeks justice in the distribution of health resources.

When health resources are allocated, a pharmacist is fair and equitable, balancing the needs of patients and society.

Figure 10.1 Code of ethics. (Originally published in "Code of Ethics for Pharmacists." *Am J Health-Syst Pharm* 1995;52:2131. © 1995, American Society of Health-System Pharmacists, Inc. All rights reserved. Reprinted with permission.)

primary purposes. Both of the purposes of technology involve the work of humans. One purpose for technology is to replace completely the work done by humans. Technology usually excels at replacing work that is repetitive and work that is often found to be tedious by humans. Ideally, technology should be considered for selection and implementation when it can free a human being to be redeployed into a work process that requires the abstract, judgmental, and higher-level cognitive processes at which humans excel.[12]

The second role of technology involves the enhancement of human work. With over 6000 articles being published every week in the biomedical literature, it is impossible for any human to "keep up" with the dynamic field healthcare represents. Evidence-based medicine experts estimate that in even the narrowest specialty, approximately 14 articles per day would need to be read from the literature to maintain one's professional competency at the highest level. Information technology can present the highest quality, empirically derived, evidence-based information that reduces a pharmacist's uncertainty while making decisions. Information technology helps to overcome the limits of human memory and helps reduce the use of conjecture (opinion) based decision-making.[13]

Another example of a performance enhancing technology can be found in the use of bar codes. In community pharmacies, hospitals, and nursing homes, bar codes can be scanned in the dispensing process and at the point-of-administration to assure that the right drug is being given to the right patient, in the right form, by the right route, in the right

strength, at the right time. Use of bar codes in healthcare is showing great promise to significantly reduce accidents and errors.[14]

Generally one can assert that, over time, technology continues to weigh less while it does more. The ubiquitous nature of the Internet, microcomputers, portable information appliances in the form of smartphones, and more recently, iPad-like tablets allow technology to touch everyone to an increasing extent in our everyday work and existence. Do you know anyone who receives more voicemail than e-mail? Can you reach certain colleagues in minutes by a text message, while voicemail may take days to receive a reply? This level of connectivity has led to a new definition of the Internet, which includes every computer, smartphone, tablet, and other portable devices being connected in wired and wireless environments, allowing text and voice communication from almost anywhere in the world. Where will it end? While it is difficult to imagine all of the permutations and possibilities, it is safe to say that pharmacy students today have had the ability to connect as much as they wish for most of their life.

Healthcare as a discipline tends to lag behind other areas and industries with regard to its adoption and diffusion of technological innovation. In fact, healthcare had been described as one of the few remaining predigital industries. Fortunately, incentives and penalties offered by the federal government for the adoption of electronic health records are beginning to change the paper-based dominance found in our care-delivery systems. The authors believe the banking and financial industries are the best examples to follow when determining how healthcare will continue to evolve. Granted, there are differences, but trust is needed in both systems and technologies used.

If people are willing to trust their finances to electronic banking technologies, it is reasonable to expect that they will become more comfortable trusting the management of their healthcare information to electronic technologies. Most pharmacists tell us that they are less than 10% paperless in their practices. Today, there are many examples today of health systems that are now 100% paperless. The care they provide has been greatly enhanced by this digital information convergence, yielding greater situational awareness in all patient care scenarios. The authors can imagine no scenario or practice setting where the digitization of transactions will not increase over time.[15]

Compare the adoption of "cash cards," a.k.a. ATM cards, and imagine that a similar card for healthcare would serve as the means for caregivers to gain access to patients' medical records. There are several technologies that provide this kind of access. Everything from biometric fingerprint or retina scanning to smart cards is being examined. No true standard has emerged as of yet, and new entries such as Google Wallet are emerging. In fact, some people say (tongue in cheek), that the nice thing about information technology standards is that there are so many to pick from. The authors do not believe the smart card is the future unless it can totally reduce the thickness of one's wallet by serving all identity functions for all health, business, travel, entertainment, and other related transactions of daily living.[16] Getting all of the businesses represented to agree on a single standard would certainly be a prodigious task or require strong government intervention.

Pharmacy informatics

"Medical informatics is the rapidly developing scientific field that deals with the storage, retrieval, and optimal use of biomedical information, data, and knowledge for problem-solving and decision-making."[17] Healthcare informatics is the umbrella term for all health-related disciplines, and pharmacy's related discipline is commonly called either pharmacy informatics or pharmacoinformatics.[18] It is impossible to consider that any individual can keep up with the flood of information that is being created concerning the safe and appropriate use of medications in humans. Information technology is, therefore, required to manage these data efficiently and effectively.

One might ask the question, "While I am providing pharmaceutical care or performing medication therapy management (MTM) services, what are my technology systems supposed to be doing?" At the core of nearly every pharmacy software program is a database application. In a pharmacy management database application program, there are multiple databases being managed. Database tables can include information relating to patients, prescribers, drugs, payors, drug interactions, and many others. Historically, pharmacists assisted by their technology, have always been challenged to deliver the right

information, to the right people, at the right time and place, in the right format. Today, information appliances are now ready to provide assistance in achieving these "rights," but the integration of this information into the workflow of the pharmacist remains the largest challenge facing all.

Years ago, the only format for the delivery of decision support information was a tertiary reference book that was, hopefully, from an authoritative source. Some of these trusted references were only updated every few years. As computer systems began to be commonplace, decision-supporting "nuggets" of information from the literature were incorporated into prospective drug utilization review (DUR) databases, and pharmacists would be "flagged" when patients were about to be exposed to duplicate therapy, significant drug interactions, or the entry of a new prescription to which a patient was potentially allergic. As these DUR products matured, monographs discussing the management of the problem were included on the systems. "Alert fatigue" is a term to describe when too many flags (representing false positive alerts that interrupt a pharmacist's workflow) are presented to a pharmacist, impairing their ability to separate the important warnings from these false alarms.

Initially, respected tertiary books were transformed to onscreen versions of the books upon which they were based and were typically distributed every three months by CD-ROM. As the Internet developed, drug information became increasingly available from providers who offered their products online. While a pharmacist's printed books might be available for new editions annually or have inserts mailed out on a quarterly basis, online drug information could be updated on a daily basis. It was also found that many busy practitioners needed information packaged in phrases rather than sentences and paragraphs. Many products now reflect a "just the facts" approach to information. The best products are workflow-sensitive and anticipate the special circumstances in which decisions are being made to include all of the information, such as patient demographics and current health status extracted from the electronic medical record. Decision support cannot be "smart" without these data.

The latest trends place these resources into the hands of practitioners in a variety of different media. One will still see books being published. One will also see CD-ROM and Internet versions of the same products. The majority of these reference tools are also available in formats that allow them to be displayed on portable devices, such as tablets and smartphones. This allows mobile practitioners to use high quality evidence in decision-making wherever they require it. These tools are also updated on a daily basis, and in some cases wireless access makes it possible for real-time updates to arrive where they are needed and when they are needed. An ideal informatics support system allows the integration, management, delivery, and display of data in support of a pharmaceutical care practice.

Technology and HIPAA

"Medical records contain intimate information about a person's physical and mental health, behaviors, and relationships. Intrusions into privacy can result in loss of trust, with an unwillingness to confide in health care professionals. Unauthorized disclosures of intimate information can cause embarrassment, stigma, and discrimination."[19] Many pharmacists remain concerned about changes due to the Health Insurance Portability and Accountability Act confidentially, and the regulations impose severe penalties for security breaches. The authors know of at least 14 different methods to secure electronically held information. In many ways, it is more secure than paper records. Events such as Hurricane Katrina in 2005 remind us that there are many limitations to paper-based records and many advantages to electronically stored information.

The regulations of HIPAA also provide that patients should have better access to their own medical records. In most US states, patients own the information contained in their medical records. Unfortunately, they do not feel as if they own it or have access to it as they desire. Some US companies are creating a collaborative medical record that allows patients, through the World Wide Web, to become partners or coproducers in their own healthcare by allowing access to their medical records. The patient can also elect to allow access to their medical record by trusted relatives and other agents. In this way, an adult child can "look in" on his parents or grandparents health status.

Other technologies such as computerized physician order entry (CPOE) are actually complementing HIPAA regulations and provide additional incentives for moving toward electronic medical record implementation. The portability aspect of the regulations can also be made possible through technology support. An Internet standard called extensible markup language (XML) allows the health information that is stored on the World Wide Web to be able to "move" between systems because the information on the web page is field-tagged so that it can be portable between systems. Technology standards will again facilitate many processes and are necessary for rapid improvement.

The HITECH Act of 2009 (a component of the American Recovery and Reinvestment Act) added a requirement for self-assessment of the security provided for protected health information concerning patients. The legislation empowered the Office of Civil Rights to investigate and assess penalties to any healthcare entity when any breach of protected health information occurs. Each entity must have undergone a self-assessment on three levels to document that steps needed to protect these data were undertaken by the entity. Failure to address these security issues and the technology of the entity could result in large fines if the healthcare organization would be found to have willful neglect regarding the requirements of the act.

Emerging technologies

"The imperatives of improving documentation, reducing errors, and empowering patients to engage in their own healthcare management will continue to motivate use of information technology in health care."[20] There are so many exciting and emerging technologies to investigate that we usually find it more interesting to look at the technological "low hanging fruit" than to elaborate on the future implications of advanced innovations, such as genomics and nanotechnologies. There are a number of futurists who predict that disruptive technologies must be anticipated because they will heavily impact organizations on both strategic and tactical levels.

A growing trend to make participatory healthcare (in which patients and their nonprofessional caregivers are fully engaged in healthcare management) has been facilitated with the rapid growth of social networking on the Internet. Previously, the Internet had the functionality of what we describe as the three "C's" to include content, communication, and commerce. A fourth functionality is that of community. Online, trusted communities allow patients to learn what to do and how to do it and partner with people who share a similar condition, to remain motivated in their active participation in healthcare. A website like http://patientslikeme.com is an excellent example of an online healthcare community.

The name for this expanded use of the Internet is Web 2.0 or Health 2.0. We have reached a point at which the majority of adult American citizens have cell phones or smart phones with them day and night, within three feet of their person. Applications are bound to assist patients and healthcare providers alike with decision-making regarding all aspects of patient care. The vision for how technology allows a higher quality of life to all citizens while keeping them in their homes and out of institutions is made possible by the integration of health enterprises that range from the intensive care unit all the way into the patient centered medical home.

A center for excellence that promotes aging in place is found at the University of Missouri at Columbia. In this community, networked homes allow for affordable, consumer electronics to provide peace of mind that the health status of each networked home's occupant is receiving monitoring and real-time communication with the health system. Thus, a true continuity of care can be achieved, and family members can be assured that their loved ones are receiving the best care possible.

Clinical drug literature

Accessing, reviewing, analyzing, evaluating, and interpreting clinical drug literature are important responsibilities of healthcare practitioners; this is particularly true for pharmacists, who are experts about drugs and medication therapy management. Pharmacists have been using and providing drug information for decades, focusing initially on drug product compounding and dispensing information. However, the need for drug information has expanded along with the pharmacists' roles. The 1975 report of the Study Commission on Pharmacy concluded that the pharmacy profession was not effective in developing,

organizing, and distributing knowledge and information about drugs. In fact, they felt that pharmacy's greatest deficiency was its inadequacy as an information transmitting system to patients, physicians, and other healthcare practitioners.[21]

Although more work is needed to fully realize the pharmacist's potential in all practice settings, the profession has certainly made great strides forward since the Study Commission's report with regard to providing enhanced drug and therapy-related information to patients, physicians, and other healthcare professionals. This is evidenced by the continual growth and development of patient-oriented pharmacy services across practice settings. Also, the establishment of the entry-level Doctor of Pharmacy degree program and the expansion of residency opportunities are helping to better prepare future practitioners to function as information specialists on the healthcare team.

The types of drug information needed by pharmacy practitioners and other healthcare professionals are varied and include, but are not limited to, information about side/adverse effects, interactions, uses, teratogenicity, stability, and compatibility; product identification and availability; dosages and administration; toxicity, pharmacokinetics, pharmacodynamics, pharmacogenomics, health-related quality of life, and pharmacoeconomics; and efficacy, including comparative efficacy among drugs in the same chemical or pharmacological class as well as among drugs from different classes. Health professionals must be knowledgeable about not only the variety of information resources available and how, why, and when to use them, but importantly, must be able to critically analyze, evaluate, interpret and apply the information they locate.

Advances in computer and hand-held technologies, the growth of the Internet, and the widespread availability of user-friendly MEDLINE and other database-searching capabilities have placed unprecedented and continually expanding amounts of information readily within an individual's grasp. In particular, patients and healthcare providers are increasingly turning to the Internet as an information resource, despite the unregulated and variable quality of information provided there.[22] A National Health Interview Survey conducted in 2009 found that approximately 51% of adults aged 18 to 64 years old had used the Internet to look for health-related information during the previous year,[23] with a 2010 Harris Poll estimating that 175 million American adults have sought health information online.[24] Key responsibilities of pharmacists and other health professionals regarding Internet use include differentiating good from poor quality information, identifying strengths and limitations of available information, appropriately applying the information patients obtain to their personal health needs, reviewing with patients the applicability of the information they locate, and recommending to patients high quality websites on topics of interest or websites that review and select Internet resources based on specified criteria (e.g., Medlineplus: http://www/nlm.nih.gov/medlineplus/).

Roles, responsibilities, and drug information

Pharmacists have diverse responsibilities that necessitate information use, including responding to medication inquiries of a variety of types from patients and health professionals, adverse drug event monitoring and management, resolving drug therapy related problems, making drug use decisions, providing educational activities, and engaging in clinical research. To accomplish these responsibilities, pharmacists must be able to locate complete, up-to-date information on which to base patient-care and other important decisions. Locating information includes selecting a proper database, using an optimal search strategy, and having the needed information readily available. It is clear that the appropriate use of technology is critical for the contemporary pharmacist as well as other healthcare professionals. A field has emerged, termed biomedical informatics, defined as the study and pursuit of "the effective uses of biomedical data, information, and knowledge for scientific inquiry, problem solving, and decision making, motivated by efforts to improve human health."[25] Biomedical informatics encompasses "medical informatics," "health informatics," and "clinical informatics;" the latter terms have been used synonymously with each other.[26]

Once acceptable sources of information are identified and retrieved, health professionals must analyze and evaluate the published literature and develop recommendations based on the best available data.

Knowledge of searching techniques, research design, and biostatistics is fundamental to the critical evaluation of literature, particularly clinical studies. Once relevant evidence from published clinical research is obtained, evidence-based medicine (EBM) principles should be applied to arrive at drug therapy related decisions. Two fundamental principles of EBM involve: (1) considering the hierarchy of evidence (e.g., observations, clinical studies and the strength of study designs) when making clinical decisions, and (2) considering benefits/risks, inconvenience, costs, and patient values and preferences together with evidence in making clinical recommendations.[27] Since EBM is being increasingly taught to and applied by healthcare practitioners, pharmacists should be knowledgeable about this process. The Evidence-Based Medicine Working Group has published an easy to carry book that reviews the essentials for applying EBM to clinical practice, and this resource is recommended to readers wishing to learn more about this area.[27]

Adverse drug events/experiences/reactions and medication errors not only result in patient morbidity and mortality, but also increase healthcare costs by millions of dollars annually. Pharmacists play an active role in preventing, detecting, and reporting adverse events. Pharmacists are one of the major groups of healthcare professionals who report adverse drug events to the Food and Drug Administration (FDA) via MedWatch. Information about this program can be found online at http://www.fda.gov/Safety/MedWatch/default.htm. Serious adverse events can be reported by calling the FDA at 800-FDA-1088, by completing the FDA 3500 Voluntary Adverse Event Report Form online or by downloading the form and submitting it by fax to 800-FDA-0178. Safety alerts that the FDA has issued over the past several years can be accessed through the website listed above, and health professionals can sign-up to receive free e-mail MedWatch updates. Pharmacists can also implement systems to prevent drug misadventures (such as errors in the prescribing, dispensing, and administration of medications) and to enhance patient adherence. The Institute for Safe Medication Practices (ISMP) operates the National Medication Errors Reporting Program (ISMP MERP), through which health professionals can report medication errors of a variety of types (e.g., dosing or calculation mistakes, route of administration errors), confusing drug packaging or names, or the misuse of medical equipment with the goal of improving patient safety. This program can be accessed online at: https://www.ismp.org/orderforms/reporterrortoISMP.asp. Pharmacists can access ISMP safety guidelines on a number of different topics from their website, as well as listings of often confused drug names that resulted in medication errors, oral dosage forms that should not be crushed, and error-prone abbreviations to avoid.

Another important role that pharmacists perform is actively participating in pharmacy and therapeutics committees that establish and maintain formulary systems and make decisions and recommendations concerning rational drug use within healthcare institutions. This type of committee is generally multi-disciplinary and reviews medication safety data, develops drug therapy guidelines, and conducts medication use evaluations. Drug use evaluation (DUE) and medication use evaluation (MUE) have often been used interchangeably, although MUE has been used to emphasize the entire multidisciplinary approach to enhancing medication use in an institution, beyond the process of evaluating the appropriateness of medication therapy through a systematic process using defined criteria and standards (DUE).[28] Through the design and conduct of DUEs and MUEs, pharmacists can play a key role in ongoing improvement in drug use and patient care.

Pharmacists are involved in many different drug information-related educational activities conducted for other healthcare professionals and patients. Since the practice of medicine and pharmacy involves lifelong learning about the ongoing advances in pharmacotherapeutics, pharmacists can contribute to the continuing education (and continuing professional development) of healthcare professionals through preparing and disseminating newsletters and by providing seminars and lectures. Pharmacists also play a key role in providing verbal and written information to patients about their medications, medical conditions, and nondrug therapies useful for managing these conditions.

Participating in clinical and practice-based research trials is another application of the drug information skills of pharmacists, allowing them to improve their understanding of how drugs work, comparative drug efficacy, and how to better deliver

medication therapy and related information to enhance patient care. Familiarity with the research process and medication use also makes pharmacists especially well suited to serve on institutional review boards, which are established to protect the rights of study subjects.

Drug information centers were established in the mid-1960s.[29,30] They are usually staffed by pharmacists who review, collect, organize, and analyze drug information and disseminate it to healthcare professionals and consumers.[31,32] Drug information centers or services often exist as functioning departments within healthcare institutions, within the pharmaceutical industry (e.g., medical information contact centers),[33] in academic settings, or as independent centers serving healthcare professionals and the public.[34–36] The activities of drug information centers or services have changed considerably since they were first established to primarily answer inquiries. A regularly administered survey of US pharmacist-operated drug information centers offering services to healthcare professionals found that 54 such centers existed in 1974; this number increased to a maximum of 127 in 1986 and the most recently published 2008 survey reported a total of 75 centers.[37] The activities reported by these centers included educating health-professions students, conducting pharmacoeconomic evaluations, providing direct patient care at bedside, providing informatics support, reporting adverse drug reactions, and providing educational in-services, among other functions. Despite the proliferation of readily available information and resources, many of the surveyed centers reported an increase in the complexity of drug inquiries received.[37] Thus, drug information centers or services can be an excellent resource for healthcare practitioners when assistance is required in handling a difficult clinical problem or when significant time or resource constraints exist.

The patient: behavioral determinants

Introduction

Health professionals often assume that the process of healthcare simply involves a patient to seek care for his or her symptoms, a physician to prescribe appropriately, a pharmacist to dispense appropriately, and a patient to follow directions and take the medication properly. Similarly, it is tempting to believe that patients, upon following physician and pharmacist suggestions, readily experience symptom improvement and better health. The reality is that many individuals needing healthcare do not receive it, receive it late, or do not follow through with directions. For example, a National Health Survey shows that at least 30% of those considering help for emotional problems do not actually seek care.[38] In other cases, there may be a considerable delay in seeking care. While most breast cancer symptoms are discovered by women, at least one third of breast cancer patients will be aware of their symptoms for three months or more before seeking an initial provider evaluation.[39] In addition, 30% to 60% of all individuals who obtain medical care do not follow through with prescribed treatment,[40] and almost half of those taking medications do not ask any questions when visiting the physician.[41]

Why do some people seek medical advice while others with similar symptoms do not? Why do some individuals who obtain medical care follow recommendations and take an active role in their care, while others with similar diagnoses and treatments do not follow through with recommendations and do not ask any questions about their treatment? To answer these questions, we need to understand the determinants of patient behavior.

Types of patient behavior in health

The three main areas in the study of patient behavior are: (1) preventing illness or detecting it in an asymptomatic stage, (2) obtaining a diagnosis and discovering suitable treatment, and (3) undertaking or maintaining treatment aimed at restoring health or halting disease progression. Kasl and Cobb[42] defined these health-related behaviors and labeled them *health behavior*, *illness behavior*, and *sick-role behavior*, respectively. The definitions are still useful today, although some terminology has changed to reflect contemporary theory and research on health behavior.

Health behavior that is preventive in nature generally is referred to as preventive health behavior. By expanding on the original definition, preventive health behavior is defined as actions taken to prevent illness and maintain physical, emotional, intellectual,

spiritual, and social well-being. Examples of preventive health behaviors include participation in health screening programs, following healthy diet recommendations, participation in relaxation and cardiovascular exercises, and creating and maintaining close personal relationships.

Illness behavior is any activity undertaken by individuals who perceive themselves to be ill that defines the state of their health and aids in discovering a suitable remedy.[43] Illness behavior is the way persons respond to bodily indications that they experience as abnormal; thus it involves the manner in which persons monitor their bodies, define and interpret their symptoms, and seek healthcare.[44] Individuals attempt to ascribe cause and meaning to their illness symptoms and may self-diagnose and treat. Alternatively, individuals may visit a doctor or another prescriber and a pharmacist in order to obtain a prescription drug.

Actions taken to restore health or halt disease progression traditionally have been referred to as sick-role behaviors and now are referred to as *treatment behaviors*. Originally, the conceptualization of sick-role behavior[45] offered a systematic approach for analyzing the behavior of sick individuals in the US and other modern Western societies. This functionalist perspective regarded illness as dysfunctional to society and considered sick-role behavior as seeing the physician, passively following his or her prescription, and regaining health. This traditional view of the patient as a passive individual has been criticized extensively in recent years.[46]

Patients today are considered to be thinking, able decision makers who can play an important role in the treatment process.[47] Because patients are now recognized as active individuals, more attention is being paid to ways of restoring health or slowing illness progression through improved provider–patient communication and patients' involvement in their own treatment. For example, patients are actively searching the Internet and other sources for health information. Emphasis therefore is placed on a range of patient treatment behaviors, including sharing beliefs and expectations, asking questions, adhering to regimens, using home monitoring devices, keeping appointments, identifying and reporting side effects and drug-taking problems, and other valuable forms of communication that are necessary in contemporary healthcare.

Patient communication

A constructive pharmacist–patient relationship is essential to sound healthcare practice and the optimal well-being of the patient. This relationship involves using both verbal and nonverbal communication. To provide quality patient care, pharmacists must have the desire and ability to communicate effectively with patients, other healthcare professionals, and the public.

Communicating and patient empowerment

Communication is the sharing of information, ideas, thoughts, and feelings where the goal is achieving an understanding between the participants. It involves the spoken word and also what is conveyed through inflection, vocal quality, facial expression, body, and other behavioral responses. The interactions of a pharmacist and a patient usually can be categorized as either an information-gathering or information-giving communication session.[48] Information gathering usually occurs during a medication-history interview, which is a conversation with a multifaceted purpose. Pharmacists initiate the interaction to investigate and acquire data about a patient's medication-taking experiences, assess a patient's understanding of previous and current medication-taking experiences, and gauge a patient's motivation for adhering to the medication regimen. In addition, pharmacists may suggest to the patient's prescriber a change in regimen if the information gathered warrants such an action.

Patient empowerment is a concept that refers to patients' rights to make their own choices about their healthcare.[49] Research has revealed that a patient who is involved in deciding on his or her treatment regimen is more likely to adhere to the treatment.[50,51] Feste argues that "the empowerment model has evolved out of the realization that patients cannot be forced to follow a lifestyle dictated by health-care professionals."[49] The patient empowerment model is based on the assumption that to be healthy, people must be able to bring about changes not only in their personal behavior but also in their social situations and the institutions that influence their lives.

Effective healthcare communication should include patient empowerment in the patient–provider

relationship. Funnell and associates explain the process and outcome of patient empowerment.[52] They suggest that "people are empowered when they have sufficient knowledge to make rational decisions, sufficient control and resources to implement their decisions, and sufficient experience to evaluate the effectiveness of their decisions. Empowerment is more than an intervention or strategy to help people make behavior changes to adhere to a treatment plan. Fundamentally, patient empowerment is an outcome. Patients are empowered when they have knowledge, skills, attitudes, and self-awareness necessary to influence their own behavior and that of others in order to improve the quality of their lives."[52] Table 10.1 provides an outline of patient empowerment as adapted from Funnell's model. This outline may be used by pharmacists to achieve more effective patient counseling encounters.

Benefits of effective patient counseling

Using effective communication strategies and engaging patients in their healthcare treatment can provide significant benefits to both the patient and the pharmacist. Patients will have a better understanding of the purpose for the prescribed therapy and the appropriate use of the medication. This leads to several potential benefits:

- Improved therapeutic outcomes and decreased adverse effects
- Improved patient adherence to the treatment plan
- Decreased medication errors and misuse
- Enhanced patient self-management by involving the patient in designing the therapeutic plan
- Decreased healthcare costs resulting from appropriate use of medications and prevention of adverse events.

The pharmacist also benefits in this process. Potential benefits to the pharmacist in this process include

- Enhanced professional status in the view of patients and other healthcare providers
- Establishment of an essential component of patient care that cannot be replaced by technicians or automation
- Enhanced job satisfaction through improving patient outcomes
- A value-added service to offer patients
- Revenue generation through payment for cognitive services
- Fulfillment of legal responsibility to counsel patients according to the OBRA 90 and other required guidelines.

The Ad Hoc Panel on Medication Counseling Behavior Guidelines of the USP has identified six desired outcomes of patient counseling.[6] It is expected that, as a result of a properly conducted counseling interaction, the patient will

- Recognize why a prescribed medication is helpful for maintaining or promoting well-being
- Accept support from the healthcare professional in establishing a working relationship and foundation for continual interaction and consultation
- Make more appropriate medication-related decisions concerning compliance or adherence
- Improve coping strategies to deal with medication side effects and drug interactions
- Become a more informed, efficient, active participant in disease treatment and self-care management
- Show motivation toward taking medications to improve his or her health status.

Patient adherence

Healthcare continues to advance in the understanding and treatment of many disease states. This has lead to the development of new treatment options for the control or cure of many clinical disorders. Despite the advances in care, treatment can fail to be successful. In order for treatment to be effective, a patient must still ultimately make the decision to follow the prescribed regimen as instructed.

This concept of compliance in healthcare can be viewed broadly as it relates to instructions concerning diet, exercise, rest, return appointments, and the use of medications. It is in discussions concerning drug therapy that the designation *patient compliance* is used most frequently. Many terms such as *compliance*, *adherence*, and *persistence* are used interchangeably, but there are differences between them.

Adherence can be defined as "the extent to which a patient's behavior corresponds with the

Table 10.1 Outline of a patient empowerment program

Healthcare professional assesses current status (physical, emotional, cognitive, etc.)
Reviews patient's actual self-care practices
Reviews patient's recommended self-care practices
Healthcare professional provides relevant medical information
Describes various treatment options
Reviews costs and benefits for each option
Healthcare professional acknowledges patient's responsibility for self care
Helps patient clarify personal values specific to their illness
Helps patient assess level of personal responsibility for their care
Helps patient select treatment goals
Patient identifies barriers and strengths related to achieving self care
Assesses medical barriers and sources of support
Assesses life/social barriers and sources of support
Patient assumes problem-solving responsibility
Develops skills to optimize support (e.g., communication and assertiveness skills to enhance support from family and friends; increases support networks)
Identifies potential barriers
Learns strategies/skills to overcome barriers (e.g., negotiation, self-care agreements and plans, conflict resolution)
Patient establishes plan with assistance from provider
Patient carries out plan
Patient and provider evaluate and review plan using problem-solving model.

(Adapted from Funnell MM, *et al. Diabetes Educator* 1991; 17(1): 37.)

recommendations of a healthcare provider."[53] When viewed in this context, adherence and compliance are synonyms and can be substituted for one another. Adherence with therapy implies an understanding of how the medication is to be used, as well as a positive behavior in which the patient is motivated sufficiently to use the prescribed treatment in the manner intended. It also implies that the patient perceives self-benefit and a positive outcome associated with the prescribed treatment, such as enhanced daily functioning and well-being.

Persistence is a similar concept to adherence but can be defined as "the duration of time from initiation to discontinuation of therapy."[54] Persistence to a regimen is maintained as long as the patient does not exceed the permissible gap (the time frame for which

a patient may discontinue medication without experiencing an adverse outcome).[55] Patients can demonstrate persistence with a given regimen while not being adherent to that regimen if they continue to take some medication but not in the prescribed manner.

Problems concerning patient compliance with instructions have been recognized for years. Hippocrates once cautioned, "Keep watch on the fault of patients which often makes them lie about the taking of things prescribed." Twenty-three centuries later, attaining patient adherence in the use of their medications continues to represent a formidable challenge for healthcare providers.

When the complexity of the illnesses and the actions of therapeutic agents are considered, the physician, pharmacist, and other health professionals easily can become preoccupied with the diagnosis of the disease state. It is often assumed that the patient will follow the instructions provided as the medications are being provided to improve and maintain the patient's health. Studies continue to show that a large percentage of patients do not take their medication in the manner intended.

Some patients make a conscious decision to deviate from the prescribed regimen (i.e., *intentional* nonadherence). However, many patients intend to take their medication according to instructions and may even be unaware that their use differs from what the prescriber intended. The term *patient non-adherence* implies that the patient is at fault for the inappropriate use of medication. While this may often be the case, the physician and pharmacist may not have provided the patient with adequate instructions in a manner that the patient understands. The most basic questions regarding drug usage must be addressed: Has the patient been provided with adequate instructions? Does the patient understand how the medication is to be taken? Nothing should be taken for granted regarding the patient's understanding of how to use their medication.

Drug education

Drug use occurs in virtually every society and culture. Whether the use of a particular drug is for a medical or a nonmedical reason, problems resulting from use often arise. Preventing drug use problems is a major concern of most societies, and it usually is highlighted when specific outbreaks of problems or inappropriate use occur. As pharmacy is the profession to which the control of drugs is attributed, it should be involved intimately with those activities aimed at preventing or reducing drug use problems. In fact, the pharmaceutical profession should be providing the leadership and directing the research in this area. It is unfortunate that, on the whole, pharmacy has been lacking in its social responsibility for the chemical substances it develops, promotes, and dispenses.

Most pharmacists are aware of the important problems that potentially can occur with the appropriate use of prescription medications, such as adverse reactions and drug interactions. Many pharmacists also are knowledgeable about potential problems inherent in self-medication with a non-prescription drug, though they probably are less familiar with the use of herbal remedies and homeopathic medications in the same context. Few pharmacists, however, are aware of potential problems that can arise with social–recreational drug use. Regardless of the situation, the problem of poisoning or overdose by a drug should be delegated to poison-control centers and hospital emergency rooms. The individual pharmacist, particularly one working in a community setting, may not feel capable of consulting or educating a particular drug consumer in these problem areas.

Most societies are in great need of learning more rational and appropriate uses of all types of drugs and of gaining control over the products (drugs) of their own technology. Humans have learned how to create (extract and/or synthesize) drug products, yet humans have not learned fully how to use these products in an optimal manner. The primary importance of drug education is its benefit to the drug user (patient or consumer); such education can improve the appropriateness of drug taking behaviors to achieve optimal health and well-being. At the center of any educational effort is the provision of drug information, the strategy with which pharmacists and pharmacy students are most familiar. In today's highly complex, technological world, the availability of current and precise information allows one to understand, to make better choices, and to prevent or solve problems.

The individual best suited to assist people in preventing drug use problems and in achieving optimal,

desired experiences from their drug taking is the pharmacist. The pharmacist is an accessible source of high-quality information and educational programs, and should be concerned with a person's drug taking behavior. Whether it be the use of a prescription medicine or a herbal remedy to achieve or maintain a state of health, the use of a drug for its socially oriented effects in a recreational setting, or the ingestion of a chemical substance to enhance a religious or aesthetic experience, the perspective presented herein considers the pharmacist to be the leader in efforts to prevent or limit drug use problems.

Although information about, and inherent problems resulting from, specific types of drug taking might vary from drug to drug or among reasons for use, the fundamental approach to educating people and fostering changes in drug use is the same. The word *drug* refers to any substance, other than food, which by its chemical or physical nature, alters structure or function in a human being, resulting in physiological, behavioral, or social changes. This includes all medicinal agents (whether defined legally as prescription or non-prescription), herbal and home remedies, alcohol and caffeine (and other substances that are often considered *food* by consumers, but are used for their pharmacological activity), substances used primarily in a nonmedical context, and even poisons.

These techniques and strategies, and their basic principles, are also applicable to educating patients about medicines or providing drug education programs in any context. It is important to realize that, conversely, ideas, strategies, and programs from the field of patient drug education can be relevant to the development of programs on the nonmedical use of drugs, and some examples of this broader view of drug education are provided.

Drug use and drug education

Human beings engage in a great variety of drug taking behaviors, but one of the most important and rudimentary considerations involves the definition of what constitutes a drug and which situations characterize drug taking. Individuals hold different beliefs and perceptions about which chemical substances they regard as being drugs. A useful and interesting exercise in a drug education program involves asking or surveying the audience about their beliefs and perceptions. The audience is shown a list of chemical substances and asked to indicate which ones are drugs and which ones are not. Not only can this exercise, and its results, provide the educator with a better idea of the opinions and level of drug knowledge of an individual or group, but it also can be used as a focal point for discussion at that time or during subsequent sessions. The belief that certain substances may be drugs is important in understanding why and how people use such substances, and it should be a primary consideration in the development of any drug education program.

The nature and extent of certain types of drug taking vary by drug, availability (or accessibility), and the reason for use. In the medical realm, drug taking may be initiated by the patient, as in self-medication, or it may be directed by another person, usually a physician, who writes a prescription. Studies of self-medication are limited. The research done in this area indicates that self-diagnosis, rather than making contact with the healthcare delivery system, occurs in the majority of illness episodes and that self-medication occurs from 60% to 90% of the time in these situations.[56] Studies of nonprescription-drug consumption indicate that, in general, approximately one-third of a population can be defined as current users of such substances and that from 25% to 60% of a population are users of such drugs during any specific period.[56] The prevalence of nonprescription drug use is even higher in the older adult population (ranging from 50% to 90%), in addition to their extensive use of prescription drugs.[56]

The annual Slone Survey (1999–2007) studies medication use of all types at the population level.[57] The most recent results of this survey determined that during 2006, 82% of adults had used at least one medication in the week prior to the study interview; 52% used at least one prescription medication; and 29% used five or more. The highest prevalence of medication use was among older women; 57% used at least five medications, and 19% used at least ten. Herbal products were used by 22% of the population, and 32% of prescription users also used a herbal concurrently. Vitamin and mineral supplements were used by 41% of the population.[57]

When a drug is prescribed for a patient, health professionals expect that the drug will be taken precisely as directed. Adherence with medication regimens is

another type of drug taking considered of major importance in a successful treatment plan. There have been many studies in this area; their results have shown that anywhere from 5% to 90% of patients may be non-adherent in some manner.[58] Although there is a wide variation in non-adherence, caused by various factors as well as the research design of particular studies, the rate of non-adherence, in general, probably ranges from 33% to 50% in any given population.[58] This situation represents a different behavior; many patients are not taking drugs when they should be.

Drug taking also occurs in a nonmedical context. Although cigarette smoking has declined steadily among adults, tobacco use has increased in young people during the past few years.[59] The prevalence of alcohol use has remained stable for many years, but there is an increase in binge drinking among young adults, especially college students.[59] Nationwide surveys of drug use, conducted by the National Institute on Drug Abuse in 2010, found that 11% of youths (less than 18 years), 41% of young adults (18 to 25 years), and 27% of adults (26 years or older) were current users of tobacco, whereas 14% of youths, 65% of young adults, and about 60% of adults were current users of alcohol.[59] The survey was sponsored by the Substance Abuse and Mental Health Services Administration (SAMHSA).

The annual National Survey also found that marijuana use is on the rise, while methamphetamine use is on the decline. The survey found the most popular drug is marijuana, with 17.4 million regular users. In 2007, 14.4 million Americans said they used marijuana. An estimated 6.9% of those surveyed in 2010 said they use marijuana regularly, compared with 5.8% in 2007. Among 12 to 17 year olds, 7.4% said they had used marijuana in the previous month in 2010, about the same percentage as 2009. Among 18 to 25 year olds, 18.5% said they had used marijuana in 2010, up from 16.5% in 2008.

The nonmedical use of most other types of psychoactive drugs has declined during the past decade, but there have been increases in the use of some substances over the past couple of years.[59] The nonmedical use of Ecstasy and some psychedelic drugs (e.g., LSD) have increased in the past two years. The nonmedical use of prescription psychotherapeutic drugs also has increased in the past year. Nonmedical use of prescription medications has increased over 500% in the past decade. This category has become the most significant problem area in nonmedical drug use. The misuse of drugs, including the development of an addiction, also decreased slightly in the past couple of years.[59] Among 12 to 17 year olds, 7.3% misuse or are dependent on any drug (including alcohol); among 18 to 25 year olds, it is 19.8%; and for people 26 years of age and older, it is 7%. Alcohol is the biggest problem, by far, followed by marijuana and then by the nonmedical use of a prescription psychotherapeutic agent (primarily pain relievers).[59] Drugs are also the cause of almost one-half of all poisoning episodes, a type of drug-taking behavior that is usually unintentional, except in cases of suicide.

Drugs clearly are used appropriately in certain situations for beneficial reasons, are not used in some instances when they should be, and are used inappropriately on many occasions. In all three circumstances, though most often in the last two examples, problems can result from drug use. The prevention or recognition and management of problems resulting from drug use are the main reasons for developing and providing drug education programs.

Two additional aspects of drug use important in assisting drug users are their type of drug use behavior and their reasons or motivations for use. The focus of many drug education programs is on the drug itself and not the behavior (drug use). This has led to programs that focus on illegal drugs, but not legal drugs; on "hard" drugs, but not "soft" drugs; and on the pharmacology of the drug, but not on how that drug is used. Instead of focusing on these ill-defined or irrelevant terms, the focus of drug education should be on behavior, how and why the drug is being used. A typology of drug taking behaviors was developed by the National Commission of Marijuana and Drug Abuse in 1973,[60] and it can be useful in orienting both the educator's and audience's focus on drug use behavior, rather than on the drug itself (Table 10.2). Reasons or motivations for using drugs are the key to understanding why individuals use drugs. These reasons also should be addressed in developing and offering drug education programs (Table 10.3).

Drug education in a medical context has occurred for some time. Patient counseling always has been a part of the health professional's role, though the assumption of this role has varied from time to

Table 10.2 Typology of drug taking behaviors
Intensity – how much (single dose)
Frequency – how often (dosing schedule)
Duration – how long (length of use)
Experimental
Short-term, non-patterned trial
Variable intensity but minimal frequency
Reason: curiosity about effects
May be a shared social activity or individual
Low risk to individual and society
Limited long-term problems
Social–Recreational
Patterned use
Variable intensity, frequency, and duration
Social setting of use
Reason: for effects or group acceptance
Voluntary act
May not escalate, but can lead to habit formation
Low to high individual risk (differs by drug and dose)
Low to moderate societal risk
Circumstantial–Situational
Patterned use
Variable intensity and frequency, limited duration
Reason: task-specific and usually self-limiting achievement of effect to cope with symptom, condition, situation, or need
Personal (individual) use (setting)
Low to moderate risk to individual (dose-dependent)

(continued overleaf)

Table 10.2 *(continued)*
Low to moderate societal risk
Can lead to escalation in drug taking behaviors
(Self-medication hypothesis)
Intensified
Long-term patterned use (duration)
At least daily use with moderate to high intensity
Reason: achievement of relief from symptoms, situation, personal problems, possibly to prevent withdrawal
All settings of use
Drug Is a part of everyday life
Moderate to high risk for individual (dependence)
Moderate to high risk for society
Compulsive
Long-term patterned use (duration)
High intensity and frequency
Reason: dependence and loss-of-functioning, lifestyle drug and its use become central focus of life
High individual and societal risk

(Natl. Comm. on Marijuana and Drug Abuse, *Drug Use in America: Problem in Perspective*. Washington, DC: USGPO, 1973.)

time, especially in pharmacy. The principal strategies have been to provide either drug information or drug education to patients through verbal interaction. Structured educational programs have been developed throughout the twentieth century, but it was only after World War II that concerted efforts to develop and implement health education programs began to occur in public health. In the 1960s and 1970s, several attitudinal and behavioral approaches were studied to expand the traditional information-based approach and improve on the effectiveness of information only programs. At the beginning of the twenty-first century, the behavioral approach has become popular in health education programs, and the use of the mass media has increased dramatically.

Early efforts in education about non-medical drug use consisted of negative portrayals of drugs and classroom moralizing about drug use and through the mass media, with little objective information being presented. Such an approach unfortunately still can be found in many contemporary drug education programs. Several studies in the 1970s found that drug information programs, consisting simply of lecturing to young people, aroused their curiosity about drugs and increased the likelihood of experimentation with drugs.[61,62]

A few researchers and educators more recently have suggested a rather different drug education and drug prevention approach in which drug taking is

Table 10.3 Reasons/motivations for drug use
For drug's effects (therapeutic or otherwise)
Accessibility and availability of drugs
Peer pressure/modeling/social acceptance
Genetic predisposition
Suggestibility
Curiosity
Information, instructions, and accounts of drug effects and experiences (including other users, mass media and advertising)
Meanings of drug effects
Inherent behavior in humans
Rituals of preparation, administration, use
Religious reasons
Social and communication networks
Group/social interaction dynamics
Symptom sensitivity
Coping response
Physical and social setting
Social–cultural background of user
Political and social control
Escape
"I don't know"& "As an excuse" (for other behavior)

considered a *natural behavior*.[63] In this context educational programs focus on the need to alter one's state of consciousness in an acceptable way and to use drugs in a responsible manner consistent with one's lifestyle. The drug taker is alerted additionally to the importance of values and the influence of societal attitudes on drug taking. These two notions are extremely important in presenting programs or for counseling patients with regard to drug use. The use of peers in educational programs also increased in the 1990s. Much of the effort started in the field of alcohol education as attempts were made to move away from authoritarian, moralistic programs with abstinence as a goal to peer-facilitated strategies based on the concept of self-discovery and the fact that alcohol use is socially approved and engendered in most societies, even if it is an illegal activity for certain segments (e.g., by age) of the population.

Professional communications

Introduction

Communication is a vital skill, necessary for success in personal and professional settings. Pharmacists often serve as the guardians of appropriate drug therapy. Therefore, communicating effectively is key to reinforcing the value of the pharmacist within the healthcare system. Pharmacists communicate with a wide variety of healthcare professionals on a daily basis. The type of information that is communicated may be the same. However, the knowledge level and expectation of the audience dictate the delivery of the message. Regardless of knowledge or expertise, pharmacists cannot actively participate in patient care unless they can communicate effectively.

Pharmacy career options have expanded into multiple, distinct settings, including institutions, community, managed care, academia, regulatory, and industry. In all of these settings, professional communication is critical. Whether verbally responding to a physician's question during patient care rounds, providing an educational program to nursing staff, or publishing results of a research project in a biomedical journal, communication skills are paramount to effective pharmacy practice. This section will discuss appropriate professional communication skills related to communications with healthcare professionals, highlighting verbal and written skills, formal presentations, formulary communications, personnel communications, and communicating with administrators, and the media.

Communicating with healthcare professionals

Verbal communications

Regardless of the practice setting, verbal communication is the most common type of communication that pharmacists utilize. It is common for a pharmacist to be approached by several different individuals (with varying backgrounds), regarding a multitude of situations, in a single day. As practitioners, pharmacists should be encouraged to remember that any type of question or interaction, regardless of how informal it may seem, is an important method of professional communication. Whether responding to a question concerning compatibility of intravenous medications from a nurse, a drug dosing question from a physician, or a request about the adverse effects of a medication from a patient; all of these interactions require excellent verbal communication skills. The most common verbal communications that pharmacists engage in involve responding to drug therapy questions and receiving verbal drug orders.

Receiving drug-related questions

A major challenge in responding to requests for drug therapy recommendations is determining the unique situation that prompted the request. Often, the original request posed by a requestor does not represent the actual information needed.[64] Requestors of information are sometimes unclear when asking questions pertaining to specific-patient needs. This most likely occurs because they are not aware of the specific information that pharmacists need to provide a comprehensive response. Therefore, pharmacists should recognize this potential challenge and use appropriate listening and questioning skills to collect pertinent background information to determine the exact context of the question. Questions that often appear simplistic in nature at first glance may actually be more complex when all appropriate background information is considered. If pertinent background is not determined and the pharmacist does not have a clear understanding of why the question is being asked, patient care could be jeopardized. For example, if a physician asks a pharmacist a question regarding the dose of a medication, inaccurate and potentially harmful information may be provided if patient-specific factors such as age, weight, and renal or hepatic function, are not considered.[64]

Consider the example of a middle-aged man who approaches a community pharmacist and asks the question "Is Advil good for muscle pain?"[65] At first glance this appears to be a relatively simple question. Advil contains ibuprofen, which is a common over-the-counter (OTC) analgesic. Therefore, it would appear that a reasonable answer to the man's request would be "yes." However, what if the pharmacist further questions the man about his medical history to determine why he was asking this question? After further questioning, the pharmacist realizes that the man had recently started lovastatin therapy. This additional background information suggests that the

patient may be experiencing symptoms of lovastatin-induced myopathy. Instead of answering the question at face value, the pharmacist in this situation is able to identify a potential drug-related adverse event by collecting important background information to determine "why" the man was asking the question.

The previous example illustrates the importance of questioning strategies to collect pertinent background information and determine the true information need. Pharmacists should apply the appropriate skills to ask logical background questions in a reasonable sequence to clarify each question. This is especially important when confronted with an impatient requestor who may not realize the value of gathering background information. When receiving drug-related information requests from healthcare professionals, it is particularly useful to ask the information requestor if his or her question is about a specific patient.[64] This allows the pharmacist to ascertain key patient data immediately and usually prompts the requestor to describe more information about the patient. Another helpful questioning strategy is to use open-ended questions.[65] Open-ended questions cannot be answered by one-word, short answers, but require responses with detailed descriptions, and enhance information exchange about the context of the question. In the previous example about Advil and muscle aches, an appropriate open-ended question could be, "Please describe your muscle pain to me." This allows the patient to provide more details about the circumstances surrounding his question. There are situations, however, when the pharmacist will need to ask direct questions to obtain certain types of factual information like patient age, weight, or current medications. For pharmacists to gain a clear understanding of the actual question, a mixture of different types of questioning strategies should be used.

In addition to asking appropriate questions, it is important to have strong listening skills. Pharmacists should avoid all possible distractions when gathering background information. If the interaction is in person, the pharmacist may use non-verbal cues such as facial expressions, eye contact, and other forms of body language to interpret the requestor's response to his or her background questions. Racial and cultural differences are also important issues to consider during in-person interactions. Communicating over the telephone is inherently more difficult, and in these situations pharmacists must be especially skilled in gathering background information. It is very important to ask for clarifications when necessary to ensure a complete understanding of the situation. Finally, an important last step to collecting appropriate background information is to repeat the question or request to verify the inquiry. This will help clarify any discrepancies between the requestor and pharmacist. Pharmacists should remember that it is their professional responsibility to collect pertinent background information to fully understand the true information request. Providing drug therapy recommendations without a complete understanding of the pertinent background is simply negligent. Table 10.4 provides a list of important background questions to consider when receiving a drug-related request. These questions allow the pharmacist to formulate the most appropriate response. Care also should be taken to identify when a response is needed. Providing timely and accurate responses establishes the value of pharmacists as drug therapy experts.

Responding to drug therapy questions

After a complete and accurate response to the request is developed, communicating the information clearly and concisely is critical. Utilization of appropriate information resources, data analysis, and formulation of responses is beyond the scope of this section. However, the reader is referred to *Drug Information: A*

Table 10.4 Questions to consider when collecting pertinent background information

What is the requestor's name, profession, and affiliation?
Does the question pertain to a specific patient?
Do I have a clear understanding of the question or problem?
Do I know if the correct question is being asked?
Do I know why the question is being asked?
Do I understand the requestor's expectations?
Do I know pertinent patient history and background information?
Do I know what unique circumstances generated the question?
Do I have insight about how the information I provide will actually be used?

(Data from Calis KA, Sheehan AH. In: Malone PM, Kier KL, Stanovich JE eds. *Drug Information: A Guide for Pharmacists*, 4th edn. New York, NY: The McGraw-Hill Companies, 2012.)

Guide for Pharmacists for more information on this topic.[64]

In the clinical pharmacy practice setting, verbal communications may be more common than written communications. Therefore, it is very important for pharmacists to have the necessary skills to communicate information verbally in an effective manner. Oral responses are generally preferred because they are more personal than written responses, and they allow for prompt clarification of information that may be unclear. Verbal responses may also be favored in situations that are of high priority (emergency situations when a prompt response is needed) or when a sensitive issue is being discussed. It is important to note that when pharmacists effectively communicate drug information in a face-to-face manner, they promote the profession of pharmacy by being recognized as valuable members of the healthcare team. However, when information is communicated orally, the risk for misinterpretation exists.[66] Factors that may potentially increase the risk for misinterpretation during oral communication include differences in vocabulary, pronunciation, accent, and speaking pace.

When communicating important drug therapy information, the pharmacist should always make sure to identify him- or herself professionally. This provides the requestor with confidence that a professional with appropriate educational background and training is responding to their request. If responding to a question that was posed during a previous interaction, it is recommended to review briefly what the initial drug therapy question was for the purpose of refreshing the memory of the requestor. For questions that are specific to a certain patient, the patient should be identified to avoid any potential confusion.[66] When verbally communicating the specifics of the response, the pertinent facts should be stated, limitations to the literature should be acknowledged, and a final conclusion and recommendation should be provided.[64,66] Pharmacists should make sure to focus on the key points in a clear and concise manner and reinforce the major point again at the end of the conversation. All relevant information should be presented. However, describing large amounts of minor details should be avoided. It may be helpful to write a brief outline using bullet points with the major issues to be communicated. This helps to ensure that pertinent information is not forgotten and that the information is communicated in a clear and concise manner. Once the response has been communicated verbally, verification should be made to make sure that the information provided to the requestor was sufficient to meet his or her needs. An offer to provide written documentation of the response should also be made.[66] Proper methods for documenting drug therapy recommendations will be reviewed later in this section.

Displaying confidence is obviously very important during the delivery of the response. If the pharmacist does not appear confident in his or her response, the requestor may certainly have reservations about the information provided. Additionally, the vocabulary and terminology that is used should be appropriate for the given audience. For example, when communicating with a physician, professional terminology should be used and all medical terms should be pronounced correctly. Finally, follow-up questions should be expected and addressed in advance to save valuable time.

Follow-up is extremely important to maintaining professional practice. This allows pharmacists to verify if their recommendations were taken and to investigate patient outcomes while demonstrating dedication to patient care. Additionally, pharmacists can learn from their experiences and develop more confidence when they conduct regular follow-up to drug therapy recommendations.[64]

Although verbal recommendations do not always include a formal written response, it is important to document oral drug therapy recommendations for several reasons, including in the event that legal questions arise. Documentation also reinforces the usefulness of pharmacists to other healthcare professionals and contributes to pharmacist workload assessment. Proper methods for documenting drug therapy recommendations in patient medical charts are reviewed in the written communications section.

Using the telephone for communications

Pharmacists are often asked to respond to questions and provide drug therapy recommendations using the telephone. Therefore, all pharmacists should be familiar with professional phone etiquette. Face-to-face interactions are preferred, as they are more personal; however, in many situations telephone interactions are necessary. Regardless of the professional setting,

the telephone should always be answered by providing a greeting that identifies the pharmacist's name and affiliation (e.g., "Pharmacy Department, this is John, a pharmacist, speaking"). It is also helpful for pharmacists to have a pen and paper readily available before answering the telephone to document any notes that are necessary during the conversation. Many pharmacists find it helpful to write down the exact date and time that a call is received. The hold option should always be used when asking someone to wait on the telephone line. This maintains a professional setting and avoids the potential for the caller to overhear background conversations while waiting for the pharmacist to return to the telephone line. Repeating information to clarify any discrepancies is also especially important to avoid any confusion.

Receiving verbal drug orders

Pharmacists may be asked to receive medication orders over the telephone. A licensed prescriber, or an agent of the prescriber, can communicate a patient-specific order directly to the pharmacist. This process challenges the pharmacist to dictate the information necessary to accurately fill the prescriber's order, as well as quickly ascertain if the prescription will be an appropriate medication for the patient. Many institutions have limits on the types of orders (e.g., chemotherapy) that may be received verbally in order to improve medication safety.

The pharmacist should ask the prescribing party to identify him or herself and to provide the appropriate contact information to verify authenticity and to ensure a method of contact in case follow-up questions are necessary. Asking questions and directing the conversation can assist the pharmacist in controlling the rate and extent of information exchange. Patient-specific information must be obtained along with a complete and accurate description of the medication regimen. The patient's medication order should always be verbally repeated back to the prescriber to verify accuracy and reduce the risk for a medication error. Repeating information to clarify any discrepancies is especially important when taking verbal medication orders from a prescriber over the telephone. All verbal orders and telephone prescriptions should be repeated back to the prescriber to reduce the likelihood of medication errors. Ideally, pharmacists receiving verbal orders should document the complete order, read it back to the prescriber, and receive verification from the prescriber that the information is correct. It should also be documented that the verbal order was repeated back to the prescriber. For words that the pharmacist may not be familiar with, repeating the word back to the prescriber by spelling the word, using phrases such as "S as in Sam" and "T as in Thomas" may be particularly helpful. Verbal drug orders are not the ideal means of communicating drug therapy orders, but this method is sometimes employed for urgent institutional orders or as a means of convenience in community settings. Verbal drug orders emphasize the importance of excellent communication skills to allow accurate and rapid decision-making processes.

Written communications

The most critical written communications between pharmacists and other healthcare professionals are undoubtedly the prescription, in community practice, and medication order, in institutional practice. Other important types of written communications, including documentation of patient care, electronic communications, professional correspondence, manuscripts for publication, and poster presentations are discussed in this section.

Documentation of patient care in the permanent medical record

The Omnibus Budget Reconciliation Act of 1990 (OBRA-90) set forth the requirements for patients' education and maintenance of records; under this legislation, pharmacies must maintain records of patients' name, age, gender, contact information, significant medical, known medication allergies and intolerances, and all concurrent medications and medical devices. Records must also reflect the thought process of the pharmacist as it relates to patient care. For practitioners who previously did not formally document their therapeutic recommendations, OBRA-90 formalized the requirement for completion of that task. The OBRA-90 legislation requires that pharmacists maintain a database of documentation regarding input into patient care which may be located such that review by an impartial, external reviewer will clearly identify the intent of the pharmacist's actions in terms of patient care.

The American Society of Health-System Pharmacists (ASHP) endorses guidelines on documenting pharmaceutical care in patient medical records.[67] In developing these guidelines, it was emphasized that recommendations made by pharmacists on behalf of their patients should be documented in a permanent manner, such that information is accessible to all healthcare professionals caring for the patient. These recommendations may include the patient's medication history, allergies, consultations to other healthcare professionals regarding drug therapy management, verbal orders, order clarification, drug-related problems, drug-therapy monitoring findings, and patient education. It is stressed that documentation by pharmacists should incorporate a standard format and be written in a legible, clear, and complete manner.

The Weed method of documentation has been utilized and accepted by healthcare professionals including pharmacists. The Weed method consists of the development of a patient problem list and SOAP note, which organizes written patient care communications into subsections related to Subjective, Objective, Assessment, and Plan components for the identified problem(s).[68,69] In addition to the components, each chart note should be appropriately titled (e.g., Pharmacy Note), dated, timed, and signed with the appropriate professional designation of the pharmacist (e.g., PharmD) along with the method for follow-up contact from the recipient (e.g., pager or telephone number). The components of each of the sections of a SOAP note are included in Table 10.5.

The authors have expanded this methodology to include two additional components, Education and Outcomes. These were incorporated into the authors' formalized documentation program because of the belief that most patients require some type of educational support to optimize therapy and because pharmacists often provide recommendations without identifying the desired specific endpoint in terms of outcomes. Addition of the latter component serves as a mechanism for follow-up to determine whether or not therapeutic goals have been met. It also provides a basis for understanding when care is passed from one pharmacist to another. Figure 10.2 contains an example SOAPEO note.

An alternative method to SOAP charting is Focused Documentation. Focused Documentation is a simplified method of charting, which reduces repetition, using components reflective of Focus, Data, and Action. In the authors' practice, Focused Documentation is the preferred method for charting except in situations where the physician requests or the pharmacist initiates a comprehensive review of a patient's medication regimen. This may be the case for documenting medication reconciliation, if polypharmacy is an issue, or if a patient demonstrates symptoms consistent with sub- or supra-therapeutic response(s) to medications and/or an adverse drug event. An example of Focused Documentation for the above scenario is included in Fig. 10.3.

Whether documented in SOAPEO, or another format, maintaining a record of pharmacist recommendations and interventions in the patient medical record is essential to the practice and advancement of pharmacy as a profession. One such advancement of the profession is Medication Therapy Management (MTM).[70] The rules for MTM outline specific requirements for documentation of care. MTM is a structured form of pharmacist-managed care entailing

Table 10.5 Components of the SOAP note[68,69]

S – Subjective: Patient's complaints or symptoms; data provided by family members should be characterized as such.
O – Objective: Patient data including age, sex, race, height, weight, vital signs, results of laboratory and diagnostic tests, and physical exam findings.
A – Assessment: The pharmacist's evaluation of therapeutic alternatives or resolution of drug-therapy problems which may define the necessity for all drugs in the patient's regimen, evaluate the potential for drug interactions, document the appropriateness of the drug regimen and/or evaluate the patient's previous response to pharmacotherapy.
P – Plan: The plan should include specific drug therapy recommendations (drug, dose, route, frequency, duration), monitoring parameters and the necessity for further studies or tests.

Scenario: AW is a 38 YOWM with duodenal ulcer diagnosed this admission following extensive work-up. PMH is significant for epilepsy, controlled since childhood with phenytoin. AW weighs 68 kg and is 5'10" tall. He is employed as a financial analyst in a high-stress, demanding firm. AW reports NKDA. The physician has ordered ranitidine 150 mg PO BID. Ranitidine is a nonformulary drug.

Pharmacist Documentation:

3/9/03 Pharmacy Note
1100
S: AW is a 38YOWM with duodenal ulcer. Dr Jones has ordered ranitidine, a nonformulary drug.
O: AW receives daily maintenance therapy with phenytoin, to control a seizure disorder.
A: Ranitidine is a nonformulary item. In light of concurrent phenytoin therapy, cimetidine is not considered a viable alternative. Suggest initiating therapy with famotidine.
P: Begin famotidine 20mg PO BID
E: Educate patient that ranitidine is not available and famotidine has been prescribed as an alternative. Therapy should be administered BID, with a 12-hour dosing interval being most desirable.
O: Control and resolution of patient's duodenal ulcer while avoiding drug–drug interactions.

Figure 10.2 Example of a SOAPEO note.

3/9/03 Pharmacy Note

1100

Focus: Ranitidine, a nonformulary drug, has been prescribed for AW.

Data: AW receives daily maintenance therapy with phenytoin, to control a seizure disorder. Therefore, cimetidine is not a viable alternative.

Action: Begin famotidine 20mg BID. Educate patient regarding alternative therapy and monitor response.

Figure 10.3 Example of focused documentation.

Table 10.6 Components of medication therapy management (MTM) documentation

Prescription medications (current and discontinued)
Nonprescription medications (current and discontinued)
Dietary supplements (current and discontinued)
Medication-related action plan (MAP):
Patient name
Primary care physician (including name and phone number)
Pharmacy (including pharmacist name and phone number)
Date prepared
Action steps for patient
Notes for patient
Follow-up information
Interventions (possibly including SOAP or SOAPEO note with or without a cover letter)
Education materials
Correspondence with other healthcare professionals
Billing information

at least an annual complete medication review followed by creation of a medication-related action plan (MAP), a patient-specific plan designed to provide the patient with a list of actions to complete in order to optimize their self-management. The MAP can also be used by patients to assess their progress over time. The MAP, in addition to several other pieces of information, must be documented (ideally electronically) through the maintenance of a chronological, patient-specific record that allows for longitudinal patient evaluation and billing submission. Table 10.6 provides a detailed list of suggested documentation elements for MTM and the components of a MAP. The primary purpose of the extensive documentation required for MAP is to facilitate pharmacist communication with other healthcare professionals while resolving drug-related problems; the documentation is also designed to improve outcomes, demonstrate the value of MTM services, and ensure legal compliance.

Electronic communication

Electronic mail

While the introduction of e-mail has greatly facilitated contact, this type of communication must be appropriately utilized in the professional environment. Within this environment, e-mail should be for professional use only. Attention should be given to one's chosen e-mail sign-on. If a pharmacist's given name is not utilized for e-mail communication, care should be taken to choose a name that reflects positively on the character of the pharmacist as a professional. Professional e-communication should be utilized in situations where the messenger has concluded that a face-to-face meeting or telephone (i.e., direct) communication would not communicate the message more effectively. When communicating by e-mail, it is important to remember that any message may be either saved or forwarded for viewing by others. Accordingly, close attention should be paid to content and format. For example, use of capital letters could be interpreted as "yelling." The subject line should clarify the intent of the message. The content of messages should be concise but thorough enough to be understood. Given that messages may be printed or shared, one should refrain from including confidential or controversial information. E-mail users are advised to compose professional communications with a word processing program initially, to facilitate spelling and grammar checks. All messages should end with a professional closing and contain the individual's name, title, affiliation, and contact information. When e-communication is utilized, it is most appropriate to respond within the same business day, but a goal would be to respond in no longer than 24 hours. It is recognized that this may be a challenge, depending on the setting.

Social media

Social media sites such as Facebook and Twitter have recently become a popular source of communication. Although access to social networking sites may provide a valuable venue for professional interaction and information dissemination, they could jeopardize one's professional reputation. Pharmacists should always be vigilant to present themselves as trusted professionals. Therefore, all photos that are viewable to the public should be appropriate in nature. Privacy settings should be carefully chosen so that information not intended to be viewed by other professionals or patients is not available on the Internet. A general guideline to follow is not to post anything online that would not be appropriate to send in a professional e-mail. Pharmacists should be careful to present themselves through social networking sites in the same manner that they represent themselves in the professional setting.

Professional correspondence

Memoranda

Most pharmacists will find a need to communicate with other healthcare providers via memos, whether or not they have administrative positions. Written memos are frequently used to communicate drug information, policy changes, or in the evaluation/discipline of employees. Memos should be formal in format and should be addressed to a specific individual or group of individuals, whenever possible. The format for a professional memorandum is included in Fig. 10.4.

Cover letters

Cover letters should accompany applications for employment. As such they offer a written "first impression" to the recipient. Much like e-mail and memos, cover letters should be addressed to a specific individual whenever possible. The cover letter should be written in standard business format, as referenced in any primary or secondary school English text. The first paragraph of the cover letter should include the purpose for writing the letter. For example, the letter may be written to introduce a pharmacist as a candidate for employment. The content would then reflect the pharmacist's background and training and his or her current position. The middle paragraph should contain a brief summary of the key strengths,

To:	Jane A. Doe, PharmD, RPh Director of Pharmacy
From:	Samuel T. Smith, PharmD, RPh Pharmacy Manager
Re:	Staffing Patterns for Ambulatory Pharmacy
Date:	September 4, 2011

Figure 10.4 Example of memo header.

which make the pharmacist a strong and/or unique candidate for a particular employment opportunity. The last paragraph should close with identification of the mechanism for follow-up. For example, the author may wish to indicate that if the letter recipient does not provide follow-up contact within a two-week timeframe, the author will initiate such contact. The letter should also specify the preferred mechanism for contact (e.g., e-mail, telephone with specific number).

Resumé

The resumé should serve as a one-page summary or snapshot of an individual's education and work experience. Frequently the resumé contains a professional objective as it is often used to facilitate an employment opportunity. Resumés are designed to highlight professional accomplishments and entice the recipient to make an offer for interview. Within today's professional environment, resumés are frequently requested at the initial point of contact, particularly in community pharmacy and the pharmaceutical industry. Following the screening of applicants, those invited for interviews in these and other settings (academic, hospital pharmacy) are often asked to submit a curriculum vitae. Typical resumé contents are described in Fig. 10.5.

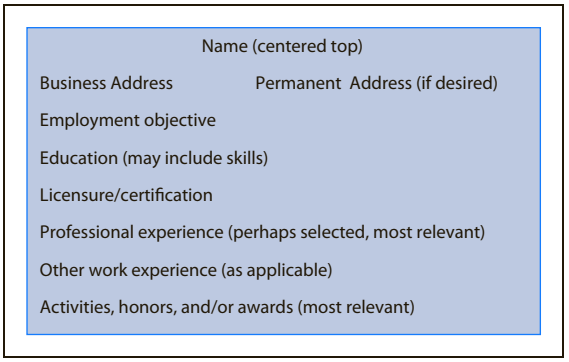


Figure 10.5 Content of the resumé.

Curriculum vitae

The curriculum vitae is intended to be a comprehensive chronology of the education, training, and work experience which also reflects professional presentations and publications. The healthcare professional should maintain a curriculum vitae that is inclusive of all types of professional activities. Potential categories for a curriculum vitae are included in Fig. 10.6. Some accomplished professionals maintain an abbreviated curriculum vitae that represents the most recent 5 to 10 years of accomplishments.

Figure 10.6 Content of the curriculum vitae.

Manuscripts for publication

Pharmacists may be involved in writing a wide variety of manuscripts for publication. These include book chapters, editorials, case reports, review articles, and clinical research studies. Publishing these types of manuscripts is essential to enhance communication among peers and advance/promote the profession. Generally, pharmacists are not trained to be writers; for this reason, preparing a manuscript for publication can sometimes appear to be an overwhelming task. However, publishing is a very fulfilling accomplishment that can lead to professional advancement and recognition.

Preparation

Preparation is the first step to any project. Because writing an article for publication is typically a long process, the first hurdle to overcome is the anxiety associated with the project. Because anxiety can sometimes lead to procrastination, it is very important to overcome any apprehensions as soon as possible. A good way to deal with this is to begin the initial preparation process by conducting background

research, gathering all necessary resources, and developing an outline for the manuscript.[71] It is also helpful to develop a working plan for completion of the project.[72,73] The writing project should be divided into small sections with attainable deadlines. Time for working on each section should be planned, similarly to other scheduled daily activities. This strategy can help avoid postponing the writing process due to an already busy schedule.

After all necessary resources have been collected the items should be organized in a systematic fashion. This will enable the writer to locate references quickly when they are needed during the writing process. An outline should also be developed to define the project clearly. When developing an outline, it is best to consider the primary objective of the manuscript and the target audience. Knowing this information will help determine which topics or sections should be included in the manuscript. An effective outline should help make the writing process easier because it determines focus areas. With computer word-processing packages, the outline can be used as a working template for the final manuscript. If the manuscript is intended for a specific medical journal or book, the publishers will customarily have requirements for the various sections that must be included. This will allow organization and provide a framework to follow during the writing process. Many biomedical journals follow *The Uniform Requirements for Manuscripts Submitted to Biomedical Journals*.[74] This is a document prepared by a group of editors to provide guidelines for manuscripts that are submitted to medical journals for publication. Table 10.7 lists the general sections that should be included in the publication of a research project.[72]

Writing the first draft

Once the outline has been prepared and all information resources have been gathered, the next step is to begin writing. Professional writing is a skill that requires continued practice. Because most pharmacists are not trained writers, this step is often quite difficult. One potential difficulty is finding the time necessary to devote to writing. As stated above, a helpful strategy to manage this problem is to reserve short blocks of time each day that are devoted to writing the manuscript. This approach may be easier for a busy practitioner than to reserve an entire day for completing the project. Progress can be made using short blocks of time, even if the daily goal is to write only one or two paragraphs. During this time, it is helpful to use a technique known as freewriting.[72,73] Freewriting involves taking about 20 to 30 minutes to write your ideas continuously without stopping to check grammar, spelling, or references.[72] Once a few paragraphs have been written in this manner, then content revisions and clarifications can made. In general, is it best to complete a first draft in its entirety before beginning the editing process.[71] However, it is sometimes difficult to avoid becoming engaged in the minor details of correcting grammatical and typographical errors in paragraphs that have already been written. This habit can lead to frustration and slow down the entire writing process. Strategies such as disabling the spelling and grammar check programs of the word-processing program and turning the computer screen off have been recommended to avoid the temptation of making corrections instead of writing new paragraphs.[72,73] Professional writing also follows a certain set of rules that are different from other types of writing. General rules

Table 10.7 Basic sections of a research project publication[72,74]

Introduction:	Background information to support "why" the project was conducted (written in present tense)
Methods:	Detailed description of all study procedures (written in past tense)
Results:	Detailed description of study findings (written in past tense)
Discussion:	Description of the clinical implications and limitations of the study findings (written in present tense)
Conclusions:	A statement of the final conclusions (written in present tense)

Table 10.8 General rules for professional writing

Use proper grammar and spelling
Keep sentences simple and direct
Avoid writing in the first person (e.g., I, we, us)
Avoid using the passive voice
Avoid using contractions
Avoid using abbreviations or acronyms
Proofread

(Data from Malone P. In: Malone PM, Kier KL, Stanovich JE, eds. *Drug Information: A Guide for Pharmacists*, 4th edn. New York, NY: The McGraw Hill Companies, 2012.)

for professional writing are listed in Table 10.8.[71] An excellent reference for general stylistic considerations including the rules of proper punctuation and grammar, and avoiding commonly misused words is *The Elements of Style*, written by William Strunk and EB White.[75]

Editing

After the first draft has been completed, editing is the final critical step. When a manuscript is submitted for publication, or any type of written communication for that matter, it represents an image of the writer. If a written manuscript is full of typographical and grammatical errors, this reflects poorly upon on the author. Because is it sometimes difficult for the author to identify noticeable errors, it is especially useful to ask colleagues to help proofread one's manuscript. Other strategies that have been suggested to aid the editing process include reading sentences out loud slowly, reading sentences in reverse chronological order, and enlarging the font on the computer screen.[72] It is also useful for the author to put the manuscript away from view for several days, and then come back to it at a later date.

Referencing

It is very important for authors to be familiar with proper referencing techniques to give credit when appropriate and avoid committing plagiarism. Plagiarism is defined as using the ideas or words of another in a way that represents them as one's own. Authors should always be vigilant of the potential for plagiarism when writing manuscripts for publication. If copying words verbatim from another authors' work, quotation marks should be used around the material and the appropriate authors should be cited. A good general rule to follow is to use quotation marks around three or more words in a row that are taken directly from a source without modification. If paraphrasing another author, the original publication should always be cited. Specific instructions for citing various types of publications can be found in the *Uniform Requirements for Manuscripts Submitted to Biomedical Journals*.[74]

Formal presentations

Verbal presentations

Pharmacists are routinely involved in the delivery of formal presentations, including continuing education and in-service programs. The pharmacist should evaluate the specific needs of the audience and target the level of the educational program accordingly. Pharmacists who know their audience can then prepare specific objectives that include content consistent with the expectations of the recipients. Presentations should be organized based upon the objectives and should not include excessive information that detracts from the key points. Because pharmacists frequently present to other healthcare professionals, provision of examples, stories, or analogies that include application of the information shared may facilitate the learning process for the participants. Although there is not one approved method for formal presentations, it is clear that "practice makes perfect." The presenter should be certain to prepare his/her talk well in advance of the presentation date, to allow ample time for practice.

In most settings, it is recommended that the presenter use some type of visual aid, which would include slides, overheads or transparencies, or flip charts. Given current technology, the development of a Microsoft PowerPoint presentation is common, as slides can quickly be converted to handouts for program participants. Whether using slides or transparencies, several formatting recommendations exist that have been summarized in Table 10.9.[76]

When properly developed, visual aids should serve as a prompt for the speaker, which should minimize the need for note cards or a complete presentation text. Presenters should be cautioned to speak from their slides or visual aids, but not to read. Other keys to effective presentation include the use of voice

Table 10.9 Characteristics of the ideal slide/transparency text

Horizontal with 2:3 ratio
Content limited to main point
Black or dark blue background
Title all in capitals
Outline format in lower case
Maximum of seven lines of text
No more than seven words per line
Readable font such as Helvetica or Arial
Limited use of capitals and italics
Graphic slide will have no more than 5–7 bars, columns, or pieces of a pie chart; clear labels or legends in corresponding colors

(Data from Casella PJ. In: *Writing, Speaking, and Communication Skills for Health Professionals*. The Health Care Communication Group. London: Yale University Press, 2001.)

inflection to maintain listener interest, incorporating gestures which accentuate voice inflection, and allowing a pause when emphasizing key points. It is important to dress consistently with the audience. Thus, a formal presentation requires formal (e.g., business suit) attire. Nonverbal communication enhances the relationship with the audience. If possible, the speaker should try to move away from the lectern or walk about the front of the room, to make a connection with a greater portion of the audience. Eye contact brings the audience into the presentation. If uncomfortable looking directly at individuals, the speaker should try looking at the top of heads. In a large room, participants will still feel the presenter is making contact with them. In a smaller setting, speakers can try to identify three or four "friendly" faces throughout the audience and use them as a gauge to the presentation as well as a link to the audience.[76]

Most presentations will include time for questions and answers. If time allows, in some settings, it is more effective to allow the audience to interrupt the formal presentation and ask questions instead of waiting until the end. This can enhance the presentation, but the speaker must be careful not to allow excessive time for discussion. Effective presenters should repeat questions to ensure that everyone in the audience has heard and understands the inquiry. As in all aspects of healthcare, if one does not know the response to a question, it is best to admit this freely and offer to follow-up or defer to an expert colleague in the audience who may know the answer. If questions do not relate to the presentation topic, the speaker should respond to the best of his or her ability and redirect the conversation to a point that does relate. The authors recommend the text *Writing, Speaking, and Communication Skills for Health Professionals* to any pharmacist who wishes to strengthen his or her presentation skills.[76]

Poster presentations

Poster presentations are a common method for sharing information at national meetings. At most national pharmacy meetings, there is an opportunity to present research ideas in a poster format. The basic components of a scientific poster are similar to the basic sections of a written research project. These sections include background, methods, results, limitations, and conclusions (see Table 10.7). Posters differ from written manuscripts in the amount of detail presented. With the exception of the background and conclusion sections, posters should not contain full sentences.[73] Information should be presented in at least 18-point font and bullet points and boxes should be used to emphasize the main points. This makes it easier for passersby to read and interpret. There are two different methods to make a poster. The first is to use separate slides (or panels) for each section. This can be done using Microsoft PowerPoint slides. Alternatively, some word-processing programs allow presenters to make single page posters. These posters still contain different slides for each section, but can be printed as a one-page sheet. This can make the poster easier to transport and arrange at the meeting. The general rules of professional writing discussed above and the importance of proofreading also apply to the preparation of poster presentations. A suggested format for a poster presentation is shown in Fig. 10.7.

Formulary communications

Written communication skills are extremely important for pharmacists who participate in formulary management. A formulary can be defined as a continually revised compilation of medications that are readily available for use within an institution and the policies addressing their use; a formulary typically is determined by the institution's medical staff

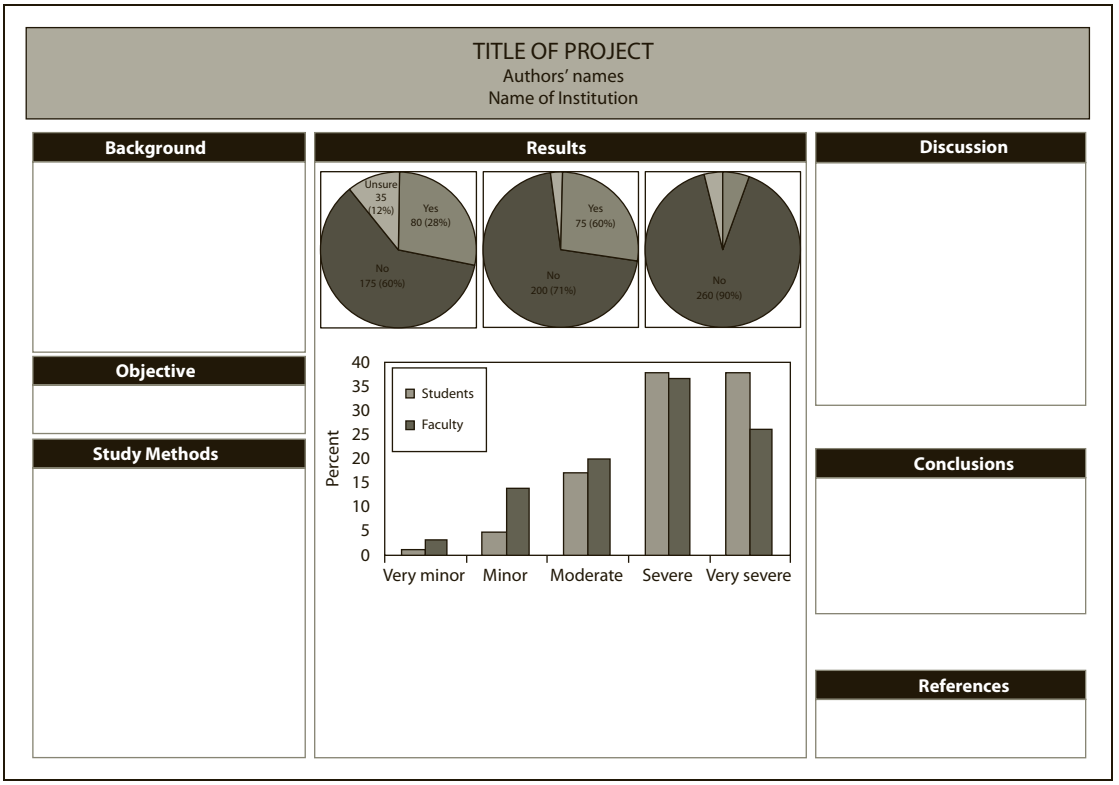


Figure 10.7 Suggested format for poster presentation.

and should be tailored for the needs of that specific population.[72,73] Medication formularies serve the purpose of decreasing inventory and allow practitioners to gain familiarity with certain drug products. Formularies also promote a decreased risk for medication errors and help the institution provide cost-effective therapy. Ideally, a formulary should contain the most cost-effective medications to treat all disease states likely to be encountered within an institution, given its expected patient population. A comprehensive review of the issues related to formulary management is beyond the scope of this section; however, the most common ways that pharmacists use professional communication skills to contribute to formulary management are through the preparation of drug evaluation monographs (or drug class reviews), medication-use evaluations, clinical practice guidelines and pathways, medication alert notifications, newsletters, and medication use policies. Basic guidelines for the preparation of these documents are listed below.

Drug evaluation monographs

A drug evaluation monograph is an objective, written appraisal of a medication (or class of medications in the case of drug class reviews) under consideration for formulary addition that allows for an organized assessment.[78] Drug evaluation monographs are almost always prepared by pharmacists. In 2009, the Food and Drug Administration (FDA) standardized the expected components of the FDA-approved labeling (i.e., package insert) to the list of headings presented in Table 10.10.[79] Drug evaluation monographs should use similar sections as a general template. The following sections describe the suggested components of a drug evaluation monograph in detail; however, the specific template used by an institution may be modified to meet the institution's needs.[77,78]

Title

This section includes basic information such as generic and trade names, manufacturer, available dosage forms, and the corresponding national drug code

Table 10.10 FDA-required prescribing information

1. Indications and Usage
2. Dosage and Administration
3. Dosage Forms and Strengths
4. Contraindications
5. Warnings and Precautions
6. Adverse Reactions
7. Drug Interactions
8. Use in Specific Populations
9. Drug Abuse and Dependence
10. Overdose
11. Description
12. Clinical Pharmacology
13. Nonclinical Toxicology
14. Clinical Studies
15. References
16. How Supplied/Storage and Handling
17. Patient Counseling Information

(NDC) numbers, the American Hospital Formulary Service (AHFS) Pharmacologic-Therapeutic Classification, and any important storage instructions. The AHFS Pharmacologic-Therapeutic Classification number is found in the classification index of the *AHFS Drug Information* reference book. *AHFS Drug Information* is published by the American Society of Health-System Pharmacists and is commonly used as an important reference book for practicing pharmacists. The AHFS Pharmacologic-Therapeutic Classification method indexes medications by pharmacologic and therapeutic effects by assigning numerical values to each drug class. Many institutions use the AHFS Pharmacologic-Therapeutic Classification system to index the medications available on the drug formulary. Use of a classification system helps organize an institution's formulary list.

Description and pharmacology

This section includes a description of the compound including the therapeutic mechanism of action. Important advantages and disadvantages in the pharmacological effects of the monograph drug as compared to current formulary agents of the same class should be discussed as well.

Pharmacokinetics

This section includes a brief review of the available pharmacokinetic data (i.e., absorption, distribution, metabolism, excretion), including information about potential pharmacokinetic changes in specific populations (e.g., geriatrics, patients with hepatic and/or renal dysfunction, pediatrics). For these data, a chart format is often preferred. This is especially helpful for drug class reviews when several agents within a given drug class are being compared.

Indications

A list of all the FDA-approved indications and any significant differences between the monograph drug and similar products within the same drug class should be provided. Because many medications are used for indications that are not officially approved by the FDA, it is also important to list pertinent off-label uses of the medication as well, particularly when these uses are supported by the primary medication literature. It is also helpful to note these potential uses when they are under-studied and/or use of the medication could potentially decrease patient safety.

Clinical efficacy

A thorough review of available primary literature pertinent to the efficacy and safety of the requested drug as it relates to the FDA-approved and off-label indications should be presented. Studies that are reviewed should include placebo-controlled and comparative trials, with emphasis on comparative trials when available. It is important to note that clinical trials that do not assess the safety and efficacy of the drug product should not be included. For example, pharmacokinetic evaluations in healthy subjects or animal toxicology studies are not appropriate for inclusion in the clinical efficacy section of a drug evaluation monograph. These types of studies may be referenced in other sections of the monograph (such as the pharmacokinetic section or the safety section), but they do not provide clinical efficacy information.

Typically, it is best to follow a general template when abstracting clinical trial data within a drug monograph evaluation. This improves readability, ensures consistency, and allows comparisons to be made between different clinical trials in a relatively simple format. The citation, objective, and study design should always be stated in a clear and concise manner. Detailed information describing the inclusion/exclusion criteria, randomization process, study treatments, and the efficacy and safety assessments

should be included in the description of the methods. Within the results section, the writer should report specific numbers to describe the efficacy and safety of the drug. For example, instead of simply reporting a "statistically significant difference between groups," the writer should report the quantitative difference in the outcome measure between study groups (e.g., 160 mg/dL *versus* 110 mg/dL). This allows the reader to interpret the potential clinical significance of the results. In addition to a short conclusion, the writer should provide a brief commentary regarding the potential strengths and limitations that should be considered when interpreting the results of the study. An example of a clinical trial summary that would be appropriate for inclusion in a drug evaluation monograph is shown in Fig. 10.8

Safety and tolerability

This section should include information regarding manufacturer-labeled contraindications, warnings, and precautions (including pregnancy and lactation information); additionally, review of safety data from additional clinical trials and tertiary medication references may be helpful. Adverse event data should be presented in a manner that emphasizes the most common and most serious adverse events, with suggested strategies to prevent or manage these events if they occur; it is also helpful to present these data as specifically as possible, highlighting the exact portion of a specific population who experienced the adverse event (i.e., "in Phase III clinical trials, 47% of patients over 65 years of age receiving nitroglycerin ointment experienced headache"). Potential drug–drug, drug–food, drug–laboratory, and drug–herb interactions should also be presented with suggested management approaches. As with all sections of the drug monograph, comparative data should be presented when available.

Medication error possibility

Information should be included about potential medication errors that could occur in dosing, medication preparation, medication administration, or concerns with look-alike/sound-alike names. If potential risks exist, methods for preventing medication errors should be introduced.

Dosing and administration

The recommended doses for specific indications and patient populations (e.g., geriatric, pediatric, obese, renal failure) should be clearly listed. If applicable, a description of dosage titration should be included. For parenteral medications, it is important to list information about reconstitution techniques, appropriate diluents, long-term stability and sterility, and compatibility with other medications. Special administration issues such as infusion rate or the need for in-line filters should also be addressed in this section.

Patient monitoring parameters and patient information

Information regarding recommended patient monitoring parameters with suggested time intervals for assessments should be presented. Additionally, patient information written in lay terms for the monograph drug should be provided.

Budget impact

This section should provide a quantitative description of the health system's cost for the new product based on the typical dosage regimen (e.g., Q8h for 10 days). The cost per bottle (or package) is not always helpful, because it does not take into account the typical dosage regimen. It is best to provide these data in a tabular format that compares the new product to currently available agents. Additionally, it is helpful to include projected use and how the item will affect the health system's total drug budget.

Summary and recommendations

The summary should briefly review the pertinent data presented throughout the document including a concise discussion of the drug class and information regarding the efficacy, safety, and cost of the new drug product in comparison to currently available formulary agents. Any important advantages of the new drug should also be highlighted in this section. Finally, the recommendation should be stated with appropriate rationale. Additional secondary recommendations, such as deletion of alternative agents from the drug formulary, restrictions of use to certain patients or practitioners, or follow-up medication use evaluation, should also be included in this section. In some institutions, the summary and recommendation are listed on the front page of the drug evaluation monograph to make it easier for reference and

Objective	Assess the safety and efficacy of fidaxomicin compared to vancomycin for the treatment of non-complicated *C. difficile* infection.
Design	Prospective, multicenter, double-blind, randomized, parallel-group, noninferiority trial
Methods	Patients included in the study were at least sixteen years of age and diagnosed with *C. difficile* infection. Diagnosis was based on greater than three unformed bowel movements (i.e., diarrhea) within 24 hours prior to randomization and presence of *C. difficile* A and/or B toxin in the stool within 48 hours prior to randomization. Patients were excluded if they received greater than four doses of metronidazole and/or vancomycin within 24 hours prior to randomization, any other treatment for *C. difficile* infection (e.g., rifaximin), and symptoms of complicated *C. difficile* infection (e.g., life-threatening infection, toxic megacolon, second recurrence). Patients were randomized to fidaxomicin 200 mg PO every twelve hours or vancomycin 125 mg PO every six hours for ten days; patients were stratified according to whether the case was a first or second occurrence. The primary endpoint assessed was clinical cure at the end of therapy. Secondary endpoints included recurrence of *C. difficile* infection within four weeks following completion of therapy and global cure. Clinical cure was de ned as three or fewer unformed stools for two consecutive days and no need for continued treatment. Clinical cure with no recurrence was defined as a global cure. Safety was assessed from study entrance through last dose of study drug or visit if the patient received at least one dose of study medication and was evaluated.
Results	A total of 629 patients underwent randomization (327 to vancomycin and 302 to fidaxomicin); of these, 309 and 283 vancomycin patients were included in the modified intention to treat population and the per-protocol population, respectively. Of the 302 fidaxomicin patients, 287 and 265 were included in modified intention to treat and the per protocol population. Baseline characteristics were similar between groups; in the modified intention to treat population, the mean age was 61.6 ± 16.9 years, 55.9% of patients were female, 59.4% of patients were inpatient. Few patients (17.1%) had experienced previous *C.* difficile disease, or contracted the virulent BI/NAP1/027 strain (38.1%). Approximately 39% of patients received treatment for *C.* difficile during the 24 hours prior to randomization. In the modified intention to treat population, 88.2% of fidaxomicin patients and 85.8% of vancomycin patients experienced clinical cure; fidaxomicin was found to be noninferior to vancomycin. Fidaxomicin clinical rate was also found to be noninferior to vancomycin in the per-protocol population (92.1% vs. 89.8%). The fidaxomicin group also had a lower rate of recurrence (15.4% vs. 25.3%; p=0.005) and a higher rate of global cure (74.6% vs. 64.1%; p=0.006) compared to vancomycin. Fidaxomicin patients also had a higher rate of diarrhea reolution without recurrence (74.6% vs. 64.1%) and a shorter median time to diarrhea resolution (58 hours vs. 78 hours) compared to vancomycin. Rates of clinical cure did not differ between clinically relevant subgroups. Rates of recurrence tended to be lower in patients with no previous *C.* difficile disease (14.2% vs. 24%; p=0.01), no *C.* difficile treatment 24 hours prior to enrolment (13.9% vs. 25%), mild (11.9% vs. 29.4%; p=0.02) and severe (13% vs. 26.6%; p=0.02) baseline disease, non-NAP1/BI/027 strain type (10.3% vs. 28.1%; p<0.001), and no concomitant antibiotics (14.5% vs. 24%; p=0.03). Safety outcomes were similar between groups with 62.3% of fidaxomicin patients and 60.4% of vancomycin patients experiencing an adverse event; 25% of fidaxomicin patients experienced a severe adverse event compared to 24.1% of vancomycin patient. Fidaxomicin patients had a higher rate of laboratory abnormalities compared to vancomycin patients (4.7% vs. 1.2%).
Conclusions	Fidaxomicin and vancomycin are both highly effective in achieving clinical cure of uncomplicated *C. difficile* disease. Fidaxomicin may be more effective in preventing recurrence of disease within four weeks compared to vancomycin. Both agents were similarly effective in achieving clinical cure with the virulent NAP1/BI/027 strain but vancomycin may be more effective in preventing its recurrence.
Comments	• Study population: Patients were not stratified at randomization according to disease severity, limiting the ability to identify the most appropriate patients who should receive fidaxomicin. Additionally, it is difficult to quantify the severity of disease in relation to the treatment guidelines as various baseline data (e.g., white blood cell count, serum creatinine trends) were not provided. • Control group: The medication (vancomycin) and dose used for the comparator are indicated in the treatment guidelines for severe *C. difficile* infection; it is unclear if this was a severe population. The authors did quantify patients by disease severity in subgroup analyses but did not elaborate as to how these distinctions were made. Additionally, the study does not provide a comparison to metronidazole. • Disease definitions: Recurrence was only measured for 28 days following study drug completion. Recurrence of *C. difficile* infection typically occurs for up to 60 days. No data was provided as to differences in timing of recurrence between treatment groups.

Figure 10.8 Example of a clinical trial summary for a drug evaluation monograph. Louie TJ, Miller MA, Mullane KM *et al*.. Fidaxomicin versus vancomycin for *Clostridium difficile* infection. *N Engl J Med* 2011; 364(5): 422–31.

discussion during the Pharmacy and Therapeutics (P&T) Committee meeting.[78]

Authorship

The pharmacist who prepared the monograph should be listed along with the date that the final document was completed. Additionally, pharmacists who served as document reviewers should be listed.

References

All references should be footnoted and listed at the end of the document in the order that they appear within the text. References should be cited using the *Uniform Requirements of Manuscripts Submitted to Biomedical Journals*.[74]

Other

Additional sections may be included in drug formulary monographs to fit the needs of individual institutions. These may include information pertaining to risk evaluation and mitigation strategies (REMS) required by the FDA, patient education materials, updated policies and procedures, and hazardous drug precautions for healthcare workers.

The use of a standard drug evaluation monograph, including the sections noted above, can help streamline the P&T review process. Additionally, some P&T Committees use a one-page executive summary in lieu of the entire drug evaluation monograph. Pharmacists typically present the executive summary of the drug evaluation monograph or drug class review verbally during the P&T Committee meeting.[78]

Medication-use evaluation

Medication-use evaluation (MUE) is a continuous improvement method used to evaluate the use of medications within a health system to identify areas for improvement in medication-related quality outcomes and aid in formulary management.[77,80] MUE is frequently completed based upon evidence-based clinical practice guidelines and clinical pathways. In addition, MUE may be based upon approved use criteria of an individual drug or drugs within a therapeutic class or designed to assess cost-effectiveness of medication therapy. MUE should focus on high risk, highly complicated, or expensive medications and is often based on preliminary internal data (e.g., a high rate of errors with a particular medication). While MUE is no longer required by regulatory agencies such as the Joint Commission, it is completed as an ongoing indicator of continuing quality improvement.

There are several key communication issues related to MUE. First, it is imperative that the criteria for MUE are approved by the medical staff and/or any other group of healthcare providers who are expected to apply the criteria in the care of their patients. Following completion of an MUE, results should be shared through appropriate channels. Within healthcare organizations, MUE is often a function of the Pharmacy and Therapeutics Committee or an associated subcommittee. The most common communication-related problems in the MUE process generally occur after results have been discussed by the committee. Discussion frequently culminates in recommendations for the improvement of care. These recommendations are often not shared with practitioners, nor is there subsequent assessment to determine the results of the recommended improvements. Thus, the 360-degree cycle associated with study completion and process improvement is not completed, and recommendations for improved care are not implemented. It is essential that the pharmacist assume accountability for completion of this process, in its entirety.

The following sections provide a general template to follow when reporting results of an MUE.

Background

This section should provide background information about why the MUE was conducted. For example, the reason may be that the medication being evaluated has been associated with medication errors, or because the medication may be associated with a serious adverse event. Pertinent literature or national guidelines that support the need for an MUE should also be reviewed. This section should end with a statement describing the primary objective of the MUE.

Methods

A detailed description of exactly how the MUE was conducted should be included. Typically, a retrospective cross-sectional, case–control, or cohort study design is used, although some MUEs may be performed prospectively. The methods for patient selection, identification, and data collection should be listed; as well as the study time period and sample size. Justification for the selected sample size should be provided. It may be helpful to list the types of data that were collected. For example, if the MUE assessed appropriate use of a particular medication with regard to renal function, serum creatinine would be recorded for all patients.

Results

Detailed results for each type of data that was collected should be presented in a tabular format that directs the audience's attention to the most important findings. The presentation of results should include patient demographics and numerical values for all data. If statistics were performed, investigators should clearly state whether results were statistically significant.

Summary

The results of the MUE should be briefly summarized, highlighting the most important findings. As with any investigation, authors should comment on any potential limitations of the study, whether results were clinically significant, and potential impact on practice.

Recommendations

Finally, the recommendations to improve medication use should be presented. These should be specific to the health system. Recommendations and plans for improvement should be specific, measureable, and achievable in the context of the particular health system.

Clinical practice guidelines and pathways

Evidence-based clinical practice guidelines have been defined as "systematically developed statements to assist practitioner and patient decisions about healthcare for specific circumstances."[82] Clinical practice guidelines may also be used as tools to promote appropriate medication used based on Pharmacy and Therapeutics Committee approval requirements. Guidelines and pathways should be based on widely-endorsed clinical practice guidelines and primary medication literature. Guidelines should include specifications for care, which may be disease-based (e.g., hypertension, asthma, diabetes) or process-focused (e.g., guidelines for the use of serum levels in monitoring aminoglycoside therapy). Clinical pathways reflect the details that support practice guidelines using clear inclusion and exclusion criteria. For example, guidelines which focus on the use of serum levels in monitoring gentamicin therapy might include patients with an elevated serum creatinine of greater than 2 mg/dL or those receiving daily dosages in excess of 6 mg/kg but exclude patients less than 2 years of age. The corresponding clinical pathway would state the exact manner in which the serum levels should be monitored, such as obtaining the trough level within 30 minutes prior to the infusion of a gentamicin dose, and the peak 30 minutes after the end of a one-half hour infusion.

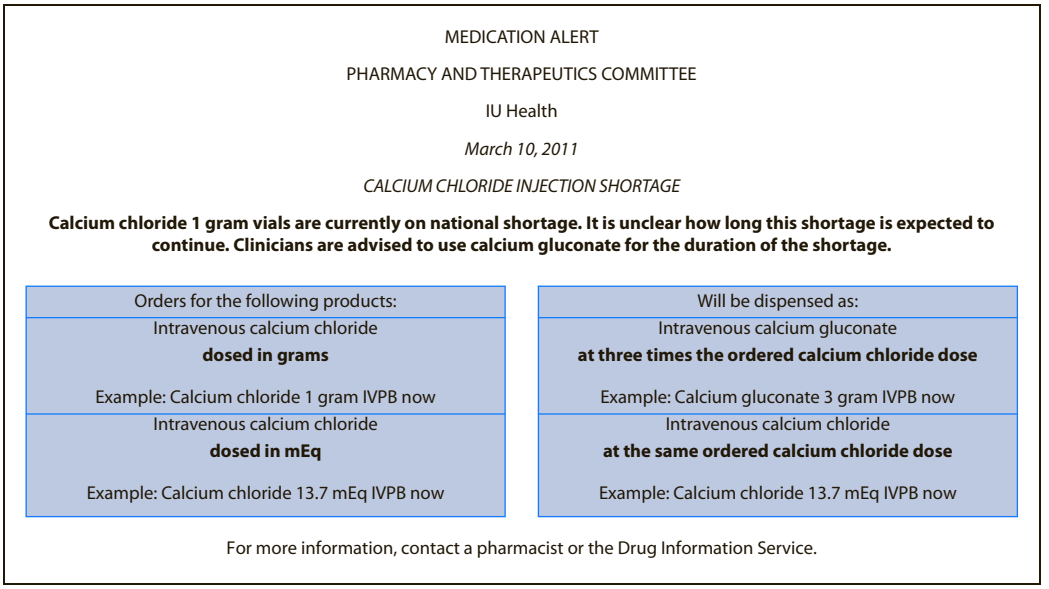
Clinical practice guidelines and pathways should be specifically and succinctly written, such that there is no confusion regarding the intent of the guideline or the exact process for application of the guideline. Healthcare organizations with sophisticated information systems (including computer-generated physician order entry) frequently incorporate guidelines and pathways into their software to provide guidance to practitioners in the care of their patients; this method of enforcement is thought to contribute to increased adherence to guidelines and subsequent improved patient outcomes.

Medication alert notifications

In many cases, there may be situations that require the pharmacy department to alert the medical and nursing staff of an important medication-related issue. Recently, one of the most important examples of these types of issues has been medication shortages. When a commonly used or critically important medication is unable to be obtained, it is vital that the pharmacy communicate with key stakeholders (e.g., medical specialties, nursing areas) to notify those individuals of the shortage and present a plan of action. Additional examples requiring drug alert notifications include change in pharmacy procedures, formulary updates, or withdrawal of a drug from the market. Typically, pharmacists are responsible for developing these types of communications. The most effective method is generally the preparation of a one-page communication that clearly states the problem or issue and provides a recommendation for managing the problem. The notification should provide contact information for potential questions or concerns. An example of a drug alert notification is shown in Fig. 10.9. It is important that medication alerts take into account the perspective and level of understanding of the intended audience and provide sufficient detail while maintaining readability.

Newsletters

Most health systems have a pharmacy newsletter or website that is published on a regular basis to communicate important formulary decisions that have been made by the Pharmacy and Therapeutics Committee. Newsletters may also be used to communicate important current events in pharmacy practice, educational information for healthcare professionals and/or patients, medication shortages updates, and changes in policy and/or procedure. As drug therapy specialists, the main writers and editors of pharmacy newsletters are pharmacists. When preparing a pharmacy newsletter the primary factors to consider are the target audience, the primary goal of publication, and professional appearance.[71] The specific format used varies greatly depending on these primary factors. Potential limitations to newsletters and/or websites to be considered include time required for preparation, financial burden, and accessible equipment resources. Professional writing strategies are discussed in detail elsewhere in this section. Pharmacy



MEDICATION ALERT

PHARMACY AND THERAPEUTICS COMMITTEE

IU Health

March 10, 2011

CALCIUM CHLORIDE INJECTION SHORTAGE

Calcium chloride 1 gram vials are currently on national shortage. It is unclear how long this shortage is expected to continue. Clinicians are advised to use calcium gluconate for the duration of the shortage.

Orders for the following products:	Will be dispensed as:
Intravenous calcium chloride **dosed in grams** Example: Calcium chloride 1 gram IVPB now	Intravenous calcium gluconate **at three times the ordered calcium chloride dose** Example: Calcium gluconate 3 gram IVPB now
Intravenous calcium chloride **dosed in mEq** Example: Calcium chloride 13.7 mEq IVPB now	Intravenous calcium chloride **at the same ordered calcium chloride dose** Example: Calcium chloride 13.7 mEq IVPB now

For more information, contact a pharmacist or the Drug Information Service.

Figure 10.9 Example drug alert notification.

newsletters serve a valuable purpose for communicating important information to the medical staff and provide visibility for the pharmacy department.

Medication use policies

Medication use policies and procedures are vital written communications that are generally written and implemented by pharmacists practicing in formulary management and/or drug information.

Personnel communication

Position description

Pharmacists, particularly those in management positions, are frequently required to write position descriptions for other pharmacists, technicians, and/or other supportive personnel. The position description should delineate the required qualifications, experience, and an overview of job responsibilities. Most position descriptions also include an overview of the required competencies for successful job performance.

The types of positions for which pharmacists might prepare position descriptions include:

Clerical

Individuals who complete tasks including word processing, filing, bookkeeping, and serving as a receptionist.

Service

Individuals involved with equipment and/or building maintenance.

Administrative

Individuals who may complete some clerical functions, with the addition of budgeting/financial management or supervision of clerical staff.

Technical

Individuals involved with product procurement and preparation, along with certain levels of customer interaction

Professional

Including pharmacists, nurses, etc.

Educational requirements may include the ability to read/write English or another language, high school diploma, vocational training, certification, college course work, associate degree, BS degree, advanced degree, or postgraduate training. Required experience should include the number of years and type of experience (i.e., directly related to the position). Other related skills might include word processing, accounting, supervision, prescription processing, and perhaps work with automated dispensing systems, to name a few. The position description should include essential

Position Description
Ambulatory Care Pharmacist

Professional Pharmacy Systems
300 North Carleton Bldg
Indianapolis, IN 44444-4444

Qualifications:

1. Doctor of Pharmacy (PharmD) degree and/or BS in Pharmacy with equivalent experience
2. Minimum of 3 years experience in progressive pharmacy practice
3. Eligibility for and attainment of pharmacy licensure in the State of Indiana
4. Involvement with medication therapy/disease state management programs (e.g., diabetes, asthma, hyperlipidemia, anticoagulation) preferred
5. Strong organizational and interpersonal skills
6. Ability to communicate effectively with patients of varying educational and ethnic backgrounds

Position Responsibilities:

1. Assist with prescription processing and patient education
2. Under scope of practice and prescribing protocols, provide direct medication therapy/disease state management for patients with chronic diseases (described above)
3. Assist in the development and marketing of additional disease management programs to support community-based physician practices
4. Serve as a preceptor for PharmD students completing advanced pharmacy practice experiences (APPE) within the practice site

Required Core Competencies:

Knowledge

1. Knowledge of procedures and laws pertaining to the processing and dispensing of prescriptions
2. Knowledge of medication therapy/disease state management for chronic diseases (described above)

Skills

1. Ability to modify disease state recommendations based upon scope of practice and prescribing protocols
2. Ability to individualize education for each patient

Behaviors

1. Monitor indicators of response including disease-based parameters
2. Provide individualized follow-up for patients to optimize outcomes

It is anticipated the ambulatory care pharmacist will have responsibilities that mirror the following:

Prescription Processing (20%)

The ambulatory care pharmacist will assist with prescription processing for clinic patients.This function includes managing and modifying therapy based upon scope of practice and prescribing protocols and educating patients regarding recommended therapy including use of over-the-counter and alternative therapies.

Medication Therapy/Disease State Management (60%)

The ambulatory care pharmacist will provide direct medication therapy/disease state management for patients with chronic diseases through a scope of practice and prescribing protocols

Program Development/Marketing (10%)

In conjunction with practice management, the ambulatory care pharmacist will assist with the identification program development and marketing of additional medication therapy/disease state management programs.

Experiential Learning (10%)

The ambulatory care pharmacist will assist with supervision of APPE students from state colleges of pharmacy.

Figure 10.10 Example of position description.

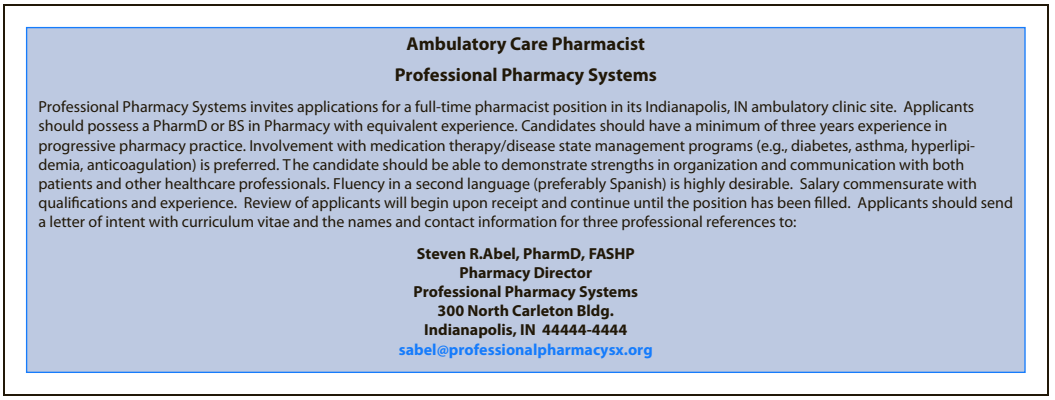
duties and the percent of effort that is designated to each duty. Figure 10.10 contains an example position description for a pharmacist.

Job postings

Once a position description has been developed, job postings reflecting abbreviated qualifications and responsibilities for the successful applicant are prepared. Job postings are commonly used to advertise for candidates in local newspapers, professional journals, and/or via the Internet. Position descriptions should include contact information for the individual responsible for recruitment and should also reflect the status of an equal opportunity employer, where applicable. An example position description is included in Fig. 10.11.

Interviewing

Interviewing is an essential skill for pharmacists, whether they serve in administrative positions and are responsible for hiring staff that will enhance their services or apply their skills in obtaining a fulfilling



Ambulatory Care Pharmacist

Professional Pharmacy Systems

Professional Pharmacy Systems invites applications for a full-time pharmacist position in its Indianapolis, IN ambulatory clinic site. Applicants should possess a PharmD or BS in Pharmacy with equivalent experience. Candidates should have a minimum of three years experience in progressive pharmacy practice. Involvement with medication therapy/disease state management programs (e.g., diabetes, asthma, hyperlipidemia, anticoagulation) is preferred. The candidate should be able to demonstrate strengths in organization and communication with both patients and other healthcare professionals. Fluency in a second language (preferably Spanish) is highly desirable. Salary commensurate with qualifications and experience. Review of applicants will begin upon receipt and continue until the position has been filled. Applicants should send a letter of intent with curriculum vitae and the names and contact information for three professional references to:

Steven R.Abel, PharmD, FASHP
Pharmacy Director
Professional Pharmacy Systems
300 North Carleton Bldg.
Indianapolis, IN 44444-4444
sabel@professionalpharmacysx.org

Figure 10.11 Example job posting.

professional position. It is important for pharmacists to be aware of the different types of interviews in which they might participate. These include the following:

Structured interview

An interview that utilizes a predetermined list of questions designed to facilitate comparison among the candidates. This format is good for a naïve interviewer because it provides a "script" for the interview process, but it may not offer enough flexibility to allow complete assessment of a candidate's strengths and liabilities.

Unstructured interview

An interview that is unorganized, spontaneous, and flexible. This format tests the listening skills of the interviewee while challenging the interviewer to remain on task and ascertain pertinent information from the candidate.

Stress interview

An interview designed to determine the emotional stability of the interviewee. Questions are asked in a direct, sometimes offensive manner in an effort to strike an emotional chord and evaluate the candidate's response.

Behavioral interview

An interview focused on identifying how the interviewee reacted in certain situations. Questions may focus on stressful, frustrating, or positive scenarios. The interview asks the candidate to describe a situation (S) with which they were involved, explain their tasks (T) associated with the situation, describe the action (A) taken in the situation and the result (R). As noted, this type of interview may also be termed the STAR format. The interviewer wishes to understand how a candidate reacted in certain situations and what they learned or might do differently as a result. The interviewee's past experiences are the focus for specific examples which offer the interviewer a chance to determine strengths and weaknesses based on "lessons learned."

Regardless of the interview technique, interviewers and interviewees alike should be prepared to discuss topics including personal interests, education, experience, and career goals. Skills related to interpersonal interactions, communication, and technical/practical competence will also be evaluated. Topics that may not be discussed in an interview are included in Table 10.11.

Performance appraisal

Pharmacists will have the responsibility to provide input into or prepare performance appraisals. The primary purpose of the performance appraisal is

Table 10.11 Inappropriate interview topics

Age
Arrest or conviction record
Credit rating
Disabilities
Marital/family status
Military record
Name, national origin, or religion
Request for a photograph

to enhance employee development. Performance appraisals are also frequently utilized to distribute rewards (e.g., salary increases). When communicating with the employee regarding performance, the discussion should focus on four characteristics of good performance criteria. Performance criteria should be achievable, measurable, unbiased, and significant to the work of the individual. It is suggested that performance criteria be developed jointly by the supervisor and employee, including the method for assessment. This approach should make the review process most valuable for the involved parties.

Several general guidelines exist for conducting the appraisal interview. Appraisals should be conducted in a quiet setting that is removed from the general workplace and other employees. The frequency and timing of performance evaluations should be known to the employee. In most settings, evaluations occur on an annual basis (e.g., at the end of each year) or on the anniversary of employment. Presentation of the appraisal is critical to its success. Managers should begin their assessment by citing specific examples or instances in which the employee made positive contributions to the site. Criticism is acceptable, but should be offered as opportunities for employee development and should always be presented after at least some positive statements are made. The evaluation should be offered as the manager's interpretation of the available facts. If opportunities for improvement are recommended, these should be delivered in a tactful, but direct manner.

Verbal evaluations should always be supported by paper documentation of performance. The employee and manager should sign the written document. This does not imply that the employee agrees with the assessment, but rather simply that they have read and understand its content. Evaluations should not be changed, but the employee should be offered the opportunity to prepare a written addendum or response that can be appended to the written document and retained in the employee record.

Progressive discipline

Unfortunately, the process of progressive discipline is a necessary component of most professional work environments. Progressive discipline occurs when there are identified problems with an individual's work habits or performance. There are five steps in the progressive discipline process. The first involves verbal counseling of the employee by the supervisor, with written documentation that the verbal counseling occurred. The written documentation simply serves as a record for the employee's file. The second step in progressive discipline is provision of a written warning. Should performance not improve, there is a follow-up to the written warning issued, which may subsequently lead to suspension and finally discharge. Supervisors should be aware of the process for progressive discipline and should carefully document all events. Without documentation, the poor performer may not be able to be terminated.

When communicating with an employee throughout the progressive discipline process, the supervisor should describe the problem(s) specifically, including the implications of why the problem(s) are of concern to the supervisor and/or within the workplace. The employee should be given a chance to provide his or her explanation, and the supervisor should actively listen during this process. The employee should be asked for input on problem resolution. When completed effectively, the act of progressive discipline should put the onus for improvement on the individual employee. At each step within the progressive discipline process, specific action should be agreed upon, and a date identified for follow-up to review progress. In general, no more than two weeks should pass between discussions. Supervisors should express confidence that the employee can improve, except at discharge. Again, the importance of documentation throughout this process cannot be overemphasized.

Policies and procedures

Policies and procedures are required in virtually all business settings; the most important types of policies and procedures for pharmacists are intended for personnel or medication management.[77] When written properly, policies and procedures should serve as the basis for completion of each function or activity within the workplace. Essentially, a policy statement describes an outcome an organization expects to achieve (e.g., "The pharmacy implements strategies to safeguard the use of high-alert medications.") and the procedures describe a stepwise approach to achieve compliance with the policy (e.g., separating storage, restricted distribution, alert labels).

Policies and procedures should be written such that a naive employee should be able to read the policy and procedure and successfully complete a given

task; it is virtually impossible for policies and procedures to be too detailed. For example, if a particular task requires use of a computer, the procedure should begin by instructing the participants to turn on the computer using the green switch on the side of the processor. The participant might next be instructed that, once the screen is visible, the cursor should be used to select the appropriate icon for execution of the task, etc. It is common for policies and procedures to be prepared by managers or individuals most familiar with the individual activity. New employees or individuals from other areas within the work environment are frequently utilized to test the depth and detail of written policies and procedures. Policy authors should make efforts to use active voice and ensure grammatical agreement when writing these documents. For example, instead of "high alert medications will be defined by the Medication Safety Committee," a stronger policy statement would be "the Medication Safety Committee defines high alert medications."

When developing a policy and procedure structure specific to medication management, it is important to consider the scope of these documents.[77] Medications and/or processes that have been shown to be high risk and complex may warrant a policy and procedure to help guide clinicians. Additionally, the Joint Commission requires development of policies regarding specific procedures (e.g., investigational medications, self-administered medications) to maintain accreditation. In health systems, the role of policy development and approval is frequently given to the Pharmacy and Therapeutics Committee.

Summary and conclusion

Professional communication, which is utilized multiple times each day regardless of practice setting, is a vital skill for pharmacists. This section provides a broad overview of the most common types of written and verbal communication skills that are necessary for successful pharmacists.

The prescription

Introduction

The prescription is a set of specific directions issued by a medical practitioner to a pharmacist for the appropriate use of a medication or medications in a particular patient: an individual plan of care to remedy a medical problem. It may be communicated in writing, verbally, or transmitted electronically but, regardless, the prescription is the framework for the processes involved in pharmaceutical care running through, and facilitating, all areas of clinical and dispensing operations for medications. The prescription may also be the means for the patient to obtain necessary medical equipment or services such as diagnostic tests or clinical referrals. The prescription connects the pharmacist with prescribers, other healthcare professionals, and, most importantly, the patient.

A prescription is issued by a physician or other licensed medical practitioner. Individual states have the authority to determine which medical professions, in addition to licensed physicians, have prescribing authority. This authority is granted to correspond only with the provider's scope of practice (i.e., a veterinarian may prescribe only for animals; a podiatrist can prescribe only for conditions of the human foot; optometrists only prescribe drugs for disorders of the eye, etc.). Some additional examples of medical professionals that may have full or limited prescribing authority are dentists, nurse practitioners and physician assistants, depending on current state and federal laws. Pharmacists can issue prescriptions under a physician approved protocol or with certain state-mandated restrictions.

The prescription can facilitate the professional relationship between the prescriber and the pharmacist for the delivery of quality pharmaceutical care to meet patient needs. The pharmacist will often advise the prescriber related to drug product selection based on clinical protocols, drug formularies or patient financial considerations. The pharmacist may also consult with the prescriber based on other patient specific knowledge such as patient drug sensitivities, previous adverse drug reactions (ADRs), concurrent medication therapies, and previous treatment successes or failures. In order to accomplish this for the best possible patient outcomes, the pharmacist must maintain a high level of practice competence, keep accurate and updated patient records, and always pursue the best working relationships with other health professionals.

The prescription is the basis for the pharmacist–patient relationship as well. It conveys the necessary information about how the patient should utilize the

prescribed medication. This information, when combined with the pharmacist's knowledge of medications and dosage forms, allows for a dialogue between the patient and pharmacist where conditions for optimal use of the medication and concerns specific to an individual patient can be accommodated for the best patient outcomes. The prescription itself is such an integral part of this exchange that often patients will refer to their medication as their "prescription" as well. Just as pharmacists must establish and maintain the trust of the physician, the trust of the patient is equally important if the pharmacist is to be assured of the patient's adherence after the visit to the pharmacy.

The vast majority of prescriptions are written for medications that can only be obtained after being prescribed by a licensed practitioner and are referred to as prescription or legend drugs. In some instances, a prescription will be generated for a medication that can be obtained without such a prescription, for example, based on payor necessity or a desire by the prescriber for the medication to appear on the patient's medication profile. These medications are termed nonprescription or over-the-counter (OTC) drugs. Legend or prescription drugs are recognizable by the statement "Caution: Federal Law Prohibits Dispensing Without Prescription" or "RX only" that must, by law, appear on the label of the product as it is provided to the pharmacist by the manufacturer.[82] OTC medications can be further divided into drugs that are available for patients without consulting any healthcare professional (traditional OTC medications), and drugs the patient must request from the pharmacist (behind-the-counter, BTC, or restricted OTC medications). BTC medications may be categorized as such by state or federal agencies and although they do not require a prescription, they are not readily available to the public without consulting with a pharmacist. Drugs in the BTC category often receive this designation because of their potential for patient harm or misuse. The pharmacist is typically required to obtain proof of the patient's identification and age and may need to maintain appropriate documentation with the patient name and quantity at the time of purchase. Examples of BTC medications include pseudoephedrine (sold only in limited quantities to prevent abuse or its use in the manufacture of the illegal and highly addictive methamphetamine) or Plan B (sold without a prescription only to patients 17 years of age or older to assure appropriate oversight in minors). Licensed prescribers may issue prescriptions for nonprescription drugs, but it is predominantly the pharmacist who is responsible for the implied prescription by reviewing directions for appropriate use with the patient.[83,84]

Inpatient medication orders

Medication orders for inpatients in hospitals and other institutions are written by the physician on forms called the *Physician's Order Sheet* or are entered directly into the institution's computer system. These orders are then sent, on paper or electronically, directly to the pharmacy serving that institution to be screened for potential problems, processed and dispensed through the institution's medication distribution system. If the medication order is written, the exact form used varies between institutions and even within an institution, depending on the unit rendering the care. Because these orders are written in a controlled environment and the medications are administered by trained healthcare professionals, many of the requirements and restrictions placed on prescription orders for outpatients do not apply in the institutional setting. The balance of this section is focused on outpatient medication orders, or prescriptions, intended for use by patients in the community who administer their own medications without intervention by a healthcare professional.

Form of the prescription order

Prescriptions usually are written on printed forms that contain blank spaces for the required information. These forms are called prescription blanks and are supplied in the form of a pad to be filled in by the prescriber or may be printed, already completed, from the prescriber's computer. Most prescription blanks are imprinted with some basic contact information about the prescriber or their practice site should additional professional communication be required. This information usually includes the prescriber's name, address, and telephone number at a minimum (Fig. 10.12).

Although most prescribers use specially imprinted prescription blanks, it is not universally a legal requirement for prescriptions; any paper or other writing material may be used. There are some situations where more stringent requirements are necessary to increase patient safety or prevent

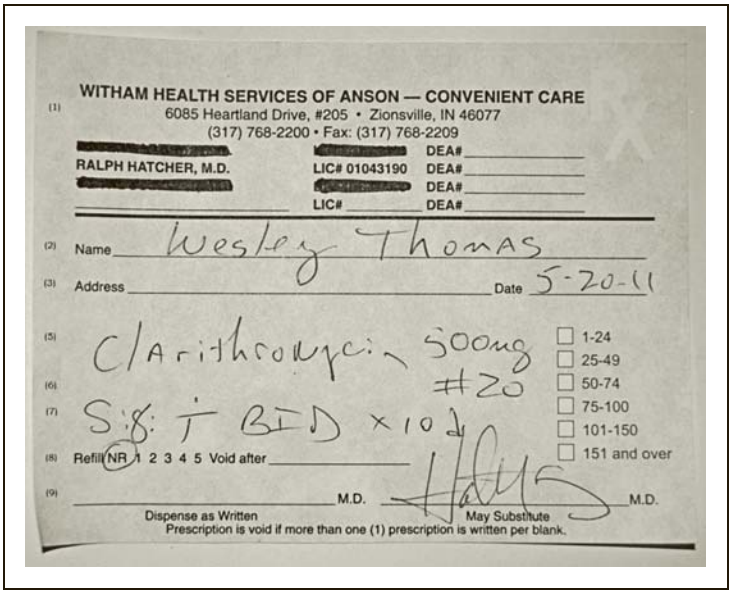


Figure 10.12 Example of a physician's prescription showing typical form and content. (Courtesy of Dawn Pearson.)

unlawful drug diversion. For example, a healthcare system such as the Veterans Health Administration (VHA) may provide prescription forms for use only in their facilities. Medicaid prescriptions must be written on tamper-evident paper, (e.g., possess a "COPY", "ILLEGAL" or "VOID" pantograph evident on any prescription photocopies or utilize erasure revealing backgrounds) if the prescription is to be transported to the pharmacy by the patient or their designee.

Controlled substances require specialized prescription blanks. Controlled substances are drugs that, because of their potential for abuse, are placed in specific schedules, I–V, by the federal government based on their relative potential for abuse. Specialized prescription blanks for these controlled substances in all or specific controlled substance schedules (such as C-II) are often required to include certain security features for the prevention of tampering or diversion. Specific modifications for controlled substance prescription forms could include, in addition to security paper: triplicate prescription forms, watermarks, sequentially numbered blanks, check-off boxes for quantities or refills, a serial number or bar code for tracking, the statement "Prescription is void if more than one (1) prescription is written per blank", or the printed, stamped, or handwritten name and license number/DEA registration number of the practitioner.

In addition to paper prescriptions transported from the prescriber to the pharmacy by the patient, most states allow prescription orders to be transmitted electronically from the prescriber by fax or direct computer-to-computer transmission. Electronic submission often eliminates the safety and security measures outlined for handwritten prescriptions, such as security paper, especially when they are transmitted via secure computer networks. The Institute for Safe Medication Practices (ISMP), has advocated that electronic prescribing – with proper systems design, implementation, and maintenance – should completely replace handwritten prescriptions as a way to reduce or eliminate the medication errors and risk to patient safety associated with illegible handwriting.[85] Other potential advantages associated with direct computer-to-computer prescribing (often referred to as "e-prescribing," "physician order entry," or POE) are prescriber access to the patient's medical record, prescription history, and third-party drug formularies. The prescriber can also, while entering the prescription, receive on-screen warning prompts with drug-specific dosing information or potential drug interactions.

Prescriptions may also be received into the pharmacy verbally by a phone call from the prescriber or their designee. In the interest of patient safety, these

prescriptions should be immediately reduced to writing or entered into a prescription processing computer by the pharmacist and repeated back, for verification from the prescriber that the repeated order is accurate.

The component parts of a prescription are described as follows and are identified in Fig. 10.12.

1. Prescriber information
2. Patient information
3. Date
4. Symbol or superscription (not shown on Fig. 10.12)
5. Medication prescribed or inscription
6. Dispensing directions to pharmacist or subscription
7. Directions for patient or *signatura*
8. Refill number
9. Prescriber's signature

In practice, some of the above information (such as the patient's address) may be absent when the prescription is received by the pharmacist. In these instances the pharmacist obtains the necessary information from the patient or physician, as is required by state law, to complete the prescription.

Prescriber's information and signature

The prescription should include sufficient information to identify and, if necessary, contact the prescriber. The top of the prescription usually includes the prescriber's name, address, and telephone number. This may be specific to an individual prescriber or may be the name of the institution (i.e., hospital or clinic) or office where all or none of the names of prescribers in that group are listed. If the prescription header is specific to the prescriber, state license or Drug Enforcement Agency (DEA) registration numbers may be present. In instances where the prescription form is preprinted with more generic institution information, the prescriber may include their own state license or DEA registration numbers by the signature lines. The prescription form should also include the prescriber's signature, often on one of two lines indicating the prescriber's wishes related to drug product substitution. A prescriber may have allowed a designee to write the prescription or telephone a prescription into a pharmacy. In these cases, the name or initials and credentials of the individual designated by the physician should also be present.

Patient information

The full name and address of the patient are necessary on the prescription for identification purposes. Names and addresses written illegibly should be clarified on acceptance of the prescription.

The patient's date of birth and allergy information may be included as well for both identification and safety purposes. Some prescription blanks used by medical specialists, particularly pediatricians, include a space for insertion of the patient's age, weight, or body surface area. This information is placed on the prescription by the physician when medication dosing is dependent on patient age or weight. This information assists the pharmacist in interpreting the prescription and verifying the dose prescribed, especially for a pediatric patient.

Date

Prescriptions are dated at the time they are written and also when they are received and filled in the pharmacy. The date is important in establishing the treatment history for the patient. An unusual lapse of time between the dates a prescription was written and when it is brought to the pharmacy may be questioned by a pharmacist to determine if the intent of the physician and the needs of the patient can still be met. For controlled substance prescriptions, the date of issue by the prescriber carries additional significance since federal and state laws govern the time period after which a controlled substance prescription is no longer valid.

℞ Symbol or superscription

The ℞ symbol generally is understood to be a contraction of the Latin verb recipe, meaning take thou or you take. Some historians believe this symbol originated from the sign of Jupiter, employed by the ancients in requesting aid in healing. Gradual distortion through the years has led to the symbol currently used. Today, the symbol is representative of both the prescription and the pharmacy itself.

Medication prescribed or inscription

The body or principal part of the prescription order contains the names, dosages, and quantities of the prescribed medications or ingredients. The majority of prescriptions are written for medications already prepared or prefabricated into dosage forms by regulated pharmaceutical manufacturers. The medications

may be prescribed under their trademarked (manufacturer's proprietary) name or by their generic (nonproprietary) name. Prescribers, generally, have the ability to indicate on the prescription if they would like the patient to receive the specific trademarked drug as written or if they will allow for substitution. This preference is generally communicated to the pharmacist by the prescriber signing on a "Dispense as Written" or "May Substitute" signature line, or utilizing similar check-boxes. When substitution is permitted by the prescriber, pharmacists, using their professional judgment, will determine with the patient's consent if substitution is appropriate. Health Maintenance Organizations (HMOs) and prescription benefit plans may have formularies for which only certain drug products within a therapeutic class may be dispensed. In these cases, the pharmacist may be directed by the prescription plan to dispense a generic product or a different drug product within a therapeutic class which was prescribed for the patient. How the pharmacist handles these payor or contractual substitutions is governed by state and federal law. Most insurance companies and prescription plans require on-line verification and authorization prior to dispensing prescription products.

Prescription orders requiring the pharmacist to mix ingredients are termed *compounded* prescriptions. Prescriptions requiring compounding contain the names and quantities of each ingredient as part of the inscription. The names of the ingredients generally are written using the nonproprietary names of the materials, although occasionally proprietary names may be employed.

Dosages or quantities for commercially available products or listed ingredients for prescriptions requiring compounding may be expressed as a concentration or unit of measure using the metric or Apothecary system of weights and measures. The ISMP has published "Medication Safety Alert" articles encouraging prescribers to use the metric system. Another significant danger outlined by the ISMP related to the expression of quantities is the use of trailing zeros (resulting in a medication ordered in a 1.0 mg dose being interpreted and administered as a 10 mg dose) and the failure to use leading zeros (resulting in a .1 mg dose being interpreted and administered as a 1 mg dose). These simple, yet critical, changes to how prescribers and pharmacists express quantities can have a significant impact on patient safety. Pharmacists need to be attentive not only to these dangers in the expression of quantities, but also make a conscious effort to educate other healthcare professionals on these inherent dangers to patient safety.

Dispensing directions to pharmacist or subscription

In the majority of prescriptions where a commercially manufactured product is dispensed, the subscription serves merely to designate the dosage form (e.g., tablets, capsules, inhalers, and transdermal patches) and the number of dosage units to be dispensed. For compounded prescriptions, specific directions for preparing the compound may be included in this part of the prescription.

Examples of prescription directions to the pharmacist include:

- *Disp #100 tabs* (Dispense 100 tablets)
- *M ft caps dtd no xxiv* (Mix and make capsules. Dispense 24 such doses)
- *Ft supp No xii* (Make 12 suppositories)
- *M ft ung* (Mix and make an ointment).

Directions for patient or signatura

The prescriber indicates the directions for the patient's use of the medication in the portion of the prescription termed the *Signatura* (commonly abbreviated *Signa* or *Sig* and meaning *mark thou*). The directions in the *signa* are frequently abbreviated forms of English or Latin terms or a combination of the two. A list of some common prescription abbreviations is presented in Table 10.12. These directions are interpreted by the pharmacist and then conveyed verbally to the patient to ensure understanding as well as transcribed, using layman's terms, onto the prescription label of the dispensed medication container for the patient's continued reference.

Examples of prescription *signa* along with the appropriate interpretation for the patient include:

- "*ii tabs po q4h*" translates to "Take two tablets by mouth every 4 hours"
- "*i cap po TID pc*" translates to "Take one capsule by mouth three times a day after meals"
- "*ii gtts right eye q12h*" translates to "Place two drops into the right eye every 12 hours"

Table 10.12 Commonly used abbreviations in prescriptions and medication orders

Abbreviation	Meaning
aa	of each
ac	before meals
ad	to, up to
a.d.**	right ear
ad lib	at pleasure, freely
AM	morning
amp	ampule
APAP	acetaminophen
aq	water
a.s.**	left ear
ASA	aspirin
ATC	around the clock
a.u.**	each ear
BCP	birth control pill
bid	two times a day
BM	bowel movement
BP	blood pressure
BPH	benign prostatic hypertrophy
BS	blood sugar
BSA	body surface area
C	with
CAD	coronary artery disease
CAP	community acquired pneumonia
caps	capsule
cc**	cubic centimeter [milliliter]

(continued overleaf)

Table 10.12 *(continued)*

Abbreviation	Meaning
CHF	congestive heart failure
COPD	chronic obstructive pulmonary disease
CP	chest pain
DAW	dispense as written
DC or D/C**	discontinue
disp	dispense
div	divide
DM	diabetes mellitus
DOB	date of birth
d.t.d.	give of such doses
Dx	diagnosis
elix	elixir
EtOH	ethanol
Ft	make, let it be made
g	gram
GERD	gastroesophageal reflux disease
GI	gastrointestinal
GU	genitourinary
gr	grain
gtt	a drop
h	hour
HA	headache
HCTZ**	hydrochlorothiazide
HR	heart rate
HRT	hormone replacement therapy

(continued overleaf)

Table 10.12 *(continued)*

Abbreviation	Meaning
hs**	at bedtime
HTN	hypertension
inj	injection
IV	intravenous injection
IM	intramuscular injection
ID	intradermal injection
IU**	international units
kg	kilogram
L	liter
lb	pound
mcg	microgram
MDI	metered dose inhaler
mEq	milliequivalent
mg	milligram
mL	milliliter
mOsmol	milliosmole
MOM	milk of magnesia
MS**	morphine sulfate
MTX**	methotrexate
MVI	multivitamin
M	mix
NV	nausea and vomiting
NKDA	no known drug allergies
NPO	nothing by mouth
NMT	no more than
non rep/NR	do not repeat

(continued overleaf)

Table 10.12 *(continued)*

Abbreviation	Meaning
NS	normal saline
NSAID	non-steroidal anti-inflammatory
NTE	not to exceed
NTG	nitroglycerin
OA	osteoarthritis
OC	oral contraceptive
OCD	obsessive compulsive disorder
OJ**	orange juice
O2	oxygen
o.u.**	each eye
o.d.**	right eye
o.s.**	left eye
OTC	over-the-counter
oz; fl oz	ounce; fluid ounce
P	pulse
pc	after meals
PCN	penicillin
PM	evening
po	by mouth
post-op	after surgery
pr or rect	rectally
prn	when necessary
pulv	powder
pv or vag	vaginally
PVCs	premature ventricular contractions
PVD	peripheral vascular disease

(continued overleaf)

Table 10.12 *(continued)*

Abbreviation	Meaning
q	every
qd**	every day
qid	four times daily
qod**	every other day
qs	a sufficient quantity
qs ad	a sufficient quantity up to
q __h	every ___ hour
RA	rheumatoid arthritis
ss	without
ss	one-half
SC,SQ,SubQ**	subcutaneous injection
Sig	write on label
SL	sublingual
SOB	shortness of breath
sol or soln	solution
sq m, m^2	square meter
stat	immediately
supp	suppository
susp	suspension
Sx	symptom
syr	syrup
T	temperature
tab	tablet
TCN	tetracycline
TIA	transient ischemic attack

(continued overleaf)

Table 10.12 *(continued)*

Abbreviation	Meaning
tid	three times a day
tiw**	three times a week
tbsp	tablespoon
TMP-SMX	trimethoprimsulfamethoxazole
tsp	teaspoon
top	topically
TUD	take as directed
Tx	treatment
U**	unit
UA	uric acid, urinalysis
UC	ulcerative colitis
ud or ut dict	as directed
ung	ointment
URTI	upper respiratory tract infection
UTI	urinary tract infection
WA	while awake
wk	week
y or yr	year
yo	years old

**These abbreviations are included on the Institute for Safe Medication Practices List of Error-Prone Abbreviations (http://www.ismp.org)

Just as it has been noted that the ISMP has identified expressions of quantity which are error-prone and compromise patient safety, there is also a significant number of literature reports and other ISMP Safety Alerts related to the dangers of abbreviations in the prescription order and documentation processes. Examples of problematic abbreviations are as follows:

- Abbreviation of drug names – an order written for HCT which could easily be filled with hydrochlorothiazide instead of the intended hydrocortisone
- Abbreviation of administration routes – a medication direction abbreviated AU intended for both ears is administered into both eyes or only the right ear

- Abbreviation of administration frequency – a once daily medication is abbreviated q1d or even a handwritten order for qd dosing which is misinterpreted as four times daily (qid) resulting in a fourfold overdose.

Whether an abbreviation is handwritten on a prescription or typed into an electronic prescription, all healthcare practitioners need to be cognizant of, and avoid the use of, the error-prone abbreviations, symbols, and dose designations listed by the Institute of Safe Medication Practices and available on their website, http://www.ismp.org. Pharmacists are a crucial part of the solution to eliminating the use of these error-prone abbreviations and designations in order forms, protocols, prescription labels, and any other print material through editorial intervention and provider education.

Refills

The number of authorized refills should be indicated on each prescription by the prescriber. In the event that no refill information is provided, it is understood that no refills have been authorized; however, it is advised that the label state such to avoid confusion. Most prescription blanks include a section where this information may be indicated (Fig. 10.12). Most states limit refills on a prescription to one year after the prescription was written. When a prescriber indicates that a prescription can be refilled *prn*, "as needed," the pharmacist should refill it only with a frequency consistent with the directions and, again, only for one year from the origination date. Controlled substance prescriptions are an exception; they are typically limited to six months rather than one year and no refills are permitted for *Schedule II* controlled substances.

Processing the prescription order

The manner in which pharmacists process a prescription order is important not only in fulfilling their professional responsibilities but also in enhancing their relationships with the physician and the patient. The pharmacist must be precise in all aspects from receipt of the prescription order through care of the patient for the duration of the therapy, and often beyond. Proper procedures are given below for receiving, reading and checking, numbering and dating, preparing, packaging, labeling, rechecking, dispensing, documenting, pricing, and refilling. Patient compliance or adherence with prescribed therapies is a source of concern for physicians as well as pharmacists. The pharmacist must be vigilant during the processing of prescription orders for indications of patient noncompliance and work with both the prescriber and patient for appropriate resolutions.

Receiving the prescription

It is desirable that the patient present the prescription order directly to the pharmacist because this initiates and enhances the pharmacist–patient relationship as well as facilitates the gathering of essential disease and drug information from the patient. This is critical for the provision of quality medication therapy management and can significantly increase patient safety. In the case of electronically or verbally submitted prescriptions where the patient does not present the prescription order directly to the pharmacist, this same exchange can be accomplished when the patient arrives at the pharmacy to pick up the prescription. The timing is not crucial as long as the interaction between patient and pharmacist occurs prior to the patient receiving the medication. In a situation when the pharmacist is unavailable to receive a prescription, other pharmacy personnel should be trained to accept it in a professional manner and obtain the correct name, address, and other pertinent patient information.

Patients having a prescription filled for the first time at a pharmacy may be asked to provide a brief health and medication history. The patient should be provided with an estimate of the time required for filling the prescription and, if possible, the anticipated cost associated with the medication. Some pharmacists make it a practice to price prescriptions before dispensing, especially in the case of an unusually expensive medication, to avoid potential conflict and allay patient concerns about the cost of their medication.

Reading and checking the prescription

Once all appropriate patient information has been added to the prescription order, the pharmacist must first review the prescription completely and carefully. There should be no doubt as to the ingredients, quantities prescribed, directions for the patient or

appropriateness for this specific patient at this time. If something is illegible or if it appears that an error has been made, the pharmacist should consult a colleague or the prescriber. A pharmacist should never guess at the meaning of an indistinct word or unrecognized abbreviation. Especially in the case of ISMP identified error-prone abbreviations, pharmacists must be especially vigilant and seek clarification from the prescriber whenever necessary to ensure patient safety.

Another concern in the interpretation of the prescription order is drugs with names that look alike or sound alike. These similar names are a potential source for errors. Knowledge of the patient's medical problems and diagnoses can often provide the pharmacist with insight into which one of the look-alike or sound-alike drugs is actually intended for the patient. In 2001, the FDA Branch Office of Generic Drugs requested manufacturers to "voluntarily revise the appearance of established names" of certain drugs that had similar names. Drugs with similar names started using TALL MAN lettering to highlight the portion of the drug name that is different from the other similar drug name. An example is the differentiation between NIFEdipine and NiCARdipine.[86] Other examples of drugs with similar names are listed in Table 10.13.

The amount and frequency of a dose must be noted and checked carefully. The age, weight, and condition of the patient (e.g., liver function and kidney function) as well as the dosage form prescribed must often be considered in determining the safety of the dose for a prescribed medication. Many printed references, on-line references and embedded databases within the software of prescription processing computer systems, are available as resources for the pharmacist evaluating the safety of a prescribed dose. In the case of a suspected error in the prescribed therapy, appropriate references should be checked thoroughly prior to consulting the prescriber. Omissions, such as the failure to specify the desired strength of a medication or its dosage form, must also be corrected prior to dispensing. The pharmacist should never make assumptions such as electing to dispense the "usual" dose or dosage form but instead should consult the prescriber.

From the pharmacy's paper or electronic records, the pharmacist determines the compatibility of the newly prescribed medication with other drugs being taken by the patient or if any drug–food or drug–disease interactions may exist. Most prescription processing computer software programs readily identify these possible interactions. In the absence of computer software to screen for these interactions, many specialized print and on-line references are available to assist pharmacists in clinical decision making. However, these software programs and references do not always identify the relative significance of the interaction, and are generally incapable of determining the interaction's magnitude for the specific patient. Only pharmacists, using their best clinical judgment combined with the right information solicited from the patient, can ascertain if the interaction is insignificant in this patient, can be managed through consultation and intervention with the patient (e.g., cautioning a patient against taking the medication with dairy products or to avoid sun exposure during treatment), or requires contacting the prescriber when a true and unavoidable contraindication exists.

In reviewing and interpreting all of these areas of the prescription medication order, pharmacists must take great care and use their broad knowledge of drug products to prevent dispensing errors. In each situation, the prescriber may be consulted by a confidential telephone call, e-mail, or electronic instant message to clarify the prescriber's intentions. These clarifications can also enhance the professional reputation of the pharmacist as a careful practitioner and valuable member of the healthcare team. Prior to contacting the prescriber, pharmacists must be thoroughly prepared to clearly and concisely explain their concerns, recommend alternative drug products or doses (including available strengths and dosage forms), and have citations for the appropriate references used in assimilating these recommendations. This information is necessary to assist the prescriber in determining the best therapeutic options for the patient. The same logic applies when a medication is prescribed for a patient who has a known drug allergy or sensitivity to the prescribed drug or other drugs of the same chemical class and the prescriber must be contacted.

Numbering and dating

It is a legal requirement to number the prescription order and to place the same number on the medication when dispensed to the patient. This serves to identify the dispensed product and to connect it with

Table 10.13 Examples of look-alike and/or sound-alike drug names

AcetaZOLAMIDE	AcetoHEXAMIDE	MS Contin	OxyCONTIN
Actos	Actonel	Mucinex	Mucomyst
Advair	Advicor	Neulasta	Lunesta
ALPRAZolam	LORazepam	NexIUM	NexAVAR
Ambisome	Amphoterecin B	OxyCODONE	OxyCONTIN
Amicar	Omacor	Paregoric	Opium Tincture
Amphotericin B	Abelcet	Plavix	Paxil
Amphotericin B	Ambisome	PriLOSEC	PROzac
Avandia	Coumadin	Retrovir	Ritonavir
AVINza	INVanz	SEROquel	Serzone
AVINza	Evista	SEROquel	SINEquan
Cardura	Coumadin	Singulair	SINEquan
CeleBREX	CeleXA	SitaGLIPtin	SUMAtriptan
CeleBREX	Cerebyx	Solu-CORTEF	Solu-MEDROL
CeleXA	Cerebyx	SulfADIAZINE	sulfiSOXAZOLE
CloNIDine	KlonoPIN	SUMAtriptan	Zolmitriptan
Cymbalta	Symbyax	TEGretol	TRENtal
DAUNOrubicin	DOXOrubicin	TiaGABine	TiZANidine
DAUNOrubicin	IDArubicin	Ticlid	Tequin
Diabeta	Zebeta	TOLAZamide	TOLBUTamide
Diflucan	Diprivan	Topamax	Toprol XL
Diovan	Zyban	TraMADol	TraZODone
Enbrel	Levbid	Tricor	Tracleer
ePHEDrine	EPINEPHrine	Ultracet	Duricef
folic acid	folinic acid	Viagra	Allegra
heparin	Hespan	VinBLAStine	VinCRIStine

(continued overleaf)

Table 10.13 *(continued)*

HumaLOG	HumuLIN	Wellbutrin SR	Wellbutrin XL
HumaLOG	NovoLOG	Xanax	Zantac
HumuLIN	NovoLIN	Xenical	Xeloda
HydrALAZINE	HydrOXYzine	Yaz	Yasmin
HYDROcodone	OxyCODONE	Zantac	Zyrtec
HYDROmorphone	morphine	Zestril	Zetia
KlonoPIN	CloNIDdine	Zestril	ZyPREXA
LamiVUDine	LamoTRIgine	Zocor	ZyrTEC
Lantus	Lente	Zocor	Cozaar
Lexapro	Loxitane	ZyPREXA	CeleXA
Lipitor	Loniten	ZyPREXA	ZyrTEC
Lipitor	ZyrTEC	Zyvox	Vioxx
MetFORMIN	MetroNIDAZOLE	Zyvox	Zovirax

(Data from Institute of Safe Medication Practices List of Confused Drug Names (http://www.ismp.org))

the original order for reference or when renewing the prescription. Consecutive numbers are assigned by prescription processing computer software packages but, in the absence of such automation, can be numbered manually by use of numbering machines.

Indicating on the prescription the date filled is also a legal requirement. This information is important in determining the appropriate refill frequency or patient compliance. This task is easily completed by utilizing prescription processing software or manually writing the date on the prescription blank.

Preparing the prescription

After thoroughly reviewing the prescription order, the pharmacist should decide on the exact procedure to be followed in compounding, if necessary, and dispensing the prescription product. Most prescriptions can be prepared using prefabricated dosage forms procured from regulated pharmaceutical manufacturers. Some prescription medications, because the formulation or dosage form is not commercially available, require extemporaneous compounding by the pharmacist or other trained pharmacy personnel prior to dispensing. The extemporaneous compounding of prescriptions is an activity for which pharmacists are qualified uniquely by virtue of their education, training, and experience.

Pharmacists must exercise care to make certain that the product dispensed is of the prescribed dosage form, strength, and number of dosage units. Unless a single unit is dispensed (e.g., an inhaler or a single compliance package of tablets) solid, prefabricated dosage forms generally are counted in the pharmacy using a counting tray such as the one shown in Fig. 10.13. Such a device facilitates the rapid and sanitary counting and transferring of medication from the stock packages to the prescription container while preventing touch contamination. Because manipulating products across this tray can generate aerosolized or surface particles of the drug product which are left behind on the counting tray, measures may be necessary to prevent cross-contamination

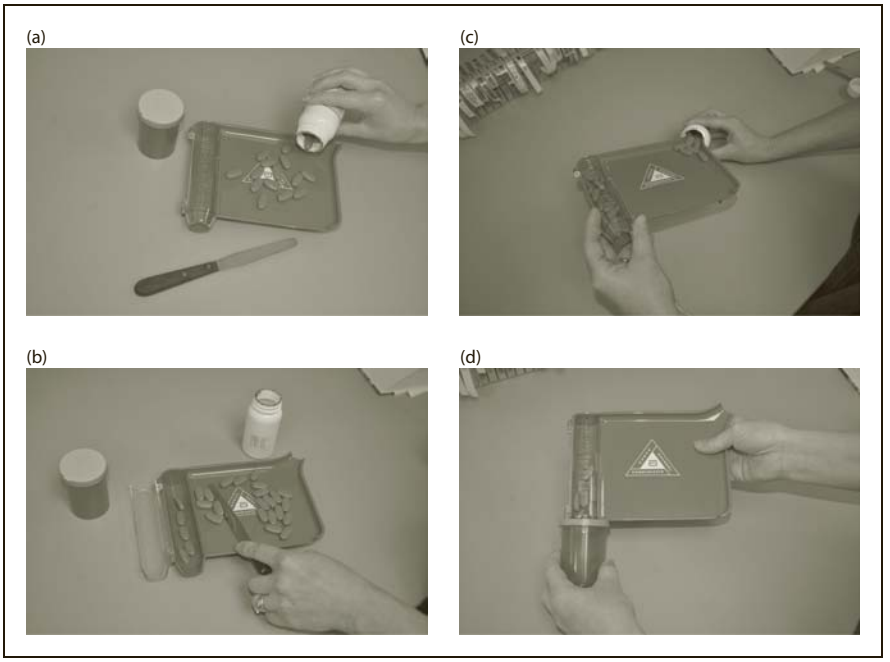


Figure 10.13 Steps in the hygienic counting of solid dosage units with the Abbott Sanitary Counting Tray: (A) placing units from the stock package onto the tray, (B) counting and transferring the units to the trough, (C) returning the excess units to the stock container, and (D) transferring the counted units into the prescription container. (Courtesy of Dawn Pearson.)

between products, especially when counting uncoated tablets. Wiping the counting tray between products and periodic cleaning will minimize the risk of cross-contamination. Many high volume pharmacies use automated counting machines (e.g., Baker Cell, Kirby-Lester, Drug-O-Matic, Auto-Script III). These systems allow for manual addition of medications to be counted, or on a larger scale, the medications are stored within the counting machines and automatically counted and packaged, without pharmacist intervention, through an interface between the counting machine and the pharmacy's prescription processing software when the prescription is processed.

Of all the activities involved in prescription processing, product selection and preparation carries a significant risk of error resulting in increased patient morbidity or mortality. For this reason, quality control in prescription processing activities is extremely important and deserves significant attention from the pharmacist. In preparing prescriptions using prefabricated products, the pharmacist should carefully inspect the manufacturer's container to be assured the original container is intact, free from contamination or deterioration, and within the stated expiration date. The manufacturer's product should undergo a "triple check" system against the prescription order by comparing them first, before preparation at the time of product selection; second, during product preparation by checking both against the computer or hand generated label; and a third time after the preparation process is complete to make certain of its correctness. Computer software programs can be very useful in the quality control step by providing actual photographs of the expected product or by using bar-coding or radio frequency identification technologies. Any technologies available to the pharmacist should be utilized to the fullest and never viewed as an impediment to prescription processing leading to the generation of "work-arounds" to circumvent this quality control process.

The pharmacist should determine a beyond-use date to the prescribed product prior to dispensing which takes the method of prescription preparation into consideration. This should not be confused with the expiration date of a medication which is "the time during which the article may be expected to meet the

requirements of the pharmacopeial monograph provided it is kept under the prescribed conditions."[87] It is also not to be confused with the expiration date of the prescription order which is typically, for non-controlled substances, the duration of therapy including refills, or one year, whichever comes first. The beyond-use date is intended to limit the patient's use of the medication within an appropriate period determined using the pharmacist's professional judgment and is based on all of the following:

- The prescriber's intent – as outlined on the prescription order.
  - The product expiration.
  - For all commercially available products it is determined by the manufacturer, clearly printed on the manufacturer's label, and valid as long as stated storage and handling procedures are followed.
- For extemporaneously compounded products, it is assigned by the pharmacist based on the expiration date of individual ingredients and the available stability information on the specific formulation. In the absence of such stability information, the pharmacist can use the beyond-use dating guidelines published in Chapter <795> of the United States Pharmacopeia.
- The type of packaging and anticipated storage conditions for the dispensed product.
- The expiration date of the prescription – total days of therapy up to one year for non-controlled substances.

Packaging

When dispensing a prescription, pharmacists may select a container from among various shapes, sizes, colors, and composition. Selection is based primarily on the dosage form, quantity of medication to be dispensed, and the intended method of administration. Containers must provide protection from "contamination by extraneous liquids, solids, or vapors; from loss of the article; and from efflorescence, deliquescence, or evaporation under ordinary or customary conditions of handling, shipment, storage, and distributions, and is capable of tight re-closure."[87]

The containers generally used by pharmacies are:

- Round vials – Used primarily for solid dosage forms as capsules and tablets
- Prescription bottles or ovals – Used for dispensing liquids of low viscosity
- Wide-mouth bottles – Used for bulk powders, large quantities of tablets or capsules, and viscous liquids that cannot be poured readily from the narrow-necked standard prescription bottles
- Dropper bottles – Used for dispensing ophthalmic, nasal, otic, or oral liquids to be administered by drop
- Applicator bottles – Used for applying liquid medication to a wound or skin surface
- Ointment jars and collapsible tubes – Used to dispense semisolid dosage forms, such as ointments and creams
- Sifter-top containers – Used for topical powders to be applied by sprinkling
- Hinged-lid or slide boxes – Used for dispensing suppositories and powders prepared in packets.

The vials, bottles, and jars are typically colorless or tinted and composed of glass or plastic. Tinted containers, the most prevalent tint being amber, provide the maximum protection of their contents against photochemical deterioration. Additional outer wrappings or cartons also may be used to protect light-sensitive pharmaceuticals packaged in non-tinted containers. Glass containers are generally used in situations where drug products are exceptionally moisture sensitive or have the potential for chemical or physical interaction with plastic. A variety of materials, polystyrene being the most common, are used to manufacture plastic prescription containers to allow a minimum reactivity while still providing appropriate product protection. Polyethylene is typically added to plastics when the container requires flexibility such as when the medication is to be administered in a dropwise manner (e.g., nose or eye drops and throat sprays) or more viscous liquids and semisolids (e.g., lotions, medicated shampoos, or creams). Tinted plastic containers are the most widely used because these provide increased product protection and durability with less weight. Examples of pharmacy containers are shown in Fig. 10.14

When determining the appropriate container for a specific prescription product, the pharmacist, although not an expert, is expected to be knowledgeable about the materials used for packaging medications to make the best container selections for

Figure 10.14 Examples of prescription containers used for packaging small numbers of solid dosage forms, such as tablets and capsules; liquid preparations administered by drops or spray; liquid preparations; powders; and semisolid preparations, such as ointments and creams. (Courtesy of Dawn Pearson.)

specific prescription products.[88] The pharmaceutical manufacturer's packaging can often provide insight as the manufacturer has already selected a container that will not adversely affect the composition or long-term stability of their product. Similar types of containers should be used by the pharmacist in dispensing the medication to the patient. Also, FDA regulations require pharmaceutical manufacturers to include in their prescription–product labeling the type of container to be used by the pharmacist when dispensing the prescription drug to preserve its *identity, strength, quality, and purity*. For example, sublingual nitroglycerin tablets are always dispensed in their original glass bottles to minimize exposure to air and moisture. If a drug product is intended to be dispensed in the manufacturer's original container, the regulation does not apply and this packaging information will likely not be available to the pharmacist.

The increased attention given to patient safety initiatives has led to innovations in design and shape for prescription packaging by some pharmacies. Some of these modifications include: shapes that provide flat surfaces for labeling so that the label can be read without turning the container; special surfaces for highlighting the most important drug information items on the container; ability to store expanded printed medication information right on the prescription container to prevent inadvertent loss; and color coding which allows products for different patients in the same household to be easily identified preventing mix-ups. See example in Fig. 10.14.

The closure on a prescription container is an essential component in protecting the product from contamination and loss. An additional consideration for closures is that they be child-resistant. The high number of accidental poisonings after ingestion of medication and other household chemicals by children led to the passage of the *Poison Prevention Packaging Act* in 1970 which requires childproof closures for both legend and OTC medications. The Consumer Product Safety Commission has ruled that manufacturers must place prescription drugs in child-resistant packages if the original package is intended to go directly from the pharmacist to the patient. However, manufacturers need not place drugs in safety packaging if the drugs are intended to be repackaged by pharmacists. Other exceptions to the requirement for childproof closures include:

- Drugs that are used or dispensed in inpatient institutions, such as hospitals, nursing homes, and extended-care facilities, unless they are intended for patients who are leaving the confines of the institution

- Specific prescription drugs which are highly reactive to common plastic containers such as nitroglycerin, medroxyprogesterone, and pancrealipase preparations
- Specific prescription drugs where the importance for direct and immediate access in an emergency supersedes concerns over potential pediatric poisoning such as nitroglycerin sublingual tablets or epinephrine syringes
- Unique packaging designed to improve patient compliance such as oral contraceptives
- Specific requests by the prescriber or patient to use non-childproof closures on individual prescription orders.

A patient may request non-child-resistant containers for a single prescription or for all of the patient's dispensed medications. If the patient is making the request that all of their prescription medications are dispensed without child-resistant containers, the pharmacist should have this request in writing and verify this blanket waiver with the patient periodically in case circumstances have changed.[89]

Other forms of medication packaging come under the broader heading of unit-dose or single-unit enclosures. Most often, unit-dose packaging places individual dosage forms, a single tablet or capsule, in its own sealed package. Less frequently, each sealed package will contain a single dose which may consist of one or more units, such as when two tablets make up a single dose. This system was originally developed for inpatient prescription processing as it allowed for simplified drug distribution and inventory control. This type of packaging is now sometimes seen in the outpatient setting due to advantages for patient safety including being able to easily visualize the product, provide complete protections from environmental hazards until administration (e.g., orally dissolving tablets), prevent product manipulations which could compromise therapy when performed incorrectly (i.e., cutting unscored tablets for a half a tablet dose), provide evidence of entry, and aid in compliance. Common types of unit-dose packaging include the strip package, the blister package, unit-dose cups and modified disposable syringes for oral, as opposed to injectable, use. Compliance packaging is typically blister packaged medications on a card where the blisters are arranged, usually with instructions next to each dose, to give the patient visual cues for administration to assure compliance with the prescribed regimen. Examples of compliance packaging include oral contraceptives and some antibiotics (i.e., dos-paks). In some instances, single unit, unit dose or compliance packages are labeled and dispensed as received from the manufacturer (Fig. 10.15). These innovations can dramatically streamline the drug packaging and dispensing process.

Medications may come from regulated pharmaceutical manufacturers in unit-dose form or may be repackaged in the pharmacy into unit-dose containers. Regardless of where the drug product is unit-dose packaged, the FDA requires that each individual unit be labeled with the drug name, strength, dosage form, expiration date (revised from the manufacturer's expiration date to reflect handling of the medication), lot or control number, and the name of the business responsible for the packaging or distribution. Controlled substances must also be labeled with the schedule designation such as C-II. The label may also contain national drug codes (NDC) or utilize bar coding technology. When the unit-dose packaging is completed in the pharmacy, the pharmacist must give adequate attention to the packaging materials used to ensure the medication will not be adversely affected by being in contact with the packaging materials and that any necessary precautions such as protection from light, excess handling, or protection from high temperatures (when mechanical packaging machines are used) are adequately considered. Sufficient controls should exist within the pharmacy to prevent product package labeling mix-ups such as only allowing one drug product to be repackaged at a time with cleaning, inspection, and use of independent double checks between products. Control logs should be kept to document medication repackaging. Some states also have regulations related to repackaging of medications by the pharmacy and all applicable state laws should be consulted prior to initiating repackaging processes.[90,91]

Labeling

Each packaged drug product for dispensing must be appropriately labeled by the pharmacist with a prescription label. This label, different from the medication label applied to manufactured products, is

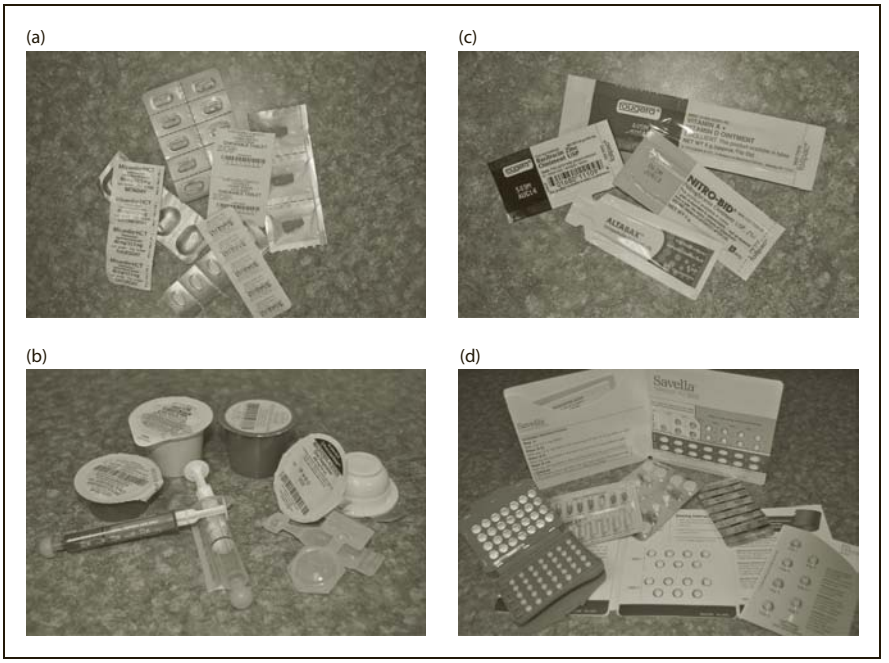


Figure 10.15 Examples of unit-dose packaging, including (A) for oral solid dosage forms, (B) for liquid dosage forms, (C) for topical semisolid preparations, and (D) compliance packaging. (Courtesy of Dawn Pearson.)

primarily intended to provide the necessary information for optimal patient compliance. There is also information on the label related to the dispensing pharmacy where the original prescription documentation is stored. This label is typically generated by a computer using prescription processing software, but may be typewritten or handwritten, if necessary. Figure 10.16 demonstrates a computer-prepared prescription, including the label, additional printed medication information, and receipt.

Readability, both initially and for the lifespan of the dispensed therapy, is of primary importance. The quality of the computer printer, the font selected (a minimum of 11-point sans serif such as "arial"), the use of white space, highlighting, ink color and the type of paper or adhesive labels used by a pharmacy can have a major effect on the readability of a prescription label. Prescription tape should be used to cover and protect a label if the ink used is prone to rubbing off or if use of the drug product itself (e.g., an oily ointment the patient will apply using their hands) may decrease the readability of the label over time. A prescription should have an aesthetic and professional-appearing label. If the label and the container are not neat and professional in appearance, the patient may conclude that the prescription medication itself was also prepared in a careless manner potentially damaging the relationship between the pharmacist or pharmacy and the patient.

The content of the label is legislated at both the federal and state levels, but there is still significant diversity in labels depending on the pharmacy or software used. Organizations such as the Institute of Medicine, the ISMP, the National Association of Boards of Pharmacy (NABP) and the *United States Pharmacopeia* have all recommended standardizing prescription labels to a more patient-centered format for increased patient safety. Legislative efforts nationwide are under way to accomplish these changes and pharmacists must stay abreast of these changes. Examples of these recommended patient-centered standardized labels can be found in the NABP report on uniform prescription labeling requirements.[92] The types of information typically on prescription labels are:

- Patient name – The patient's legal name is required. In the case of veterinary medications, the last name of the owner and the animal species should be included.

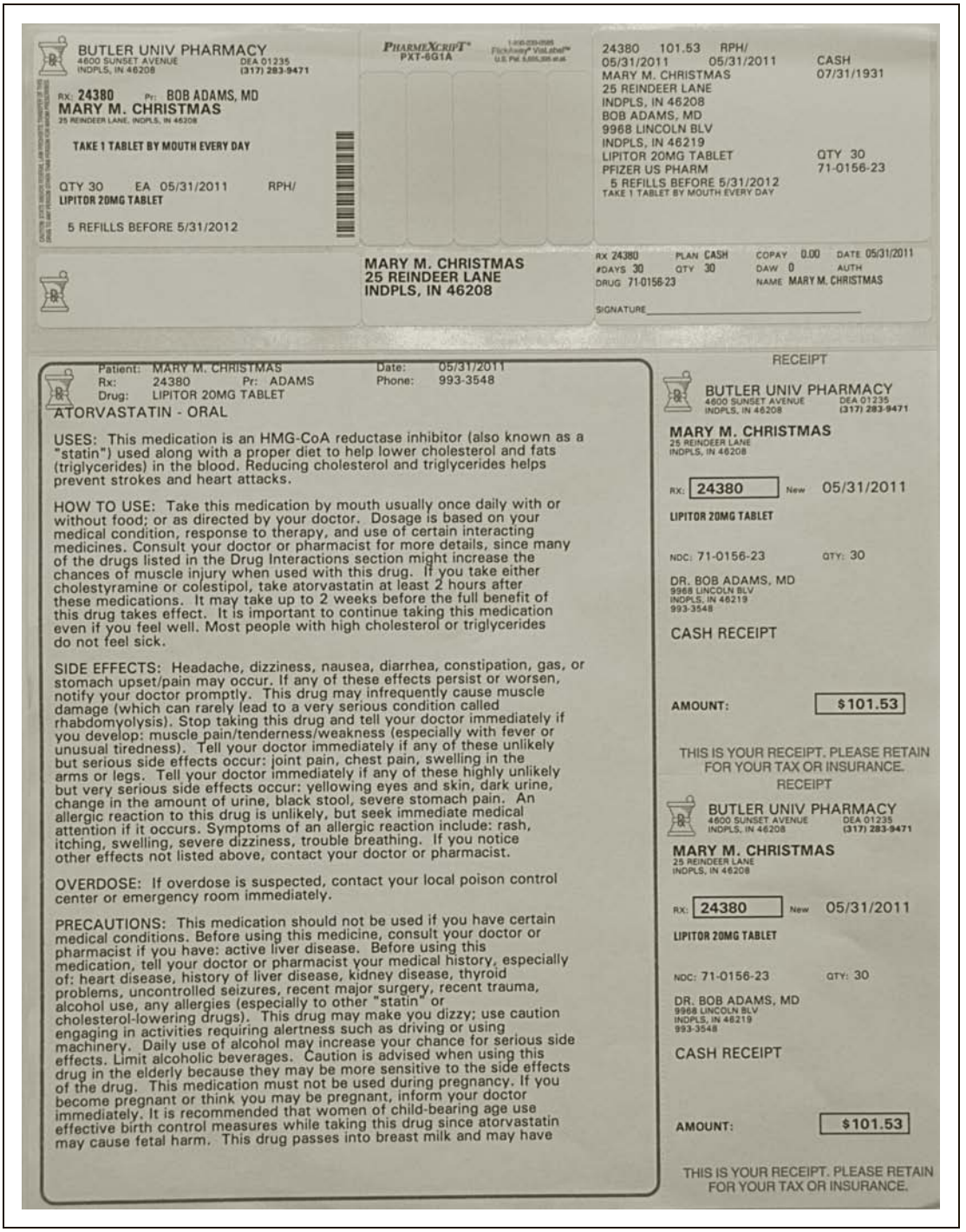


Figure 10.16 Example of a computer-prepared prescription record, label, patient receipt, and patient-counseling information. (Courtesy of Dawn Pearson.)

- Directions for use – A simplified, concise translation of the directions for use as indicated by the prescriber along with the medication's indication (when provided by the prescriber) without unfamiliar terms or medical jargon facilitates the best patient outcomes. Directions should clearly separate the dose itself, or the number of dose units to be taken, from the frequency of doses. To assist patients with low literacy skills, doses should be described using numeric rather than alphabetic characters (e.g., "Take 2 tablets" rather than "Take two tablets"). Also, vague instructions such as "twice daily" should be replaced with more explicit terms (i.e., "in the morning and again at bedtime") as appropriate. Following these basic guidelines will translate a prescribed signa of "ii po bid" to "Take 2 tablets by mouth in the morning and 2 tablets in the evening" rather than "Take two tablets twice daily" which has been misunderstood by even highly literate patients. The challenge for pharmacists is when the prescriber's instructions will not fit on the prescription label or are ambiguous such as "take as directed." In these cases, clear and unambiguous supplemental materials and verbal counseling must be provided. A clear statement referring the patient to these materials should be included on the prescription label. In certain circumstances, it may be necessary for the pharmacist to clarify ambiguous instructions with the prescriber, especially when, in the judgment of the pharmacist, additional directions for the patient are imperative for appropriate dosing and patient care. In these cases, the pharmacist may add the clarified directions to those indicated by the prescriber on the original prescription (with documentation of how, when, and by whom the clarified directions were obtained) and subsequently, to the prescription label.
- Drug name and strength – The drug name must accurately represent the specific product dispensed. If the name differs from the prescribed name, such as when a generic drug is dispensed, a phrase indicating the substitution should be present (i.e., "generic for [prescribed name]"). The dosage form is typically included in this notation as well, although it is not imperative. Some states require that the name of the manufacturer be included and some pharmacies choose to include information such as the original manufacturer's lot number or expiration date. This information is generally considered superfluous and only clutters the prescription label and diverts patient attention from the critical information. The manufacturer's information is better suited for prescription documentation and not labeling.
- Beyond use date – This is the date by which the medication should be used and should not be confused with the expiration date of the drug product or the prescription.
- Pharmacy name, address, and telephone number – Regardless of corporate names or the use of central "filling" pharmacies, the information for the dispensing pharmacy, which may include details such as the store number, must be included on the prescription label. Although current recommendations suggest the pharmacy address may only serve as a distraction on the prescription label, and is unnecessary in the presence of the telephone number, it is currently a legal requirement.
- Prescription number –This number is assigned by the pharmacy and correlates the dispensed product to the original prescription records.
- Date of dispensing –Because the "fill date" provides a better indication of the timeframe for the dispensed medication and can be useful in reconciling the product with pharmacy documentation, it is recommended for the prescription label to use the dispensing date instead of other dates such as the date the prescription was generated by the prescriber.
- Quantity dispensed.
- Number of refills – Whole numbers should be used to indicate the number of refills remaining on the original prescription order after the current dispensing or "No refills" as appropriate. This field on the prescription label should not be used to manage partial fills.
- Prescriber name.
- Other items which may appear on the prescription label include bar code and radio frequency identifications for the use of technology to eliminate human error in dispensing, and the dispensing pharmacist's initials, although specific pharmacist identification is typically part of the pharmacy's prescription documentation and is not necessary on the label itself.

- The label of any drug listed as a controlled substance in Schedules II, III, or IV of the Controlled Substances Act must, when dispensed to a patient, contain the following warning: "CAUTION: Federal law prohibits the transfer of this drug to any person other than the patient for whom it was prescribed."

The current evidence-based recommendations related toward more patient-centered prescription labels and associated materials are intended to address problems associated with nonadherence and patient misunderstanding of prescribed therapies. These recommendations also include designating the critical information on a prescription label and giving it emphasis through highlighting, font selection, font size and the use of increased white space in these areas. The prescription label items designated as critical information include: patient name, directions for use, drug name and strength, and beyond use date.

The pharmacist must also give special attention to the associated materials provided with the dispensed product to all patients (i.e., the auxiliary labels and the printed medication information). Auxiliary labels are used to emphasize important aspects of the dispensed medication and provide cautionary statements from the pharmacist including the medication's proper use, handling, storage, administration, and potential adverse effects. A "shake-well" label is indicated for a prescription containing ingredients that may physically separate on standing (e.g., suspensions, lotions, and emulsions). The use of labels such as "For the Ear", "For the Eye", and "External Use" is recommended because of the added safety these offer, even when the primary directions indicate their proper use. Other auxiliary labels may be used to warn that the medication should not be swallowed, used internally or left within the reach of children. Auxiliary labels are available in various colors to give them special prominence but should complement the prescription label. They should be placed in a conspicuous spot on the prescription container; the number used should be minimized to avoid distracting patients with nonessential information; and only evidence-based auxiliary information, both text and icons, should be utilized. Examples of some auxiliary labels in English and Spanish are shown in Fig. 10.17.

Printed medication information, or patient product information (PPI) is often provided with prescription medications to ensure that the patient is apprised of proper use, benefits and risks, and signs of adverse reactions. Examples of PPIs are shown in Fig. 10.18. For certain high risk medications, this printed information is not only responsible professional practice, but may be required by federal or state law. Prescription processing computer software typically interfaces with drug databases to provide this supplemental information upon dispensing (Fig. 10.16). PPIs may be used by pharmacists to reinforce individualized patient counseling efforts. Pharmacists may need to customize these materials to fit the individualized patient needs or to assist patients in understanding and applying the information to their prescribed therapy. This is especially important when dealing with patients who have low health literacy, impaired cognitive function, or take many different medications.

Despite all the attention given to recommended legislative changes related to the prescription label and associated materials, the NABP Report of the Task Force on Uniform Prescription Labeling Requirements points out that "The prescription label cannot and should not replace critical pharmacist care responsibilities, such as appropriately identifying the patient at the time of dispensing and providing patient counseling."[93]

Rechecking

The importance of this step cannot be overemphasized. Every prescription should be rechecked and the ingredients and amounts used verified by the pharmacist. All details of the label should be rechecked against the prescription order to verify directions, patient's name, prescription number, date, and prescriber's name. The ISMP recommends dedicating an area of the pharmacy as a "sterile cockpit" in reference to safety standards first implemented by the aviation industry highlighting, as with pilots, a pharmacist's need for focused, uninterrupted attention. This creates a visual cue reminding pharmacy workers that the pharmacist should not be interrupted during the crucial rechecking process. If another worker needs the pharmacist, they should use a non-verbal method of making their need known (e.g., placing a placard at the station) and waiting patiently for the pharmacist's attention. Even errors that would not result in patient

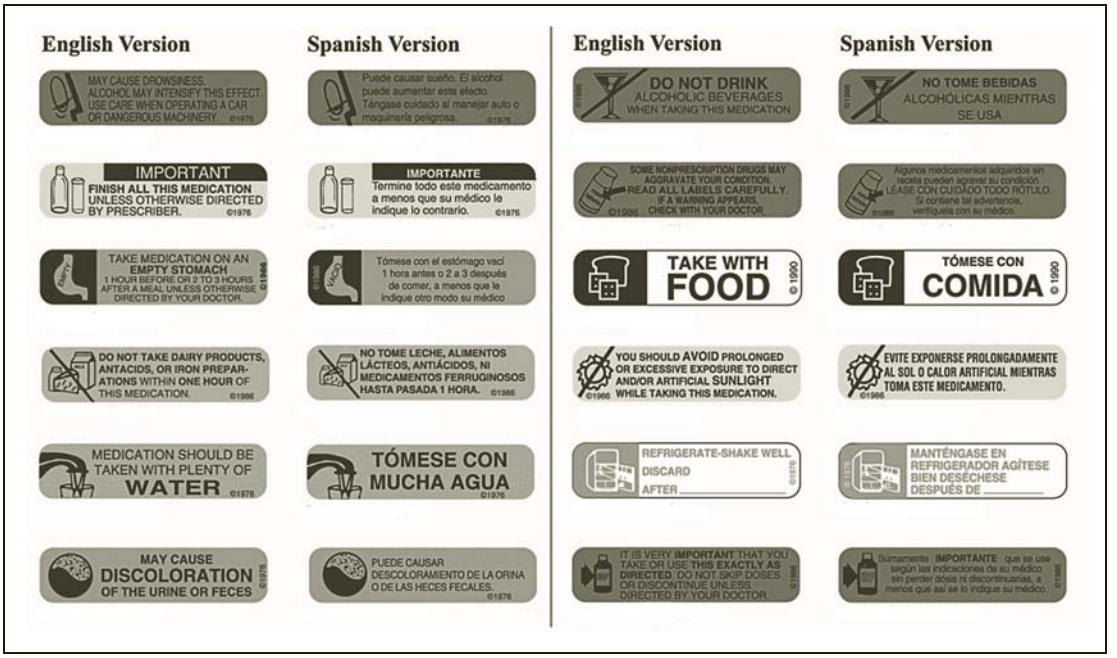


Figure 10.17 Examples of pharmacy auxiliary labels in English and Spanish. Actual labels available in color.

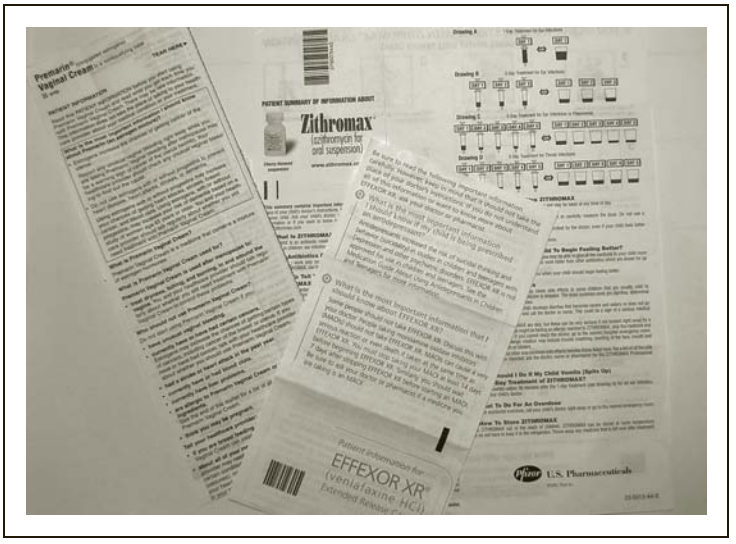


Figure 10.18 Example of manufacturers' patient package inserts used to enhance patient understanding of the medication prescribed. (Courtesy of Dawn Pearson.)

injury can still jeopardize the pharmacist–patient relationship. Something as basic as an incorrect spelling of a patient's name on a prescription label might cause concern for the patient as to the accuracy of the prescribed medication.

Dispensing

Whenever possible, the pharmacist personally should present the prescription medication to the patient (or family member, caregiver). Unfortunately, in too many organizations, this is not how the workflow

processes are designed. The interaction between the pharmacist and patient each time the patient receives a prescription medication provides crucial measures for increased patient safety and compliance. There is heightened awareness that labeling instructions alone are inadequate to ensure patients' understanding of their medication, including administration instructions, potential side-effects, monitoring parameters and general safe and effective use of their therapy. Even if the patient has been on the prescription medication in the past, or for a period of time (i.e., when a prescription order is being refilled), there is no certainty that the patient understands how to best use their therapy or that there has not been a change in the patient's status that could affect their therapy. Reinforcement of not only the labeled instructions but also any additional printed medication information (see Fig. 10.16 and Fig. 10.18) through verbal communication between the pharmacist and patient is key. This should not be merely a listening exercise for the patient, but should involve a dialogue between the pharmacist and patient to ensure understanding of the therapy. During this exchange, pharmacists have the opportunity to review the labeling information and drug product itself for accuracy as they review it with the patient. These discussions also frequently allow the patient an opportunity to share vital information with the pharmacist that would not be available by any other means. The pharmacist must also use these discussions to ensure that patients know how to measure their prescribed dose and have any necessary devices (e.g., calibrated dosing cups or spoons for liquids as seen in Figs. 10.19 and 10.20).

When the pharmacist is not able to personally interact with the patient or caregiver (i.e., the pharmacist is temporarily unavailable or the medication is being delivered to the patient's home), the pharmacist should make every attempt to personally interact with the patient in a different manner such as the telephone or e-mail.

The patient or caregiver should always be reassured that the pharmacist welcomes their questions both at the time of dispensing and at any time during the therapy by making sure contact information is clear and readily accessible for the patient.

Documenting prescription process

A record of the prescriptions dispensed is maintained in the pharmacy through the use of computer and hard copy prescription files. The use of computers in pharmacy practice has significantly eased the burden on

Figure 10.19 Examples of medicinal spoons of various capacities, calibrated medicine droppers, an oral medication tube, and a disposable medication cup. (Courtesy of Medi-Dose.)

Figure 10.20 An oral liquid dispenser for the accurate delivery of small doses of liquid medication to infants. (Courtesy of Baxa.)

pharmacists to maintain and retrieve important information related to prescription dispensing activities. Computers have the ability to store when, how often, by whom, quantities and the specific products used in processing prescription orders and quickly retrieve that information to meet patient needs, respond to drug recalls, etc. Newer centralized computer systems used by many chain drug stores allow pharmacists from any workstation in the specific company's system to access a patient's records for a prescription previously dispensed at another store, whether in another part of town or a totally different state.

Pricing the prescription

For a pharmacy to be financially stable, the pharmacist must be an effective manager of the financial aspects of the operation. To maintain the types of pharmaceutical services necessary for quality patient care, the pharmacy must make a fair and equitable profit. A pricing method should be established to ensure the profitable operation of the prescription department. A uniform and consistently applied system is beneficial to the pharmacist and helps to avoid misunderstandings from patients.

The charge applied to a prescription should cover the costs of the ingredients, including the container and label, the time of the involved pharmacy staff, the cost of inventory maintenance and other operational costs of the department, as well as providing a reasonable margin of profit on investment. Pricing structures may be based on a "cost + % markup", "cost + set fee" or a combination of the two.

Another source of funding currently available to pharmacies is fees for professional services that may or may not be associated with dispensing activities. One example is Medication Therapy Management Services (MTM) where the pharmacist's time and clinical expertise related to management of chronic diseases (i.e., asthma, diabetes, or hypertension) are billable.

Refilling and renewal

Instructions for refilling a prescription are provided by the prescriber as part of the original prescription. For non-controlled substances, most states limit the life of a single prescription to one year from the date the prescription was written. The logic behind such legislation is to prevent patients from using legend drugs, which require the oversight of a licensed prescriber, indefinitely without being under the care of their physician. No prescription for a Schedule II controlled substance may be refilled. Prescriptions for Schedule III or IV controlled substances may be refilled, if so authorized. These prescriptions may not be filled or refilled more than 6 months after the date issued.

When a prescription order has expired or the prescribed number of refills has been exhausted, physicians and pharmacists must work together so that prescriptions are renewed in a frequency that is consistent with the directions for use. Pharmacists should check with the prescriber (in person, over the telephone, utilizing e-prescribing software, etc.) as is prudent and reasonable to be assured the prescriber's intent is being met and the patient's therapy is uninterrupted. No prescription should be renewed indefinitely without the patient being reevaluated by the prescriber to assure that the medication as originally prescribed remains the medication of choice.

Renewals should be noted on the reverse side of the prescription order or in the prescription computer with the date, the quantity dispensed if different

from the original, number of additional refills if different from the original, and the name or initials of the pharmacist procuring the renewal. When verbal authorization has been obtained from the prescriber, it should be recorded as such.

The maintenance of accurate records of renewals is important for following federal and state laws and providing an accurate patient medication history.

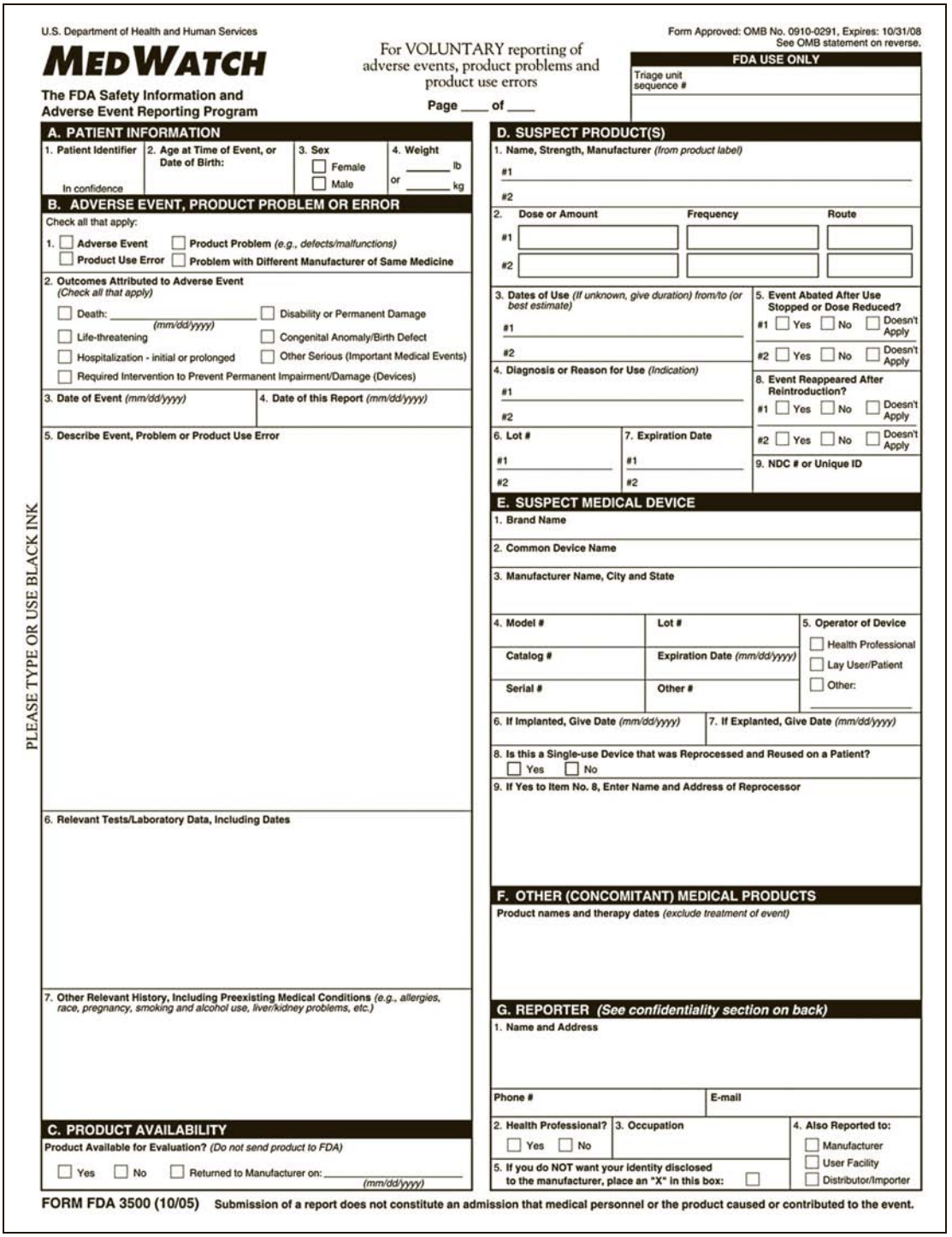
For a variety of reasons, patients will occasionally request that the balance or refills remaining on a prescription order for a non-controlled substance be dispensed by another pharmacy. This transfer of a prescription order could be due to a change in the patient's insurance plan or a temporary or permanent change in the patient's location. For safety reasons, patients should be discouraged from "price shopping" where they may have prescriptions at a variety of pharmacies based on the price of individual medications. (If the patient is determined to do this, each pharmacy should ensure they have a record of all medications and supplements the patient is taking and not just the ones obtained from their pharmacy.) State pharmacy law will dictate the specifics related to prescription order transfers, such as if a prescription may be transferred across state lines or the number of times a single prescription order can be transferred. Chain pharmacies that have centralized computer systems can access a patient's prescription records from any of their pharmacies throughout the United States and can easily transfer any remaining refills on the original prescription order. When a prescription is being transferred without benefit of a centralized computer system, it requires a phone call between licensed pharmacists at the patient's request.

Appropriate documentation of the transfer, as indicated in state pharmacy law, is necessary. The pharmacist transferring the prescription must void the balance on the original prescription and document the date of the transfer, the pharmacy and pharmacist receiving the prescription, as well as the transferring pharmacist's signature. If the original prescription order is part of an electronic record keeping system, just the name of the transferring pharmacist will suffice in place of the actual signature. The transferred copy should include the original prescription number, the name and address of the transferring pharmacy, original date of prescription, date of initial dispensing, date of last refill, number of refills remaining, and full name of transferring pharmacist.

Additional rules are in place related to the transfer of controlled substances. Prescriptions for Schedules III, IV and V drugs may be transferred between pharmacies for refill purposes. The transfer of original prescription information for a controlled substance listed in Schedules III, IV or V for the purpose of refill dispensing is permissible between differently owned pharmacies on a one time basis only.

Drug product safety reporting programs

Monitoring drug product quality and preventing harm to the public is an important function of the practicing pharmacist. The medications dispensed subsequent to prescription orders and those sold directly to patients from behind- or over-the-counter should meet high standards of manufacturing quality to assure safety and efficacy when used properly. Any encounter of a significant medication problem related to serious adverse events, product quality problems, product use errors, therapeutic inequivalence/failure or a suspicion of product counterfeits for any FDA-regulated drug, biologic, medical device, dietary supplement or cosmetic should be reported to the FDA immediately through the MedWatch Program.[93] This reporting is voluntary for consumers and healthcare professionals and is completed using Form FDA 3500 (Fig. 10.21) by telephone (1-800-FDA-1088), fax (1-800-FDA-0178), US mail (using the postage-paid addressed form), or electronically through the FDA's website (http://www.fda.gov). The FDA 3500 may also be embedded in some pharmacy prescription processing software packages which can assist in completion and distribution to the FDA. Reporting of these problems is mandatory for investigators, manufacturers, distributors, and medical facility personnel associated with investigational new drugs in clinical trials. These events are reported using Form FDA 3500A. Death of a patient also results in mandatory reporting to the FDA or the medical product manufacturer by facilities such as hospitals or nursing homes. Although the FDA also requests reports on vaccines, veterinary medicines and suspected unlawful sale of medical products on the Internet, separate reporting mechanisms are in place for these categories and the Form 3500 is not



U.S. Department of Health and Human Services

MEDWATCH

The FDA Safety Information and Adverse Event Reporting Program

For VOLUNTARY reporting of adverse events, product problems and product use errors

Page ____ of ____

Form Approved: OMB No. 0910-0291, Expires: 10/31/08
See OMB statement on reverse.

FDA USE ONLY
Triage unit sequence #

PLEASE TYPE OR USE BLACK INK

A. PATIENT INFORMATION
1. Patient Identifier (In confidence) | 2. Age at Time of Event, or Date of Birth: | 3. Sex ☐ Female ☐ Male | 4. Weight ____ lb or ____ kg

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR
Check all that apply:
1. ☐ Adverse Event ☐ Product Problem *(e.g., defects/malfunctions)* ☐ Product Use Error ☐ Problem with Different Manufacturer of Same Medicine
2. Outcomes Attributed to Adverse Event *(Check all that apply)*
☐ Death: _____ *(mm/dd/yyyy)* ☐ Disability or Permanent Damage
☐ Life-threatening ☐ Congenital Anomaly/Birth Defect
☐ Hospitalization - initial or prolonged ☐ Other Serious (Important Medical Events)
☐ Required Intervention to Prevent Permanent Impairment/Damage (Devices)
3. Date of Event *(mm/dd/yyyy)* | 4. Date of this Report *(mm/dd/yyyy)*
5. Describe Event, Problem or Product Use Error
6. Relevant Tests/Laboratory Data, Including Dates
7. Other Relevant History, Including Preexisting Medical Conditions *(e.g., allergies, race, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)*

C. PRODUCT AVAILABILITY
Product Available for Evaluation? *(Do not send product to FDA)*
☐ Yes ☐ No ☐ Returned to Manufacturer on: _____ *(mm/dd/yyyy)*

D. SUSPECT PRODUCT(S)
1. Name, Strength, Manufacturer *(from product label)*
#1
#2
2. Dose or Amount | Frequency | Route
#1
#2
3. Dates of Use *(If unknown, give duration) from/to (or best estimate)*
#1
#2
4. Diagnosis or Reason for Use *(Indication)*
#1
#2
5. Event Abated After Use Stopped or Dose Reduced?
#1 ☐ Yes ☐ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply
8. Event Reappeared After Reintroduction?
#1 ☐ Yes ☐ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply
6. Lot # | 7. Expiration Date
#1 | #1
#2 | #2
9. NDC # or Unique ID

E. SUSPECT MEDICAL DEVICE
1. Brand Name
2. Common Device Name
3. Manufacturer Name, City and State
4. Model # | Lot # | 5. Operator of Device ☐ Health Professional ☐ Lay User/Patient ☐ Other:
Catalog # | Expiration Date *(mm/dd/yyyy)*
Serial # | Other #
6. If Implanted, Give Date *(mm/dd/yyyy)* | 7. If Explanted, Give Date *(mm/dd/yyyy)*
8. Is this a Single-use Device that was Reprocessed and Reused on a Patient? ☐ Yes ☐ No
9. If Yes to Item No. 8, Enter Name and Address of Reprocessor

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS
Product names and therapy dates *(exclude treatment of event)*

G. REPORTER ***(See confidentiality section on back)***
1. Name and Address
Phone # | E-mail
2. Health Professional? ☐ Yes ☐ No | 3. Occupation | 4. Also Reported to: ☐ Manufacturer ☐ User Facility ☐ Distributor/Importer
5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: ☐

FORM FDA 3500 (10/05) **Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.**

Figure 10.21 FDA MedWatch reporting form.

used. If a patient or caregiver would like to initiate a quality complaint, the FDA will accept complaints directly but encourages them to file their complaint through a healthcare professional with access to their medical record in order to provide the most accurate clinical information.

Regardless of the source or nature of the complaint, all the information collected during the reporting process is shared between the FDA and the manufacturer for evaluation whether corrective action, by either organization, is required. The person filing the report is always given the option by the FDA to remain anonymous in subsequent communication with the product manufacturer or distributor.

Complaints or concerns specifically related to drug product quality may relate to any factor of quality or effectiveness, including dosage form integrity, authenticity, stability, contamination, appearance, odor, taste, color, device malfunction, packaging (or product mix-up), and labeling. Regardless of whether the problem occurred during manufacturing, shipping, storage or administration, the MedWatch program can still be utilized for reporting.

The postmarketing surveillance of pharmaceuticals for adverse reactions is essential in establishing a complete safety profile for marketed drugs. Once marketed, the number and diversity of patients receiving a new drug is far greater than during the controlled clinical trials. Thus, some adverse drug reactions (ADRs) or adverse drug experiences (ADEs) and drug interactions that escape detection during the clinical trials are only seen after the drug product is marketed through routine surveillance by healthcare professionals or during postmarketing clinical studies. Serious reactions (including the detection of rare but potentially lethal ADRs or drug interactions), observations of events not described in the package insert, and reactions to newly marketed products are of particular importance.

Regardless of the type or magnitude of the reported concern, MedWatch reports are taken very seriously. Data collected have resulted in changes to product labeling, warning letters to healthcare professionals regarding safe conditions of use, requirements for further clinical or safety studies or, in some instances, withdrawal of the product from the market. Reports of safety alerts and other changes as a result of MedWatch surveillance are available on the FDA website, through e-mail updates, RSS news feeds to your computer or wireless device, or even via social networking tools such as Twitter so that healthcare professionals can stay informed.

Providing a framework for ensuring medication use safety

Introduction

The US healthcare system is paradoxical, offering at once the promise of state of the art care, and also the threat of injury, and even death, resulting from flawed and sometimes dysfunctional performance. In 1998, the Institute of Medicine sponsored National Roundtable on HealthCare quality, published a report that called attention to an alarming problem:[94]

> Serious and widespread quality problems exist throughout American medicine. These problems . . . occur in small and large communities alike, in all parts of the country, and with approximately equal frequency in managed care and fee-for-service systems of care. Very large numbers of Americans are harmed as a result.

This realization was brought sharply to public and professional attention with the publication in November 1999, of *To Err is Human: Building a Safer Health System*, the first report of the Institute of Medicine (IOM) Committee on Quality. This benchmark report reframed medical error as a chronic threat to public health and galvanized media attention to the issue. Some startling findings included[95].

- 98 000 Americans die annually as a result of preventable medical errors
- National costs (including lost income, lost household production, disability, and healthcare costs) of preventable adverse events – medical errors resulting in injury – are estimated between $17 and $29 billion, of which healthcare cost represents over half
- More Americans die of medication errors annually than from workplace injuries
- Even medication errors that do not result in actual harm have a cost, calculated at as much as $2 billion annually.

Because these hospital-based studies do not even account for errors in other settings, where they may occur with at least equal frequency, the figures offer only a modest estimate of the real target of actual errors. *Err* recommended a comprehensive approach to improving patient safety, which would demand a broad-based response. There was no magic bullet, no single solution, and no single recommendation as *the answer*. Preventing errors means designing the healthcare system to build in safety at all levels.

Err offered a similar conclusion relative to safety: flaws are unacceptable and common. The effective remedy is not to brow-beat the healthcare workforce by asking them to try harder to give safe care, when in fact, the courage, hard work, and commitment of healthcare workers are the only real means to stem the tide of errors latent in the healthcare system.[95] Unfortunately, workers rely on outmoded systems and poor workflow design that sets them up to fail, despite efforts to the contrary.

One realizes that knowledge of best practice is not applied systematically or rapidly; in fact, the diffusion of innovation of best practice is frustratingly slow. An average of 17 years is required for new evidence-based knowledge to be incorporated into common practice.[96] The IOM committee set forth six Aims for Improvement, establishing what should be attainable common goals: care should be safe, effective, timely, patient-centered, efficient, and equitable. Yet *Chasm* reports that, as it exists, the American healthcare system is incapable of providing the public with the quality it expects and deserves, offering only few of these basic aims consistently. Quality problems occur typically, not because of failure of goodwill, knowledge, effort, or resources, but rather because of fundamental shortcomings in the way care is organized.[96] If, as *Err* suggests, exhortation, blaming, and trying harder cannot get the necessary job done, what system redesign considerations must be considered?

Chasm called for change at four levels (Fig. 10.22):

- *Experience of patients and communities* – The focus for improvement must shift from the healthcare system itself to being patient-centric, tying quality issues more closely to patient's values and expectations, actual experiences, cost, and social justice.
- *Microsystems of care* – The small work units that actually give care to patients represent the microsystem level. This team of people, with their information system, client population of patients, and a defined set of work processes, represents where *work* or *care* happens. Care at the microsystem level must be knowledge-based, patient-centered, and systems-minded. The quality of a microsystem is its sustained ability to provide ever-improving levels of care: safe, effective, patient-centered, timely, efficient, and equitable.
- *Healthcare organizations (or macrosystems)* – The quality of an organization lies in its ability to support microsystems' ability to sustain ever-improving care levels. Through their culture, policies, and the tools provided for work, healthcare organizations frame the capacity for microsystems to achieve care improvements. Organizations need to develop more robust and persistent systems for identifying, diffusing, and adopting best practice. Access to information and decision support systems must be available to create a supporting network of knowledge at the microsystem level. Because human assets are a fundamental differentiating factor, organizations need to invest in recognition and development in the persistent improvement of knowledge, skills, and competency within the workforce. Beyond individual knowledge, skills, and competency, effective and collaborative teams and teamwork will be essential to achieving improvement goals, as will coordination of care among services and departments and across the continuum of care, particularly with respect to patients with chronic illnesses. Finally, organizations need to commit philosophically and in practice to a data-driven measurement and assessment of performance and outcomes.

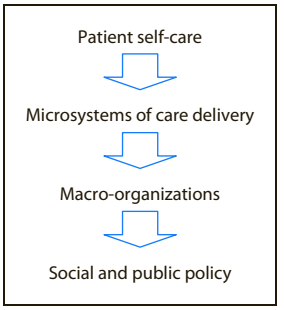


Figure 10.22 Levels of quality-focus in healthcare. (Data from Berwick DM. A user's manual for the IOM's "quality chasm" report. *Health Aff* (Millwood) 2002; 213: 80.)

- *Healthcare environment* – Sweeping and difficult changes will be necessary in the external environment, including capital and operating financing, regulation, accreditation, litigation and tort reform, professional education, and social policy. Who would pay for telemedicine or e-mail care? What will be the source of capital for much needed information technologies? A safety culture functions on the basis of openness, transparency, and trust, but without tort reform to ease pressures of litigation and in an environment of *blame* and *shame*, can that be a reality? The quality of the healthcare environment may determine how well organizations and microsystems can achieve their quality goals.

Err and, to an even greater extent *Chasm*, reflect a solid base in systems thinking. Solidly tying experiences of patients to the fundamental definitions of quality, judgments of performance, delivery systems, organizations, and policies and procedures can only be made in the context of health status, satisfaction, and reduction of morbidity and mortality. Improving patient safety relies on an understanding of systems thinking, complex adaptive systems, and learning in complex systems.

While *Chasm* has provided the framework for improvement, additional work by the IOM, through the *Quality Chasm Series* continues to build the body of evidence, understanding, and necessary action steps to keep patients safe. In January 2003, the IOM released the report entitled *Priority Areas for National Action Transforming Health Care Quality* that clearly identified 20 priority areas that collectively address preventive measures, care coordination, patient self-management, and health literacy issues that cross acute, chronic, and palliative care domains.[97] A subsequent report, *Fostering Rapid Advances in Health Care: Learning from System Demonstrations* identified the need for primary care redesign, improved information and technology infrastructures, insurance coverage changes, and malpractice reform strategies necessary to make care patient-centered and safety focused.[98]

In *Leadership by Example: Coordinating Government Roles in Improving Health Care Quality*, the IOM goes further to recommend a multi-pronged approach to care improvement by suggesting that the federal government take advantage of the influence it has to set the standards for national healthcare quality.[99] Specifically, the report indicates that clinical data reporting requirements, purchasing strategies, standardized performance measures, and quality reports should be developed to accelerate the development of knowledge and tools that have been demonstrated to improve quality. An additional report, *Patient Safety: Achieving a New Standard For Care*, outlines the IOM recommendations for enhancing knowledge, developing tools, disseminating results in order to build the necessary health data interchange and work plan to develop data standards applicable to the collection, coding, and classification of patient safety information.[100]

The IOM also identified that to provide safe and effective care, health professional education requires a major overhaul to address changing health system expectations, evolving practice requirements, new information and technologies, and staffing arrangements. The first report released by the IOM, *Health Professions Education: A Bridge to Quality* provides a mix of approaches necessary to improve training environments, research, public reporting and leadership.[101] The focus of this report identifies the need to integrate a core set of competencies – patient-centered care, interdisciplinary teams, evidence-based practice, quality improvement, and informatics – into health professions education. A second report, addressed nursing workforce issues, *Keeping Patients Safe: Transforming the Work Environment of Nurses*, identifies necessary safeguards for safe and effective care.[102] While specifically focused on an evaluation of nursing practices, resources, and environment, the report highlights changes that could impact all care professionals and patient safety efforts: effective leadership, adequate staffing, organizational support for ongoing learning, interdisciplinary collaboration, appropriate work design, and organizational support through governance and culture that supports safety as a priority.

The IOM published a report in 2006, titled *Preventing Medication Errors*,[105] which expanded upon their earlier reports. This book set an agenda for improving the safety of medication use, by providing an overview of the system for drug development, regulation, distribution, and use. *Preventing Medication Errors* also examined the peer-reviewed literature on the incidence and the cost of medication errors and

the effectiveness of error prevention strategies. The report provided action agendas, detailing the measures needed to improve the safety of medication use in both the short- and long-term. Patients, primary healthcare providers, healthcare organizations, purchasers of group healthcare, legislators, and those affiliated with providing medications and medication-related products and services will benefit from this guide to reducing medication errors.[103]

The IOM and other groups continue to build the body of evidence necessary to identify strategies for sustainable and effective care improvement. What has been identified to date? There are clear conditions and priorities for care improvement action that require attention. A need exists for leadership to be passionate and engaged for safety improvement to occur. Comprehensive strategies must be implemented to develop the workforce to provide the sustainable change needed to improve care delivery. The findings in the *Quality Chasm Series* to date highlight the breath and diversity of issues that must be addressed to improve local as well as natural healthcare quality.

Conclusion

The IOM reports titled *To Err is Human,*[97] *Crossing the Quality Chasm*[98] and *Preventing Medication Errors*[105] paint a vivid landscape of the crisis in the American healthcare system and offer recommendations to point to a path for change. Mindful that the Chinese word for crisis contains two elements, danger and opportunity, we are reminded that that the edge of chaos is where change occurs and where systems unfreeze and reform with renewed capacity to respond to environmental forces and to adapt.

The path to safer medication use and improvements in patient safety is not about a destination. This is a journey that must involve iterative learning. There are no absolute solutions, no mystical pronouncements that will tell the profession of pharmacy what to do to fix the system. The problems it faces will not be solved by the level of thinking that created them. The profession is forced to consider new approaches, and new knowledge and to consider ways of thinking, acting, and being that are outside our traditional approaches.

Some hard lessons learned from other transformational change initiatives in healthcare and other industries provide insight and wisdom for the journey:

- Gather and use evidence to define the path and to persuade others to follow it.
- Realize that if you build it, they may not come. People always do want what makes sense to them in their own context, in their own time. The context cannot be overlooked because it is believed that content is impressive and persuasive. Allow some time for sense-making and learning to occur, but remember to front-end-load the learning with vision, direction, and feedback.
- Wanting to do the right thing is not the problem. The aggregated consequences of how things are done creates the outcomes, morbidity, mortality, and cost experienced. Redesign will be essential. Make it easy to do the right thing, not harder. Simplification is a key.
- Engage the culture. Do not wait for it to change. Miracles happen when knowledge and context are shared through feedback. Build on best knowledge to engage the culture, with the realization that culture changes when knowledge shifts occur.
- Knowledge is sticky. Without a systematic process, enablers, and system supports, it doesn't move easily. Posters, senior leaders' speeches, newsletters, and slogans typically do not cause knowledge to blow. Use data, make personal connections, and use champions to move knowledge to influence culture to create change.
- Think about absorptive capacity. What issues might compete or conflict with the priority of the safety issue? Consider timing and how full individual plates are, and craft a compelling message to engage people in the process.
- Consider ways to increase the dialog about safety. Communities of practice and successful microsystems are powerful tribes. When they work, knowledge flows, and best practices can be replicated. Dialog is the key to effective information flow and to uncovering tacit knowledge that holds keys to success strategies.

Clearly, a new approach is needed within healthcare organizations to improve the safety of medication use. Building the required safer medication use system will mean redesigning processes of care to ensure patients are safe from accidental injury. A number of practices have been shown to reduce error in the medication process and are recommended to be in place

in healthcare settings. Recommendations for building a safer medication use system include redesigning processes that govern medication use, involving all members of the medication use team, and creating a new culture that identifies medication safety as a priority for the organization.

Ultimately, the judge of the quality of work, the services delivered, and the outcomes of care is an increasingly well-informed patient, as well as payors and regulators from the public and private sectors. Focus on patients' needs and wants and less on "how we do it around here."

Adverse drug reactions

Introduction

Drug availability and use have risen steadily for the past several decades. In 1961, only 656 drugs (prescription and over-the-counter (OTC)) were marketed in the United States. By 1989 this number had increased to 8000 and by 2011 well over 11 000 drugs were marketed in the United States.[104,105] The United States drives drug development, with almost 45% of the world's new medicines originating in the United States.[106] Since 2000, an average of 24 new molecular entities or biological license applications (i.e., new products marketed for the first time) have been approved each year in the United States.[107] Physician office visits result in over 2.3 billion prescriptions or drug samples supplied annually, and although the US population grew by 9% between 1999 and 2009, the number of prescriptions increased by 39%.[108,109] In 2009, prescription drug sales topped $300 billion, nearly eight times the amount spent in 1990.[109,110] This is in addition to OTC medicines, dietary supplements, and "natural" or alternative products consumers commonly use.

Medications unquestionably have provided tremendous benefits to society. Whether preventing childhood illness through vaccination, treating or preventing infections with antimicrobials, or forcing cancer into remission with antineoplastic agents, the benefits of modern drug therapy are immense. However, such therapy is not without risk. Encephalitis has been associated with vaccines; allergic reactions to antimicrobials are well documented; and antineoplastic agents can severely impair a patient's immune system, exposing them to life-threatening infections. The negative and undesirable effects of drug therapy are adverse drug reactions (ADRs).

All medical products, whether drugs, biologicals, diagnostic agents (e.g., radiocontrast dye), natural products, or nutritional agents can cause adverse reactions. These reactions may be caused by: the drug itself or one of its metabolites; interaction between two or more drugs or between a drug and food; an excipient in the product, such as a dye or preservative. Some reactions occur with most or all drugs in the class (a drug class is made up of medications with identical or very similar mechanisms of action; for example, penicillin antibiotics, beta-adrenergic blocking agents, tricyclic antidepressants, etc.). An example of a so called "class effect" is cough from angiotensin converting enzyme (ACE) inhibitors. Other reactions are unique to the drug. Among antibiotics, chloramphenicol causes aplastic anemia, a reaction rarely seen with other antimicrobials. Some drugs can affect multiple organ systems; for example, amiodarone may cause pulmonary fibrosis, dermatological reactions, hyper- or hypothyroidism, ophthalmologic changes and arrhythmias. Adverse effects from other drugs can be highly specific; for example, toxicity from aminoglycoside antibiotics is limited primarily to the kidney and vestibular/cochlear systems. And while drugs and biologicals marketed in the United States are required to be proven safe and effective, safe does not mean risk-free. Thus, the decision to use any medicinal product is always the result of examining its risk to benefit ratio.

Defining an adverse drug reaction

Although there are many definitions of an ADR,[111–113] an internationally accepted description is that of the World Health Organization (WHO): "A response to a drug that is noxious and unintended, and that occurs at doses normally used in humans for the prophylaxis, diagnosis, or therapy of disease or for the modification of physiological function."[114] Notably, this definition tacitly excludes the failure of a drug to have its intended effect (i.e., a therapeutic failure), and situations of drug abuse, drug overdose or poisonings.

It is important to distinguish an ADR from an *adverse drug event (ADE)*. While the two terms have been used interchangeably, the differences

are important. An ADE is an injury resulting from taking a drug.[115] ADEs encompass all steps that can go wrong with drug therapy including preventable mistakes in prescribing, administering, dispensing, monitoring, and documenting (that is, medication errors), and non-preventable ADRs. That is, an ADR is the result of the intrinsic properties of the drug and cannot be prevented.

Tremendous attention has been paid to adverse medical events and medical errors, which include ADEs, largely as a result of the Institute of Medicine publication *To Err is Human: Building a Safer Health System*.[116] This report reviewed and summarized the literature on medical errors in the US healthcare system and concluded that between 44 000 and 98 000 deaths occur annually as a result of preventable medical mistakes. Drug-related errors account for an estimated 7000 of these deaths.

As progress is made toward better assessment and management of drug risk, the line between ADRs and ADEs blurs. While much of the research in recent years has been on identifying risk factors for ADEs and ADE prevention, much of what is learned can apply to ADRs as well. Indeed, comprehensive management of drug risk requires that ADRs and ADEs be considered equally. To this end, FDA has identified four sources of risk from medical products: known side-effects (both avoidable and unavoidable), medication errors, product defects, and "remaining uncertainties," which include side-effects not yet known or reported, long-term effects, and unstudied uses and unstudied populations.[117]

Summary

Medication use continues to increase in the United States and, while offering tremendous benefits, it does so with the potential for patient harm. ADRs are a significant cause of morbidity and mortality and have a significant financial, emotional, and societal impact. There are numerous risk factors for developing ADRs; the role genetics plays in drug response is being increasingly recognized and is having an impact on drug development, testing, dosing, and prescribing. Postmarketing safety monitoring of drugs is essential, as not all reactions a drug may cause are known at the time of its approval. Although the passive postmarketing surveillance system in place for several decades has functioned as intended, significant improvements including active surveillance and risk mitigation strategies have been implemented to make drug use safer.

Drug interactions

Introduction

Although some drug-related problems develop unexpectedly and cannot be predicted, many are related to known properties and actions of the drugs and can reasonably be anticipated. However, as drug therapy becomes more complex and because many patients are being treated with two or more drugs, the ability to predict the magnitude of a specific action of any given drug diminishes. These circumstances point to a need not only for maintenance of complete and current medication records for patients but also for closer monitoring and supervision of drug therapy so problems can be prevented or detected at an early stage in their development. The pharmacist is in a unique position to meet these needs, and opportunities exist for greater involvement in the provision of drug therapy that is both efficacious and safe.

Many drug-related problems are caused by drug interactions. As a basis for this discussion, a drug interaction may be considered a situation in which the effects of one drug are altered by prior or concurrent administration of another drug (i.e., drug–drug interactions). The concept of drug interaction often is extended to include situations in which

1. Food or certain dietary items influence the activity of a drug (i.e., drug–food interactions), or
2. Herbs or other natural products influence the activity of a drug, or
3. Environmental chemicals or smoking influence the activity of a drug, or
4. A drug causes alterations of laboratory test results (i.e., drug–laboratory test interactions), or
5. A drug causes undesired effects in patients with certain disease states (i.e., drug–disease interactions).

Considerable attention has been focused on the subject of drug interaction, and information pertaining to these occurrences has been widely publicized. Several comprehensive references, such as *Drug Interaction Facts*,[118] *Drug Interactions Analysis and*

Management[119], and *Pocket Guide to Evaluation of Drug Interactions*[120] deal exclusively with this subject. Computerized references such as Micromedex® and Lexi-Comp™ also provide drug interaction information and are widely used.

One of the most important consequences of a drug interaction is an excessive response to one or more of the agents being used. For example, a significantly enhanced effect of agents like digoxin and warfarin can result in serious adverse events. Not as well recognized, but also very important, are those interactions in which drug activity is decreased, resulting in a loss of efficacy. These interactions are especially difficult to detect since they may be mistaken for therapeutic failure or progression of the disease.

Despite the fact that some drug interactions are well documented and recognized, the drugs are still given concomitantly, resulting in adverse outcomes. Digoxin and a diuretic often are given concurrently, and rationally so, in treating patients with congestive heart failure. It is well known that most diuretics can cause potassium depletion that, if uncorrected, could become excessive and lead to an increased action of digoxin and adverse events. Yet problems continue to occur as a result of this interaction.

Even with the extensive publicity that drug interactions have received, it is still often difficult to determine their incidence or clinical significance. However, numerous studies have demonstrated that many patients receive multiple drug therapy with agents of recognized potential for interaction. As the number of drugs in a patient's therapeutic regimen increases, the greater becomes the risk of occurrence of a drug interaction. Although there are only limited data regarding many of the potential drug interactions that have been suggested, considerable progress has been made in defining the level of risk associated with the use of a number of combinations of drugs. Indeed, the risk of serious interactions involving the use of astemizole, cisapride, mibefradil, and terfenadine was sufficiently important for these drugs to be withdrawn from the market in the United States.

Factors contributing to the occurrence of drug interactions

A number of factors contribute to the occurrence of drug interactions, ranging from alterations in pharmacokinetics, opposing or additive pharmacologic effects, multiple prescribers; the addition of OTC medications, or even drugs of abuse, may cause adverse drug reactions because of a drug–drug interaction. Since there are many avenues of entry for a drug interaction to occur, pharmacists can play a proactive role in identifying an otherwise unidentified potential for interactions.

Pharmacokinetic alterations

Situations that interfere with the absorption, distribution, metabolism, or excretion of drugs have the potential to significantly alter the pharmacokinetic profile and result in drug interactions. Such interactions have the potential to reduce the efficacy or increase the risk of toxicities of affected agents.

Multiple pharmacological effects

Most drugs used in current therapy have the capacity to influence many physiological systems. Therefore, two drugs concomitantly administered will often affect some of the same systems. When considering the potential for interactions between drugs, there often is a tendency only to be concerned with the primary effects of the drugs involved and to overlook the secondary activities they possess. Combined therapy with a phenothiazine antipsychotic (e.g., chlorpromazine), a tricyclic antidepressant (e.g., amitriptyline), and an antiparkinson agent (e.g., trihexyphenidyl) is initiated in some patients. Each of these agents has a considerably different primary effect; however, all three possess anticholinergic activity. Even though the anticholinergic effect of any one of the drugs may be slight, the additive effects of the three agents may be significant.

Multiple prescribers

It is necessary for some individuals to see more than one physician, and it is very common for a patient to be seeing one or more specialists in addition to a family physician. Some individuals also are seeing other health professionals (e.g., dentists, podiatrists) who may prescribe medication. It is difficult for one prescriber to be aware of all the medications that have been prescribed by others for a particular patient, and complications could arise from such situations. For example, one physician may prescribe a medication capable of causing tiredness/sleepiness

(e.g., certain antihistamines, opioid analgesics) for a patient for whom another physician has prescribed an antianxiety agent, with the possible consequence of an excessive depressant effect.

Even though the patient is seeing different physicians, he or she often will have the prescriptions dispensed by the same pharmacy. Therefore, the pharmacist has an important role in the detection and prevention of drug-related problems.

Use of nonprescription products

Many reports of drug interactions have involved the concurrent use of a prescription drug with a nonprescription drug (e.g., aspirin, antacids, decongestants) or herbal (St John's wort) or other natural product. When a physician asks patients about medications that they are taking, the patients often will neglect to mention the nonprescription products they use. Many patients have been taking preparations such as antacids, analgesics, laxatives, dietary supplements, and herbal products for such long periods and in such a routine manner that they do not consider them to be drugs or to be important with respect to the effectiveness and safety of medications. Patients also may think that since a drug is nonprescription, it is safe, and thus, the importance placed on mentioning it diminishes. This information often may be missed when interviewing a patient, and some physicians and pharmacists prefer to use a list of symptoms that might ordinarily be treated with nonprescription products in trying to obtain this information from the patient.

Interactions also may result from the concurrent use of two or more products available without a prescription. In some situations two nonprescription products promoted for different purposes contain the same active ingredient(s), increasing the risk of an excessive response to these agents. Acetaminophen is included in many products for its antipyretic and analgesic actions and is included in many nonprescription sleep-aid formulations. Patients often are unaware that products they purchase for different conditions may contain the same active ingredients and that they, therefore, are at increased risk of problems with the use of products they might assume to be safe because they do not require a prescription.

Although many individuals will have their prescriptions dispensed in their local pharmacy, they often purchase nonprescription drugs elsewhere, thus making identification of potential problems extremely difficult for the pharmacist as well as the physician. For this reason, patients should be encouraged to obtain both their prescription and nonprescription medications at a pharmacy. Such advice is justified, however, only when the pharmacist personally supervises the sale of nonprescription medications while simultaneously reviewing the patient's complete medication profile.

The precautions observed with respect to potential interactions involving products that are typically designated as nonprescription drugs also apply to the use of herbal products, dietary supplements, and other related products that are available without a prescription. Although much is still to be learned about the properties of these products, many have a potential to interact with prescription medications, and patients should be asked whether they are using such products.

Patient noncompliance

For a variety of reasons, many patients do not take medication in the manner intended by the prescriber. Some have not received adequate instruction from the prescriber and pharmacist as to how and when to take their medication. In other situations, particularly involving patients who are taking several medications, confusion about the instructions may develop even though the patient may have understood them initially. It is understandable that older patients who may be taking five or six medications several times a day at different times can become confused or forget to take their medication, although these occurrences are by no means unique to the geriatric population.

Although the situations involving noncompliance usually would result in a patient not taking enough medication, some circumstances could lead to excessive use of certain medications, thereby increasing the possibility of drug interaction. For example, some patients, if they realize they have forgotten a dose of medication, double the next dose to make up for it. Some other patients may act on an assumption that if the one-tablet dose that has been prescribed provides partial but not complete relief of symptoms, a two-tablet dose will be even more effective.

Drug abuse

The tendencies of some individuals to abuse or deliberately misuse drugs also may lead to an increased

incidence of drug interactions. The antianxiety agents, opioid analgesics, and amphetamines are among the agents most often abused, and the inappropriate use of these drugs can result in a number of problems, including an increased potential for drug interaction.

Many interactions that occur are undetected or unreported. Koch-Weser observed that detection of drug interactions by clinicians is inefficient and cited six reasons for the existence of this situation.[121] Although initially noted in 1972, many of these observations are just as valid today.

1. In most cases the clinical situation is too complex to allow recognition of an unexpected event in a patient's course as related to his or her drug therapy.
2. With few exceptions, the intensity of action of drugs in the therapeutic setting cannot be quantitated accurately.
   One reason for the many reports of interactions involving anticoagulants, antidiabetic agents, and antihypertensive agents is that there are specific parameters, such as prothrombin time, blood glucose concentrations, and blood pressure that can be measured and can provide a quantitative indication of drug activity. Therefore, any change in these values that may be caused by introducing another drug into therapy can be measured with relative ease. In contrast, when one considers drugs like the antipsychotic agents and analgesics with which it is far more difficult to measure degree of activity, it becomes increasingly difficult to observe and measure the effect of other drugs on their activity.
3. Even when a deficient, excessive, or abnormal response to one or both drugs is recognized clearly during concomitant administration, it is attributed usually to factors other than drug interaction.
   When an unexpected response to a drug develops, it often is attributed to something other than a drug interaction, such as patient idiosyncrasy in the case of an excessive response, or tolerance in the case of a deficient response.
4. The index of suspicion of most clinicians concerning drug interactions is quite low, and many practicing physicians are hardly aware of the phenomenon.
5. Practicing physicians tend to doubt their observations concerning drug interactions unless the same interaction has been reported previously.
   Although physicians are now well aware of the occurrence of drug interactions, there are situations in which a drug interaction may be occurring, but there are other factors that also could contribute to the altered response noted. Therefore, physicians often accept a reasonable explanation, albeit incomplete, based on information with which they are familiar, rather than suspect a possibility that has not been reported previously. Although many interactions that have been reported via case reports have not been confirmed by other observations or additional study, many single-case reports have served as the stimulus for additional study that has resulted in warnings about potentially dangerous interactions.
6. Physicians frequently fail to report drug interactions even when they have unequivocally recognized them. Several factors, no doubt, contribute to this situation. The time it would take to write up a case report to submit to a journal is a deterrent to many physicians and pharmacists. Also, since drug interactions often represent an undesirable experience for the patient, health professionals often are reluctant to expose themselves to possible criticism, or even liability, regarding the therapy. However, it is important that health professionals communicate information that will be useful to others or will help others to avoid the same problems.

Reducing the risk of drug interaction

Although other mechanisms may be involved in the development of drug interactions, the ones cited are the most important. As often stated, more than one mechanism may be responsible for certain interactions; these mechanisms may work in concert or in opposition as determinants of the resulting effect. Still other drug interactions develop by mechanisms yet to be identified. However, an awareness of the factors predisposing to the development of drug interactions, as well as the mechanisms by which many of them occur, will be of value in the identification and prevention of potential problems.

It is evident that significant limitations still exist in trying to predict the results of combination therapy. In the following section, guidelines are provided to reduce the risk of the occurrence of drug interactions. The reduction of the risk of drug interactions is a challenge that embraces a number of considerations. Although they could be applied to drug therapy in general, the following guidelines to reduce and manage drug interactions are offered to assist healthcare professionals who have the responsibility of selecting and monitoring therapeutic regimens:

- *Identify the patient risk factors* – Factors such as age, the nature of the patient's medical problems (e.g., impaired renal function), dietary habits, smoking, and problems like alcoholism will influence the effect of certain drugs and should be considered during the initial patient interview.
- *Take a thorough drug history* – An accurate and complete record of the prescription and nonprescription medications a patient is taking, as well as products such as herbal products and dietary supplements, must be obtained. Numerous interactions have resulted from a lack of awareness of prescription products prescribed by another physician or nonprescription medications the patient did not consider important enough to mention.
- *Be knowledgeable about the actions of the drugs being used* – The knowledge of the properties and the primary and secondary pharmacological actions of each of the agents used or being considered for use is essential if the interaction potential is to be assessed accurately.
- *Consider therapeutic alternatives* – In most cases, two drugs that are known to interact can be administered concurrently as long as adequate precautions are taken (e.g., closer monitoring of therapy or dosage adjustments to compensate for the altered response). However, in those situations in which another agent with similar therapeutic properties and a lesser risk of interacting is available, it should be used.
- *Avoid complex therapeutic regimens when possible* – The number of medications used should be kept to a minimum. Therapeutic duplications in which agents are given that have overlapping pharmacologic actions should be avoided unless clinically necessary. In addition, the use of medications or dosage regimens that permit less frequent administration may help avoid interactions that result from an alteration of absorption (e.g., when a drug is administered in close proximity to meals).
- *Educate the patient* – Patients often know little about their illnesses, let alone the benefits and problems that could result from drug therapy. Individuals who are aware of, and understand, this information can be expected to be in greater compliance with the instructions for administering medications and more attentive to the development of symptoms that could be early indicators of drug-related problems. Patients should be encouraged to ask questions about their therapy and to report any excessive or unexpected responses. There should be no uncertainty on the part of patients as to how to use their medications in the most effective and safest way.
- *Monitor therapy* – The risk of drug-related problems warrants close monitoring, not only for the possible occurrence of drug interactions but also for adverse events occurring with individual agents and noncompliance. Any change in patient behavior should be suspected as being drug-related until that possibility is excluded.
- *Individualize therapy* – Although the development of a therapeutic regimen that meets the specific needs of individual patients is inherent in many of the above guidelines, the importance of individualization of therapy cannot be emphasized too strongly. Wide variations in the response of patients to the same dose of certain individual drugs are well recognized. It is difficult to predict the response of many therapeutic agents when they are given alone; the challenge and limitations in anticipating the response with a multiple-drug regimen are even greater. Therefore, priority should be assigned to the needs and clinical response of the individual patient rather than to the usual dosage recommendations and standard treatment and monitoring guidelines.

The pharmacist will be involved actively in the observance of the guidelines described above. In addition, the need to not only maintain complete and current patient medication records but also to supervise and monitor drug therapy more closely places

the pharmacist in a strategic position to detect and prevent drug interactions. By observing the preceding guidelines and recommendations and by strengthening communication with patients and other healthcare professionals, the pharmacist has a valuable opportunity to make a significant contribution toward the further enhancement of the efficacy and safety of drug therapy.

Poison control

It is estimated that there are between five and ten million poison exposures annually in the United States. Accidents cause more deaths in children over one year of age more often than the five leading fatal diseases combined. Also, suicide is among the most common causes of death in preadolescents, adolescents, and adults. Often these accidents and suicides involve poisons. Another important cause of morbidity and mortality is the intentional use of illicit drugs and also various chemicals, especially among the young. Even though the reporting undoubtedly is incomplete, there are known to be more than 40 000 deaths annually in the US attributable to poisoning.[122] The majority of these are intentional self poisonings. In addition to the fatalities caused by poisoning, there are staggering numbers of nonfatal cases requiring medical treatment.

In most instances, unintentional poisonings are preventable. This is especially true of unintentional poisonings in young children by medications and chemicals found in the home. Acute and chronic poisonings are of great public-health significance. The solution to this problem requires the efforts of individuals in many various disciplines as well as of the lay public. Among these instrumental persons are pharmacists, who can play a key role in preventing or mitigating the consequences of unintentional poisonings, especially those caused by medications.

Role of the pharmacist

There is much that a pharmacist can do to help prevent poisoning and to improve the treatment thereof. Pharmacists direct and staff many regional poison centers. They actively provide consultation to physicians treating poisoned patients to assure quality care.

Undoubtedly, the most important role played by a pharmacist is in the area of prevention. This role, relative to poison-prevention packaging of prescription drugs, was mentioned previously. However, the role of the pharmacist is particularly critical with regard to nonprescription or OTC items. With prescription medications there is involvement of a physician who may provide instructions and precautionary advice. However, with OTC products, the pharmacist is often the only person who is in a position to serve these functions.

The pharmacist can and should provide, explain, and amplify directions for proper use of potentially toxic materials, bearing in mind that the concern is for the safety of the patient and that of other household individuals. Thus, the dispensing of a toxic medication provides an opportunity to warn the buyer about the hazards of leaving the material within reach of unsuspecting children.

In some instances, it is desirable to affix warning labels on the products that a pharmacist dispenses or to hand out patient information materials. The dispensing of a drug also provides an opportunity to inquire and give advice about facilities for safe storage. Because of this contact, the pharmacist can play a personalized role in cautioning about prescription and commercial products. The pharmacist can do much to reduce the aforementioned limitations of labeling. Although the public often may not read or appreciate precautions on labels, the effectiveness of the latter are increased significantly if a pharmacist takes time to explain them. The pharmacist also has a unique role to play in detecting product or labeling defects and an obligation to call to the attention of appropriate manufacturers or regulatory agencies potential labeling or product defects.

There has been a tendency in the past for the development of too many small and ineffectual poison centers, the activities of which could be carried out more effectively and efficiently if they were amalgamated with others in the same area. Local pharmacy associations should support the trend toward centralization and regionalization of poison information and treatment facilities.

Finally, pharmacists can assist greatly in the educational efforts of a community by distributing literature and by providing space for displays related to poisoning prevention.

Medication disposal

Introduction

Proper disposal of medications is a challenging and complex issue. Many variables should be considered when determining the most appropriate method for medication disposal, including federal and state laws, environmental impact, type, volume, and toxicity of medication being disposed, setting (acute care institution, long-term care institution, community pharmacy, clinic, personal supply, etc.), and risk for diversion. While the optimal method of medication disposal is incineration, there are several barriers to optimal disposal such as cost, incinerator accessibility, and confusing or cumbersome laws and regulations.

Multiple regulatory agencies are involved in pharmaceutical waste management, including the Environmental Protection Agency (EPA), Department of Transportation (DOT), Drug Enforcement Administration (DEA), Occupational Safety and Health Administration (OSHA), state pharmacy boards, state/local environmental protection agencies, and Local Publicly Owned Treatment Works (LPOTW).[123] Additional federal, state, and local laws may also dictate medication disposal. The Joint Commission accredits healthcare organizations, including hospitals, home care, laboratory, ambulatory care, and behavioral healthcare organizations. Joint Commission standards EC.3.10 and EC.9.10 address appropriate management of hazardous materials.

We will focus on (a) distinguishing types of pharmaceutical waste, (b) federal laws and best practices regarding the management of hazardous pharmaceutical waste, regulated medical waste, and universal waste, (c) medication disposal in the community, and (d) minimization of pharmaceutical waste. Pharmaceutical waste management in healthcare facilities will be discussed first, followed by management of pharmaceutical waste in the community.

Pharmaceutical waste management in healthcare facilities

Types of pharmaceutical waste

Distinguishing the type of pharmaceutical waste and identifying the appropriate waste stream for disposal is critical for not only ensuring compliance with state and federal regulations, but also for maintaining a healthy environment. The following sections describe various applicable types of waste streams for pharmaceuticals.

Hazardous waste

There are very specific laws for managing waste from products that are defined as "hazardous." According to the Resource Conservation and Recovery Act (RCRA) of 1976, waste is considered hazardous if it exhibits certain characteristics (ignitability, corrosivity, reactivity, or toxicity) or if it is included on specific "lists" of wastes that the EPA has deemed hazardous.[123] The RCRA established requirements on generators of hazardous wastes, including healthcare facilities. These regulations are set forth in the United States Code of Federal Regulations (CFR) at 40 CFR Parts 240–282.[125]

Pharmaceuticals considered hazardous based on characteristics:

- *Ignitability* – Pharmaceuticals that are considered hazardous based on ignitability include, but are not limited to, any aqueous drug formulation containing >24% alcohol by volume,[126] oxidizers or materials that readily supply oxygen to a reaction in the absence of air (example: silver nitrate applicators), and flammable aerosol propellants meeting the DOT definition of compressed gas (example: Primatene aerosol).[127]
- *Corrosivity* – Corrosive agents are those with a pH < 2 or > 12.5. Occasionally ingredients used in pharmaceutical compounding may fall into this corrosive category (examples: glacial acetic acid, sodium hydroxide).[126]
- *Reactivity* – Nitroglycerin may fall into the reactive category; however, most medical formulations of nitroglycerin are not reactive,[5] and nitroglycerin regulations vary by state. [126]
- *Toxicity* – Toxicity characteristics apply primarily to heavy metals such as barium, selenium, and thimerosal.[126]

In addition to the four characteristics described above, wastes can also be "listed" if they are acutely hazardous (fatal to humans or animals at low doses) or if they contain any of the toxic constituents listed in 40 CFR Part 261, Appendix VIII and are capable of

posing a substantial present or potential hazard to human health or the environment.[124]

There are four lists of hazardous wastes:[124]

- The F List (non-specific source waste)
- The K List (source-specific waste)
- The P List (discarded commercial chemical products that are acutely hazardous)
- The U List (discarded commercial chemical products that are identified as toxic).

Pharmaceuticals are included in the P and U Lists. Examples of medications included in the P List are warfarin, arsenic trioxide, epinephrine, phentermine, nicotine, and physostigmine. Examples of pharmaceuticals on the U List include mitomycin, chloral hydrate, chlorambucil, cyclophosphamide, diethylstilbestrol, lindane, phenol, and selenium sulfide.

All dangerous pharmaceuticals are not technically considered hazardous waste under RCRA. Since the RCRA was written in 1975, many drugs have been brought to the market that are equally or more toxic than those specifically mentioned in RCRA. The pharmaceuticals on these lists have not been updated regularly. Although not technically regulated as such, it would be considered best practice to treat similar, more recently approved agents as hazardous waste as well. According to the American Society of Health System Pharmacists (ASHP), pharmaceutical waste should be considered dangerous if it contains any of the following: [126]

- P or U listed drugs
- Chemotherapy agents
- Drugs with LD_{50}s (lethal dose in 50% of test animals) of $< 50\ mg\ kg^{-1}$
- Endocrine disruptors
- Immunosuppressants
- Drugs meeting National Institute for Occupational Safety and Health (NIOSH) or OSHA criteria
- Drugs with potential toxicity due to chromium, selenium, or cadmium (including multivitamin/mineral preparations).

Regulated medical waste

It is important to understand terminology regarding regulated medical waste (RMW). RMW may also be called biohazardous waste or infectious medical waste. Exact definitions of regulated medical waste may vary slightly by state or institution. However, a key component of these definitions is that the waste is contaminated with blood, body fluids, or other potentially infectious material, posing a risk for transmission of infection. Sharps (items capable of cutting or piercing the skin such as needles with or without syringes, scalpels, etc.) are considered regulated medical waste. It is important to note that in pharmacy circles, "biohazardous" is a term that is often erroneously used to describe chemotherapy waste.[123] Although chemotherapy is hazardous to living/dividing cells, chemotherapy waste is not "biohazardous" unless it also contains body fluids or other potentially infectious material. This confusion may be compounded by the availability of auxiliary labels that have both "chemotherapy" and "biohazardous" on them.[123] There are situations where waste is both RMW and hazardous waste. Proper management of this dual waste would be determined by both the drug being dispensed and the administration instrument used.[123]

Disposing of hazardous and regulated medical waste

ASHP recommends that healthcare facilities have a multidisciplinary waste management team responsible for maintaining compliance with RCRA and state waste management regulations.[126] Hazardous waste must be incinerated at an EPA-approved facility to dispose of RCRA defined hazardous waste.[126] Nonhazardous pharmaceutical waste should be disposed of in a medical waste or municipal incinerator that is permitted to accept nonhazardous pharmaceutical waste.[126] Although some states may allow nonhazardous waste to be disposed of in sewers, this method of disposal is not optimal for the environment. There are many waste management companies which specialize in disposal of medical waste. Healthcare facilities should partner with an appropriately approved waste management company to ensure compliance with all federal, state, and local laws and to ensure environmentally appropriate disposal methods.

Universal waste

The universal waste rule is a modification of hazardous waste rules (RCRA),[127] designed to reduce

requirements and foster environmentally sound disposal of certain types of commonly generated hazardous wastes. Currently, the universal waste rule applies to items such as batteries, pesticides, mercury containing products, and bulbs/lamps. The EPA proposed the addition of hazardous pharmaceutical wastes to the federal universal waste rule.[128] The proposed rule would not only add hazardous pharmaceutical waste to the universal waste rule, but it also encourages generators to dispose of nonhazardous pharmaceutical waste as universal waste thus removing unregulated waste from wastewater treatment plants and municipal solid waste landfills.[128] This proposed rule applies directly to healthcare facilities that generate pharmaceutical waste (pharmacies, hospitals, physician and dentist offices, outpatient and residential care facilities, veterinary clinics, etc.). It also makes possible the collection of personal medications from the general public at various waste management facilities.[128] As of August 2011, the proposed rule to add pharmaceuticals to the universal waste program had not been finalized and "the Agency does not have a projected date for the finalization of the rulemaking . . . ".[128] Concerns have been expressed about safety and security, as well as notification and tracking. The EPA is considering additional regulatory options that address these concerns.[128]

Controlled substance waste

Properly disposing of controlled substances is especially challenging due to risk of drug diversion, varying state laws, differing regulations based on type of healthcare facility, and additional regulations imposed by the Controlled Substance Act (CSA). Individual state laws differ, but frequently in the hospital setting when controlled substances must be "wasted," they need to be destroyed such that they are beyond recovery and witnessed and documented by two qualified healthcare professionals. This situation occurs commonly when a partial dose needs to be wasted; for example when a patient needs 6 mg of morphine. Morphine is available as 5 or 8 mg syringes, thus an 8 mg syringe is partially used, and the remaining 2 mg is destroyed. Some states mandate the method of destruction, others do not. Unfortunately, in some areas, this type of controlled substance waste is accomplished via drain disposal. Given the environmental impact of medications in our sewer and water systems, this method of disposal is increasingly discouraged.[123] In the retail pharmacy setting, expired or unwanted controlled substances are managed via DEA-registered reverse distributers (see below) and/or pursuant to DEA forms 41 Registrant's Inventory of Drugs Surrendered[129] or 222. In the long-term care facility setting, management of unwanted/unused controlled substances is challenging, and policies and procedures at individual facilities may vary. Most long-term care facilities are not registered with the DEA and there is no provision currently in the CSA that would allow a non-registered facility to return controlled substances to the dispensing pharmacy.[130]

The verbiage in the original CSA makes the disposal of unwanted/unused controlled substances in the long-term care and general community environments difficult. However, the Secure and Responsible Drug Disposal Act[131] that was signed into law on October 12, 2010 amends the CSA. This act authorizes the Attorney General to issue new regulations to allow for disposal of controlled substances by long-term healthcare facilities, and allow individuals in the community, who have lawfully obtained prescription controlled substances, to deliver them to an authorized person for proper disposal. As of January 2012, the Attorney General has not yet issued these new regulations.

Reverse distribution

Pharmaceutical reverse distribution is the process of returning recalled or expired pharmaceuticals for manufacturer's credit. Potentially creditable medications, in the original manufacturer's packaging, are processed through reverse distributors. If the conditions of the product coincide with the return policies of the manufacturer, the item is returned to the manufacturer, or its designated agent (which may be a reverse distributor), and credit is issued to the pharmacy. Non-creditable medications include, but are not limited to: samples, repackaged products, partially used products, compounded pharmaceuticals, patient owned medications, and products that are inherently waste-like (such as those that are broken, spilled, used, or unidentifiable). Creditable medications are not considered waste and do not count toward a healthcare facility's waste generator status. Once transferred to the reverse distributor, it

is their responsibility to return the product to the manufacturer, or dispose of the medication in a manner that complies with federal and local regulations, as well as Return Industry Association (RIA) standards.[126]

Disposal of medications in the community/private sector

Accumulation of unused or "leftover" medications in a community setting can occur for a variety of reasons, such as patient non-compliance, medication expiration, or changes in drug therapy.[132,133] A survey by Kuspis and Krenzelok published in 1996 found that only 2% of study participants took their medications completely prior to reaching their expiration dates. Most of the survey participants who had unwanted medications, threw them in the trash (54%) or used the toilet or sink (35.4%) for disposal, while others (7.2%) did not dispose of their medications at all.[134] A more recent survey, published in 2006 in the *Journal of the American Board of Family Medicine*, asked 301 outpatient pharmacy customers about their unused or expired medication disposal practices. The authors found that >50% of those surveyed stored their unwanted medications in their homes and another 50% said they flushed them down the toilet. Only 20% reported ever receiving advice from a healthcare provider on the proper disposal of unwanted medications.[132]

There are concerns with these disposal practices. Disposal by sink or toilet has resulted in increased levels of pharmaceuticals in our rivers, streams, and drinking water supplies.[134] A US Geological Survey that studied wastewater and surface, ground, and drinking waters in Minnesota found organic contaminants in 90% of the samples tested, most of which were prescription and nonprescription drugs.[126] Current water treatment systems do not remove pharmaceuticals in drinking water and long-term exposure, even in trace amounts, could potentially be dangerous.[132] Such disposal practices could lead to adverse outcomes such as water quality degradation, endocrine disruption (potentially leading to problems with physical, mental, or sexual development), antibiotic resistance, and negative public perception regarding water cleanliness.[126] On the other hand, disposing of unwanted medications in the trash has its own set of concerns. Medications thrown away with prescription labels still on them contain personal information which can promote identity theft. Furthermore, disposing of medications in the trash can lead not only to accidental exposure by children, pets, and wildlife but it can also be a source for pharmaceutical drug diversion.[131,134] The nonmedical use of prescription drugs continues to be a concern and throwing controlled substances out in the trash or simply not disposing of them at all can lead to inappropriate access to prescription medications.

As a result of these concerns, as well as the confusion and uncertainty surrounding medication disposal, various organizations have developed programs or published guidelines on the proper disposal of prescription drugs. In February 2007, the White House Office of National Drug Control Policy (ONDCP), the Department of Health and Human Services (HHS), and the EPA issued guidance for consumer drug disposal. Around the same time, the American Pharmacists' Association (APhA), the Pharmaceutical Research and Manufacturers of America (PhRMA) and the United States Fish and Wildlife Service's (USFWS) partnered and developed the SMARxT Disposal2122 program.[134,135] This campaign was designed to educate consumers about disposing of medications in a safe and environmentally protective manner.[138] Both the ONDCP guidelines and the SMARxT™ disposal program have the same goal – to increase public awareness of safe disposal practices when medications are no longer needed. The following are main points made by both guidelines:

- Utilize medication collection programs whenever possible
- Do not flush away medications
- When disposal programs are not available, throw away unwanted medications in the trash using appropriate safeguards.

Collection events

The best way for consumers to dispose of unwanted medications is to utilize medication take-back programs or other hazardous waste collection events in their communities, whenever possible. These programs give the public an opportunity to bring unused/unwanted medications to a central location

for proper disposal. They are designed to ensure that unused, expired, or unwanted medications are collected and destroyed in a safe, legal, and environmentally sound way and not stolen or used by unauthorized individuals. They also provide an opportunity for unused drugs to be inventoried – to determine the types and amounts of pharmaceuticals wasted and identify reasons why they were not used.

There are various types of collection programs available, ranging from small, one-day events to continuous, on-going programs. One initiative, the National Prescription Drug Take Back Days, is conducted by the DEA along with state and local law enforcement agencies in all 50 states. The National Prescription Drug Take-Back event that took place on April 30, 2011 yielded over 376 593 pounds (171 tonnes) of unwanted or expired medications.[137] As mentioned above, when the Secure and Responsible Drug Disposal Act of 2010 is implemented, additional "authorized parties" will be allowed to collect and properly dispose of unwanted and expired medications throughout the community. Prior to passing this law, controlled substances returned by consumers at take-back programs are only allowed to be collected and inventoried by law enforcement.[134] Until the regulations are finalized, the DEA will continue offering take-back opportunities.[138] More about these national take-back initiatives can be found on the DEA's Office of Diversion Control's website at http://www.deadiversion.usdoj.gov/drug_disposal/takeback/index.html.[137]

City, county, or state sponsored take-back programs are also available. One can often find information regarding prescription take-back programs by contacting local waste management agencies or utilizing the Drug Take-Back Network website at http://www.takebacknetwork.com. Community pharmacies may offer drug disposal programs as well. Some pharmacies take back unwanted or expired medications at any time, while others hold periodic take-back events to collect expired, unused, or unwanted medications. Dispose My Meds (http://www.disposemymeds.com) is a website that provides information not only on medication safety and its environmental effects, but also includes a Pharmacy Locator that allows consumers to find a pharmacy in their community that offers safe disposal of unwanted medications.

Flushing

Current guidelines have strong warnings against flushing. Most prescription medications should NOT be flushed down the toilet or washed down the drain.[134–136] A few, select medications, mostly high-potency opioids and other controlled substances, may be especially harmful and/or deadly if taken by someone other than for whom the medication was prescribed, so the FDA[139] recommends flushing these down the toilet when controlled substance take-back programs are not available (see Table 10.14).[140] The most complete and up-to-date list of expired, unwanted, or unused medications recommended for flushing may be found on the FDA website at http://www.fda.gov.

Trash disposal

If a collection program is not available and the medication is not one that is recommended for flushing, both the federal and SMARxT™ disposal guidelines suggest throwing unwanted and expired medications away in the household trash.[136,139] However, consumers should first:

- Take drugs out of their original containers and crush or dissolve oral medications.[136] Topical patches should be folded in half, adhesive side in, and should remain intact.[135]
- Mix the medications with an undesirable substance, such as used coffee grounds, sawdust, or kitty litter to make them less appealing to children and animals. This will also make it more difficult for individuals who intentionally go through the trash to recognize the drugs.[136,139]
- Place the mixed contents in a sealable bag, empty canister, or other container to prevent the medication from leaking or breaking out of a garbage bag. These steps will further assure the drugs are not diverted.[136,139]
- Throw the container away in household trash.[140]

Additionally, when disposing of medication containers, it is advised that consumers first remove any personal information by peeling off the label or removing all identifying information prior to throwing the containers away in the garbage.[136] This will, once again, minimize the risk of illegal activities such as personal identity theft and drug diversion.

Table 10.14 List of medications recommended by the FDA for disposal by flushing when controlled substance take-back programs are not available.[142]

Brand name	Dosage form	Active ingredient(s)
Abstral	Sublingual tablets	Fentanyl
Actiq*	Oral transmucosal lozenge	Fentanyl citrate
Avinza	ER capsules	Morphine sulfate
Daytrana	Transdermal patch system	Methylphenidate
Demerol*	Tablets, Oral solution	Meperidine HCl
Diastat AcuDial	Rectal gel	Diazepam
Dilaudid*	Tablets, Oral liquid	Hydromorphone HCl
Dolophine HCl*	Tablets	Methadone HCl
Duragesic*	ER patch	Fentanyl
Embeda	ER capsules	Morphine sulfate, Naltrexone HCl
Exalgo	ER tablets	Hydromorphone HCl
Fentora	Buccal tablets	Fentanyl citrate
Kadian	ER capsules	Morphine sulfate
Methadone HCl*	Oral solution	Methadone HCl
Methadose*	Tablets	Methadone HCl
Morphine sulfate*	Tablets, Oral solution	Morphine sulfate
MS Contin*	ER tablets	Morphine sulfate
Nucynta ER	ER tablets	Tapentadol
Onsolis	Buccal soluble film	Fentanyl citrate
Opana	Tablets	Oxymorphone HCl
Opana ER	ER tablets	Oxymorphone HCl
Oramorph SR	SR tablets	Morphine sulfate
Oxecta	Tablets	Oxycodone HCl
Oxycodone HCl	Capsules, Oral solution	Oxycodone HCl

(continued overleaf)

Table 10.14 *(continued)*

Brand name	Dosage form	Active ingredient(s)
OxyContin*	ER tablets	Oxycodone HCl
Percocet*	Tablets	Acetaminophen, Oxycodone HCl
Percodan*	Tablets	Aspirin, Oxycodone HCl
Xyrem	Oral solution	Sodium oxybate

* These medications have generic versions available or are only available in generic formulations.

Minimization of pharmaceutical waste

Another way to address pharmaceutical waste management is by actively minimizing the amount of waste generated. Healthcare providers can help minimize waste by controlling inventory levels, using just-in-time dispensing and compounding practices, dispensing smaller quantities (especially on initial fills), reconsidering 3-month supplies or automatic refills, using available tools to prevent adverse drug reactions and interactions, improving compliance, and minimizing prescription drug therapies when appropriate.[141]

Short cycle prescribing

To help minimize waste and increase savings, some managed care organizations are offering programs that encourage dispensing of smaller quantities, when appropriate, especially at the beginning of therapy.[142] They encourage prescribing and dispensing small, trial amounts when patients are starting a new medication regimen since new therapies are sometimes not effective or patients experience an adverse effect.

The Centers for Medicare and Medicaid Services (CMS) has revised Medicare to implement a Medicare Part D long-term care "short-cycle" rule which went into effect on January 1, 2013. As a component of the Patient Protection and Affordable Care Act (ACA), CMS proposed a ruling that would require long-term care facilities to dispense drugs in 14-day increments. This rule applies to all brand name, solid oral dosage prescription drugs dispensed to long-term care residents. So any pharmacy that serves long-term care facilities will have to comply with this rule.[143] The rule also states that a resident's total co-payments may not exceed the amount that would have been collected with the usual, longer cycle. This short-cycle dispensing program is intended to decrease the amount of medications that are wasted or unused with traditional 30 to 90 day supplies by changing to daily, biweekly, or weekly prescription fills. The Congressional Budget Office estimated that implementing short-cycle dispensing would result in Part D program savings of $5.7 billion. However, others argue that without baseline data and credible evidence there is no way to objectively determine whether or not short-cycle dispensing will actually save money for the Medicare Part D program. In fact, the increase in dispensing costs associated with shorter fills may erase the potential savings from reduced waste.[144] CMS plans to collect data from Part D plan sponsors to determine how effective short-cycle dispensing is at reducing medication waste and saving money.

Drug recycling

Another initiative gaining popularity is prescription drug recycling. Many states now allow unused prescription drugs to be collected and reused or given away to those who are uninsured or poor. Although individual states may have their own regulations regarding drug reuse and recycling, some allow prescription drugs in single use or sealed packages to be returned from state programs, nursing homes, and other medical facilities.[145] A small number of states allow donations from individuals. The National Conference of State Legislatures (NCSL) identifies and tracks state legislation on prescription drug recycling, repository, or redistribution programs for unused medications.[145] Their website (http://www.ncsl.org/default.aspx?tabid=14425)

provides the most up-to-date information about the specific recycling laws for each state. Common requirements of these programs include:

- Drugs must not be expired
- A licensed pharmacist or pharmacy is involved in the verification/distribution process
- Each patient receiving a medication must have a valid prescription in her/her own name
- Controlled substances are typically excluded from these programs.

Conclusion

Healthcare professionals should play a significant role in minimizing pharmaceutical waste and educating consumers about appropriate disposal of medications. Proper disposal of pharmaceutical waste and unwanted medications is a complicated issue, involving many regulatory agencies and healthcare organizations. New initiatives are being developed to reduce medical waste, minimize its impact on the environment, and limit drug diversion. It is recommended that healthcare facilities partner with accredited waste management companies to ensure compliance with complex federal, state, and local laws regarding disposal of pharmaceuticals. In the community setting, it is currently recommended that medications be disposed of via prescription take-back programs and not introduced into the sewage system, whenever possible. Implementation of the Secure and Responsible Drug Disposal Act and the possibility of pharmaceutical waste being re-classified as Universal Waste may drastically change how pharmaceutical waste and expired and unwanted medications are disposed of in the future.

Surgical supplies

A professional service rendered by many pharmacists consists of supplying surgical instruments, sutures, surgical dressings, and other equipment employed by the surgical personnel during and after a surgical operation. Some pharmacists who have obtained the necessary background of information carry a complete line of such supplies and are even able to provide operating tables and other heavy equipment.

There are comparatively few such completely equipped pharmacies; the major outlet consists of surgical supply houses. Every pharmacist, however, should be familiar with two of the products mentioned above: *surgical dressings* and *sutures*. The selection of the correct type of surgical dressing or suture is crucial to safeguarding the welfare of the patient undergoing surgery. Many items in these categories are handled routinely by pharmacists, and all of these items come within the purview of their professional responsibility.

Health accessories

Pharmacists are trusted and relied upon to provide their expertise and knowledge to patients seeking home medical equipment (HME) in a variety of settings. The transitioning role of pharmacists providing care as well as medication segues well with their ready accessibility almost anywhere patients are located. Physicians and other health professionals recognize the value pharmacists provide in fulfilling a patient's HME needs. In recent years there has been much consolidation in HME delivery, driven by payors, mergers, and competition. However, there are still many opportunities for pharmacists to provide HME to their patients. There are large numbers of people who do not have insurance or a third party source of payment. These people are looking for a source of supply for their needs and they will frequently look to their pharmacy as their source for medical equipment and their other healthcare needs. The specially trained pharmacist is becoming recognized more widely as an expert in this area by other health professionals and *this area of expertise* can provide a professional and profitable adjunct to the pharmacy's other services.

A comprehensive HME department may include a wide variety of surgical dressings and supplies; and home medical equipment including wheelchairs, walkers, hospital beds, hydraulic patient lifters, urology and incontinence supplies, ostomy appliances, elastic supports, compression stockings, mastectomy breast forms, and orthopedic braces. In addition, many pharmacies specialize in home healthcare equipment such as traction devices, blood-glucose monitors, diabetic shoes, blood-pressure-monitoring devices, suction machines, oxygen and respiratory-therapy equipment, nerve and muscle stimulators, phototherapy lights, apnea monitors, and rehabilitation equipment. Fewer pharmacies are specializing in providing intravenous medications and supplies

for enteral or parenteral nutrition due to exclusive contracting and national conglomerates. The cost of establishing a sterile environment for the preparation of intravenous medications can be steep.

Even more important than merely providing a wide range of health accessories is the pharmacist's role in selecting and fitting them, and in instructing the patient in their proper use and maintenance. HME products and services, in many cases, require specialized training if the patient is to be properly served. Collaboration with and referral to, when necessary, other healthcare professionals who are more knowledgeable ensures that a patient's needs are properly met.

To provide these services the pharmacist may need to acquire new skills and expertise that can be obtained through a variety of sources, such as special courses given by health-accessory distributors and manufacturers, professional associations, and college or university-based programs. A thoroughly trained staff and informed provider community also will contribute to your success. Medicare and some insurance payors also require certification through one of the accreditation organizations, a list of which can be found on the CMS website.

The initial step in selecting the appropriate health product is a thorough evaluation of the patient's needs and then matching these needs to the available options. Multiple factors must be considered including age, disability related factors, lifestyle, patient equipment measurements, diagnosis, patient ability for self-care, prognosis, and reimbursement sources. Note that the option may very well be referral to another source for care.

Each of these factors should be considered when selecting the most appropriate health accessory for the patient. It is often necessary to verify insurance coverage, including whether particular equipment is mandated by a health maintenance organization and which equipment will be considered for reimbursement by Medicare, Medicaid, or insurance companies. Although a standard "prescription" may not be required, some form of a physician order and possibly a prior authorization are required as verification of medical necessity by most third parties. Reimbursement will not be made without this order. Along with supplying medical equipment the pharmacist should also take the necessary steps to ensure that the equipment can be used where it is needed. For instance, a wheelchair will not be utilized properly if the patient's home has doors or hallways too narrow for the wheelchair to fit through. An assessment, whether on site or through verbal communication, needs to be performed to determine whether the environment will allow the medical equipment to fulfill the patient need. The pharmacist has the ability and expertise to provide this service.

Other steps may include consulting with the patient, physician, and family; selecting the accessory from stock or ordering it from the manufacturer or distributor; and checking the accessory to ensure that it meets the appropriate specifications. Usually, follow-up adjustments or modifications are necessary.

Useful forms (e.g., certificates of medical necessity (CMN) which is a written statement by a physician verifying that the necessary criteria for the use of the equipment or supplies is met, disability analysis, measurement, prescription and ordering forms) are usually available from health-accessory manufacturers, insurance companies, and government agencies. In fact, some insurance companies and government agencies may mandate the use of their customized forms. Documentation of patient analysis, measurements, and what was sold/dispensed is an essential part of record keeping, especially with more stringent Fraud, Waste and Abuse regulations established by the Center for Medicare and Medicaid Services.

Professional approach

Pharmacists should not conclude hastily that they will be successful in this field, regardless of their estimate of the local market, their inventory, and their display facilities. The pharmacist must be willing to devote time and intelligent effort to the venture or he or she will fail. Their attitude must be professional, and their approach to prospective referring physicians and the public must be made on that basis, not on mere availability or price. They must become knowledgeable in the areas of reimbursement and accreditation. Most important, they must have developed the expertise to recommend the right equipment and supplies and instruct their patrons in their proper use.

Pharmacists who seriously are considering developing this specialty will need to expand their reading list of relevant professional journals and periodicals. In addition to the major pharmacy journals,

the following publications will broaden their knowledge and perspective concerning home health equipment: *HomeCare Magazine, HomeCare News, HME News, Medical Product Sales, Home Care Provider, Home Health Products, Ostomy/Wound Management, Home Healthline*, and journals in specialty fields such as physical therapy, occupational therapy, or respiratory therapy.

The National Community Pharmacists Association (NCPA) created a special division of Home Health Care Pharmacy Services. This division can provide additional information to pharmacists on changes in government programs that affect pharmacists providing home healthcare accessories. The NCPA publishes a newsletter, the *Alternative Pharmacist Monthly*. The NCPA, an accredited Accreditation Council for Pharmacy Education (ACPE) provider, also provides educational programs concerning ostomy, incontinence, wound management, orthotics, and prosthetics. An advanced certificate program in orthotics and prosthetics is offered by the National Community Pharmacists Association, and a number of other certification programs are available.

The surgical supply department of the modern community pharmacy is recognized by physician and layman alike as a proper extension of the pharmacist's professional service. Physicians and allied health professionals quickly assess this new service as an important contribution to the health-team concept.

The entrepreneurial and intrapreneurial pharmacist

Entrepreneur and *entrepreneurial activities* are well-understood terms. In this section, we broaden the interpretation of these terms and suggest that small business ownership alone is insufficient to describe entrepreneurism fully. A community pharmacy owner is certainly an entrepreneur, and entrepreneurial activities occur in a community pharmacy. In addition, entrepreneurial activities regularly occur within large and medium-sized corporations and organizations – defined by some as *intra*preneurship.[146] As the profession of pharmacy moves from a primarily independent ownership model of practice to a more employee-based profession, the opportunities for creative ventures within these corporate entities cannot be ignored, and a return to the entrepreneurial spirit in pharmacy practice provides limitless opportunities. This section focuses on these entrepreneurial activities and opportunities.

The *Oxford English Dictionary* defines an entrepreneur as "one who undertakes an enterprise; one who owns and manages a business; a person who takes the risk of profit or loss."[147] According to the *Cambridge Dictionary Online*, an entrepreneur is "someone who starts their own business, especially when this involves seeing a new opportunity."[148] The *Raynet Marketing Dictionary* says "the owner or manager of a business who by risk, initiative, and innovation attempts to make a profit" is an entrepreneur.[149] Peter Drucker[150] states that entrepreneurship and innovative business activities are neither an art nor a science but should be seen in the context of a practice and discipline. He states that entrepreneurship is not mysterious, or some special gift, talent, or inspiration, but purposeful tasks that can be organized as systematic work. Finally Collins and Moor,[151] in their classic book *The Organization Makers*, suggest that an entrepreneur is someone "who created out of nothing an ongoing enterprise." These definitions and insights provide the underlying theme for this section – the entrepreneurial pharmacist is one who assumes risk, takes responsibility, looks for opportunity, is creative, and assumes a leadership role in the inception and evolution of a new pharmacy-related business concept.

"Managing" the enterprise was not included in our entrepreneurial themes. This in not because we believe that the activities and skills of a manager are not important – they are. Managerial activities are essential to the ongoing success of all business ventures. However, as stated earlier, while not all business owners are entrepreneurs, the same can be said of managers – not all managers are entrepreneurs. Stewart and Ross,[152] in their evaluation of the primary differences between entrepreneurs and managers, found a higher risk-taking propensity among entrepreneurs than managers. Additionally, the type of entrepreneur influenced the magnitude of the difference. Income-oriented entrepreneurs (i.e., business owners) had slightly elevated risk propensity scores when compared with managers, whereas growth-oriented entrepreneurs had much higher risk propensity scores than individuals identified as managers. Discussion in this section focuses

on the pharmacist-entrepreneur. One aspect that differentiates the pharmacist-entrepreneur from the pharmacist-manager is his or her comfort with and willingness to take calculated risks.

Intrapreneurship

Does entrepreneurial activity happen only as a business venture of a single or small group of individuals? Clearly, the answer is "no." Pinchot and Pinchot[153] coined the term *intrapreneurship* to describe the entrepreneurial activities that occur within organizations. The *Oxford English Dictionary* defines the intrapreneur as "an employee given the freedom to work independently within a company with the objective of introducing innovation to revitalize and diversify its business."[149] In this section we will use the more familiar terms *entrepreneur* and *entrepreneurial* in our discussions, with the understanding that we are using the terms to refer to innovative opportunistic risky business ventures both inside and outside formal organizations (Fig. 10.23).

Entrepreneurial actions

Small business and entrepreneurship overlap, but are not the same. The key difference is the focus on growth and market planning.[154] Carland *et al.*[155] proposed the following definitions to differentiate entrepreneurial ventures from small business ventures.

- Small business venture: "Any business that is independently owned and operated, not dominant in its field and does not engage in new marketing or innovative practices."
- Entrepreneurial venture: "A business whose principal goals are profitability and growth, and the business is characterized by innovative strategic practices."

These definitions were based on earlier work by Schumpeter[156] and Vesper,[157] who identified five strategic behaviors that described entrepreneurial ventures:

- Introduction of new products or services
- Introduction of new methods of production
- Opening new markets
- Opening new sources of supply
- Industrial reorganization.

Specific pharmacy-based ventures can be used to illustrate each of these strategic behaviors.

Introduction of new products or services

Several pharmacy ventures fall into the category of introducing new products or services. Long-term care

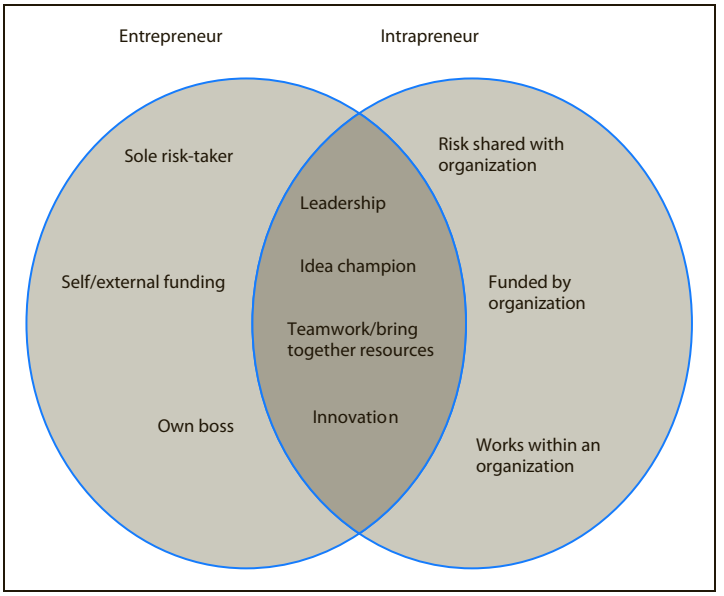


Figure 10.23 Characteristics of entrepreneurs and intrapreneurs.

consulting is a good example. In 1965, passage of the Medicare/Medicaid legislation provided guidance for the provision of pharmacy services in nursing homes. Following the development of drug distribution systems for this unique setting, the role of the consultant pharmacist soon evolved. This new practice model (service) is now part of the established standard of care in long-term care facilities throughout the United States.

Introduction of new methods of production

Unit-dose drug distribution systems in institutional pharmacy practice may be an exemplar of new methods of production. The need to reduce medication errors, monitor the medication administration process, and manage an ever-increasing product inventory was the driver for the early innovators (intrapreneurs) of unit-dose dispensing systems. Unit-dose distribution systems are considered a standard of practice in inpatient facilities today, and are being utilized in outpatient pharmacies as well.

Opening new markets

Pharmacists have long understood the service component of the dispensing process – home delivery being one of those service components. When the US healthcare system moved away from inpatient care, it provided an opportunity to deliver intravenous drug therapy in the home. Early home-infusion entrepreneurs saw the opportunity and met the need.

Opening new sources of supply

When independent pharmacy owners found themselves in a noncompetitive environment with regard to drug purchasing, their creative and risk-taking skills came into play. One of the solutions to this problem was the creation of pharmaceutical buying groups. Today most independent pharmacy owners are associated with a pharmaceutical buying group.

Industrial reorganization

Beginning in the 1970s and continuing into the 1980s, pharmaceuticals became an increasingly important but costly component of employee health plans. A few pharmacists realized that their knowledge of drug therapy, knowledge of the sources of supply, and understanding of formulary management were needed by the health insurance industry. The result was the creation of pharmacy benefit management firms. Today these firms influence virtually all medications delivered to persons who have a pharmaceutical benefit.

Practice-based pharmacists have created successful entrepreneurial ventures using each of these strategic behaviors. If past success provides any insight into the future, it would seem that there are great opportunities ahead.

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11

The scope of pharmacy practice

The practice of community pharmacy

A practice in transition

The image of what was once considered community pharmacy practice has been blurred both by the multiple types of practice in this setting and by the speed of change now occurring. Traditional independent ownership and chain pharmacy continue to exist along with a growing presence of pharmacies in grocery and mass merchandiser operations. Many factors have resulted in a rapid evolution of the distribution system for the ambulatory patient, such as the growth of virtual community pharmacies in the form of insurance company-driven mail order pharmacy, consolidated healthcare providers such as Health Maintenance Organizations (HMOs), growth of community health centers, with pharmacies dispensing products with federally reduced product cost, and the availability of medications from neighboring countries and from the Internet. The change in the reimbursement system for medications has progressed on an equal pace. The passage of the Medicare Modernization Act in 2003 resulted in the creation of Medicare Part D, an outpatient prescription drug benefit for Medicare beneficiaries. This and the growing penetration of prescription insurance have significantly reduced the numbers of cash-paying patients. The community pharmacy environment is increasingly

impacted by these changing forces, while at the same time it is attempting to fully implement the patient-oriented practice that has been envisioned since the early 1990s. Continuing to maintain control of the responsible distribution of medications, while increasingly providing direct patient care services in an environment of reduced reimbursement, are the challenges that now face community practice as it strives toward the Joint Commission of Pharmacy Practitioners Future Vision of Pharmacy Practice in 2015. In meeting this challenge, pharmacists will be the healthcare professionals responsible for providing patient care that ensures optimal medication therapy outcomes.[1]

Distribution and control of medications

The pharmacist's role in assuring the safe distribution of medications continues as a major area of responsibility in the community setting, as elsewhere. Pharmacists, as the most readily available healthcare provider, are maintaining this role while becoming more involved clinically. The retail setting was the place of employment for 65% of the nation's 270 000 pharmacists working in 2008.[2] The need for pharmacists in this setting remains high because the percentage of Americans taking prescription medications has increased over the past decade, along with the percentage taking multiple prescription medications.[3] Over $234 billion, or approximately 10% of overall national health expenditures, was spent on retail outlet sales of prescription drugs in 2008, nearly twice the amount spent in the year 2000.[4] In 2010 the number of prescriptions totaled over 3.6 billion, of which approximately 48% were filled in traditional chain pharmacies, 20% in independent pharmacies, 25% in supermarket and mass merchandiser pharmacies combined, and 7% via mail order pharmacy. That same year, generic prescriptions accounted for 71.2% of prescriptions, with 28.8% being brand name drugs. The average price of a prescription had risen to nearly $80 in 2010, up from approximately $64 in 2005, $46 in 2000, and $30 in 1995.[5] The increased use of prescription drugs and associated increase in cost come at a time of a number of changes in the marketplace for outpatient prescription medications. Patients are paying a smaller percentage of prescription drug spending. While out-of-pocket consumer spending for prescription drugs was 56% in 1990, it decreased to 26% by 2001, and declined further to 21% by 2008. At the same time, private health insurance covered 26%, 50%, and 42% of prescription drug costs in 1990, 2001, and 2008, respectively. A steady increase in coverage has occurred in publicly funded programs such as Medicaid, Medicare, and other government programs. In 1990 these programs accounted for 18% of expenditures, rising to 24% in 2001, 28% in 2005, and 37% in 2008.[6] The accelerated rise after 2005 is reflective of the Medicare Part D benefit going into effect and its new function as the primary coverage for beneficiaries having both Medicaid and Medicare drug benefits. With this rise in third party reimbursement for prescription drugs has come continued pressure from insurance plans and their pharmacy benefit managers (PBMs) to contain medication expense. Strategies such as increasing beneficiary co-payments and establishing co-pay tiers to limit use of non-preferred or expensive drugs, use of formularies to direct therapies to preferred or contracted drug entities and to exclude others, limiting the quantity to be dispensed, and requiring pre-approval of medication selection and reimbursement prior to dispensing have all impacted the community pharmacist in practice. Beyond increasing the complexity of the pricing systems that must be maintained for the many different plans accepted by a community pharmacy, these schemes are also confusing for the beneficiary, and considerable time is spent by pharmacists assisting the patient in both understanding their benefit and working with their providers and the PBM to get the patient the needed medication. Cost reduction strategies for the reimbursement of pharmacists for the distribution of the prescription by insurance companies provides another challenge because decreased professional fees must often be accepted by a pharmacist to avoid the loss of patients eligible to receive services from their practice.

These pressures greatly affect the profitability of community pharmacy. Information from the 2010 National Community Pharmacists Association (NCPA) Digest suggests that 21% of independent community pharmacies are operating at a loss, with another 23.4% having just a 0–2% net profit.[7]

In order to most efficiently process prescription orders and attempt to maintain a high level of quality at the lowest cost, community pharmacies are

increasingly utilizing technology. The processing of electronic prescriptions and automated refill requests are now becoming part of the daily routine in pharmacies. Utilization of computer systems to facilitate prescription processing is nearly universal because processing of insurance with real time adjudication of claims is the standard of practice. These same systems also assist the pharmacist in screening for drug–disease and drug–drug interactions and therapeutic duplication. They also help with monitoring of adherence to therapy. Importantly, the utility of these database solutions is limited in cases in which fragmentation of care prevents compilation of a complete and accurate record of a person's medication history, including non-prescription medications and complementary and alternative medications. The future availability of accessible personal health records should allow for improved functionality in this regard. This is especially true as patients utilize a variety of medication sources to minimize out-of-pocket expenses.

In addition to computer systems to process prescription orders, pharmacists are increasingly making use of other technologies to increase efficiency. Many pharmacies use interactive voice response (IVR) systems to allow patients to request refills on medications using their telephones. This functionality is also available using the Internet and with applications on smart phones. A variety of mechanical devices have taken the place of the counting tray in regard to getting the correct number of capsules or tablets into a container for the patient. Stand-alone counting machines have evolved into dedicated counting devices for individual medications. Dispensing system interfaces with banks of these devices was an important step toward the development of robotics, which are practical for the community pharmacy. Many community pharmacies now have one of the several available automated counting or robotic dispensing devices that count the solid dosage forms and place the counted medication into a labeled container. These devices can decrease prescription filling time; however, this improvement does not necessarily gain efficiency or assure increased care will be provided. Knowledge on how to best meld technology with human activities in these new environments is still developing.[8,9] Other technology, such as bar code scanning, allows the pharmacist to better ensure accuracy in dispensing by checking ordered medication against product selected, assuring the correct medication is added to counting devices and robots, and performing final verification on filled prescriptions. Software solutions with these systems assist in work flow management, quality assurance, inventory management, and automated ordering. Technology innovation has resulted in many changes in how the basic dispensing functions are completed in a community pharmacy, and, consequently, have produced new management challenges in the day to day practice of pharmacy.[9,10]

Additional challenges to the practice of community pharmacy grow from other strategies to control costs associated with prescription medication. Alternative distribution strategies such as centralized filling of prescription orders with delivery to distribution site pharmacies can change the relationship between the pharmacist and patient. These systems also require a different approach to pharmacy management to assure efficiency. Mail order delivery of prescription services has been a challenge to community pharmacy as established pharmacist–patient relationships are broken, and access to the provision of services for involved patients is limited when plan sponsors and PBMs promote this system as a way to reduce prescription costs. While generally assumed to be a most cost-effective way of delivering prescription drugs, the design of mail order plans and incentives used to promote their use can increase the cost to the plan sponsor.[11] These system-oriented changes in practice can further fragment the medication-related care a patient receives, and make the provision of pharmacist-provided care, which takes into consideration all of the patients medications, more difficult.

Patients can also complicate the ability of a single pharmacy to have a complete record of their medications. This can occur when patients shop for the lowest prices for their medications. This could occur at other local pharmacies or over the Internet. Increasing the risks to the patient from this latter activity go beyond provider knowledge of medications taken by the patient. Studies completed by the US Food and Drug Administration (FDA) and National Association of Boards of Pharmacy (NABP) find that many of the prescriptions filled from Internet pharmacies are adulterated and do not contain the labeled ingredients.[12] Patients also obtain prescription medications from neighboring countries. In some of these cases, quality

also becomes an issue.[13] A relatively recent development to reduce prescription cost to the patient is the offering of $4.00 generic medications by a number of retailers. These patient-initiated methods need to be considered by the pharmacist as they are working with each individual. Other issues, such as the high rate of both initial and ongoing non-adherence with prescribed medication, also reduces the pharmacist's ability to know what a patient is really taking without a detailed medication history.

Areas of specialty practice

The Practice of Community Pharmacy has expanded from the conventional role of prescription dispensing to include many other health related services, such as compounding medications, integrating complementary and alternative medications, supplying durable medical equipment, and administering immunizations.

Although compounding medication is not new to the practice of pharmacy, it has gained popularity for the ability to individualize patient medications and produce pharmaceuticals that are not commercially available. Hospice medications, bio-identical hormones, pediatric preparations, veterinary medications, and gluten-free, preservative-free, or dye-free preparations are just a few of the examples of commonly compounded pharmaceuticals. Thousands of community pharmacies offer compounded medications; however, the volume of compounded prescriptions varies from practice to practice. Some pharmacies may base their primary business on compounded medications alone. Pharmacies that specialize in compounding may choose to become certified by the Pharmacy Compounding Accreditation Board.

Complementary and alternative medication (CAM), which also has roots in early pharmacy practice, is becoming more widely used in the United States as an option to prevent and treat health conditions. According to the 2007 National Health Interview Survey, 38.3% of Americans used some form of CAM.[14] This category of treatment encompasses a wide range of therapies, including herbals and other natural products, acupuncture, meditation, chiropractic care, or massage. Many herbals and natural products have become a mainstay in the community pharmacy and these pharmacists are positioned to help patients safely integrate CAM therapy with traditional medications to assist in patient self-care efforts.

Another expanded community pharmacy service beyond the prescription counter is durable medical equipment (DME). The Medicare Modernization Act of 2003, which established Durable Medical Equipment, Prosthetics, Orthotics, and Supplies (DMEPOS) Quality Standards, requires suppliers of these products to become accredited in order to bill Medicare.[15] Some pharmacies may be exempt from this accreditation, such as those with DME sales billed to Medicare of less than 5% of the total pharmacy sales. Accreditation must be from a CMS-approved, independent national Accreditation Organization, and accreditation can cost more than $3000 for a three-year period.

As of 2010 all states allow pharmacists to immunize; however, each state differs in their laws and regulations for pharmacist immunization administration.[16] Many local, state, and national programs are available to pharmacists to obtain training on vaccine administration. Accessibility to the community pharmacy allows pharmacist-administered immunizations to make a positive impact on public health and improved vaccination rates.

Current issues in community pharmacy practice

Provision and reimbursement for patient care

Community pharmacy continues to evolve in its ability to provide medication-related patient care services. Since the description of pharmacist responsibilities in providing pharmaceutical care over 20 years ago[17] and the inclusion of those principles in professional organization statements,[18,19] community pharmacists have endeavored to incorporate these precepts into the routine practice of pharmacy. To this end, early investigations found that community pharmacists providing patient-centered care, as opposed to drug-centered care, could identify and address drug therapy problems beyond those associated with prescription writing error or drug interaction. When pharmacists providing this care collected information necessary to evaluate patients' drug therapy, problems such as the need for additional therapy, availability of more appropriate drugs, adverse drug reactions,

and unnecessary drug therapy were identified at a higher rate.[20,21] Processes used by community pharmacists in providing pharmaceutical care to patients address many of the issues associated with the quality of the medication use process and common types of medication errors.[22,23] The provision of pharmaceutical care by pharmacists is consistent with the methods recommended by the Institute of Medicine report, *To Err is Human*, to identify and address drug therapy problems (medication-related errors).[24] Subsequent studies have found that pharmacists working in the community setting can positively affect both the clinical, economic, and humanistic outcomes of drug therapy by providing patient centered care.[25–32]

The term used to describe pharmacist provided patient care is also changing. Names such as Comprehensive Medication Review, Comprehensive Medication Therapy Management, and Pharmacist Care may be used synonymously. Pharmaceutical care was generally accepted for years, but with the implementation of Medicare Part D, and the inclusion of medication therapy management (MTM) as a part of that benefit, MTM is the current term used most often. Although MTM was mandated to be provided by the PBMs, which administered the benefit, it was not necessarily referring to care provided by a pharmacist to optimize an individual patient's drug therapy. Its intent was to assure that measures were in place to limit the cost and assure quality of the benefit delivered by an individual PBM, focused on high utilizers of care. The number of Medicare Part D plans utilizing the community pharmacist to provide MTM is variable, as are the criteria for beneficiaries to be eligible for the benefit from a Part D plan or an insurance plan.[33] The addition of the MTM benefit did give rise to a set of codes within the Current Procedural Terminology (CPT) codes published by the American Medical Association. These standardized codes are used for pharmacist billing of MTM services provided to patients under Medicare Part D.

Having billing codes for use with Medicare or other insurers does not ensure these services will be paid for by third parties. Delivering a consistent set of care services to patients, and doing so with an agreed upon value, is necessary to solidify the community pharmacists' standing in the healthcare system. Clarifying this first in the private sector may be necessary at a time when others look to third parties for reimbursement.[34]

Role of pharmacy technicians

The use of technicians in community pharmacy has increased considerably as pharmacists try to maximize efficiency in prescription processing while maintaining high quality standards. The training and incorporation of technicians into the workflow in a community pharmacy has transitioned from an informal process to one which includes accredited training programs[35] and regulated practice.[36] All but six states and the District of Columbia regulate technician practice. Certification of technicians is required in sixteen states.[36] As of June 2011, over 400 000 pharmacy technicians were certified by the two national certification exams.[37,38] The role of technicians and limitations on their practice varies from state to state.[36] Community pharmacists hoping to maintain profitability at the same time they are providing more patient care services are increasingly utilizing technicians. They can reduce the amount of time spent by pharmacists in the dispensing process and allow increased effort to be focused on providing patient care activities. How the use of technicians ultimately balances with practice change of pharmacists, increased use of technology, and evolution of pharmacy law remains to be seen.

Residency training for pharmacists

As more pharmacists provide patient care to patients, the necessary training for pharmacists beyond completion of a doctor of pharmacy degree program has been up for debate. Some national professional organizations envision a future which includes residency training for all pharmacists providing direct patient care.[39,40] Important in this discussion are the number and types of residency programs available to achieve this vision. While the number of hospital pharmacy Post Graduate Year One (PGY1) Residencies approached 2000 in 2011, the number of positions in PGY1 Community Pharmacy Residencies was only 110.[41] This number is clearly insufficient to train a substantial proportion of the pharmacists that choose community pharmacy as a career. As the number of patient care-focused community pharmacies increases, so will the need for these sites to increase their role in residency development to expand advanced training opportunities.

Community pharmacy accreditation

Beyond State Board of Pharmacy licensure of community pharmacies, a movement to establish Community Pharmacy Accreditation is in its early stages. The proposed voluntary program will have standards that will be focused on patient care activities and continuous quality improvement.[42] This effort is in concert with other healthcare quality assurance activities and is being proposed in a way to ensure that pharmacy, rather than an outside organization, leads this quality initiative.[43]

Pharmacist credentialing

Certification of individual pharmacists with credentials beyond licensure is performed by the Board of Pharmacy Specialties (BPS). Qualified pharmacists are able sit for a Board exam in several practice areas and subsequently recertify through exam or continuing education. Historically, some community pharmacists became Board Certified Pharmacotherapy Specialists. This credential did not pertain to the community setting well, and in 2011 an examination for Board Certified Ambulatory Care Pharmacist came into fruition. Whether or not this becomes the credential sought out by patient care-focused community pharmacists remains to be seen.

The patient centered medical home and accountable care organizations

The concept of the patient centered medical home (PCMH) has developed as a model to address identified needs in the delivery of healthcare. The process of definition and setting standards is still in process but includes components such as a focus on the patients getting access to the components of care they need, a coordination of care with planning and tracking of care, assisting in self-care as appropriate, and measurement of performance data to improve care.[44] Pharmacist involvement in the care of patients can assist in improving the outcomes of care in a number of areas envisioned in the PCMH model. Given the track record of pharmacists working with physicians in ambulatory care environments and increasingly in community pharmacy environments, a case can be made for roles for the community pharmacist in PCMHs.[45] Issues remain for how best to link, utilize, integrate and reimburse pharmacists in this model. The eventual outcome for these ideas and how they will look in practice remains to be seen.

The 2010 Affordable Care Act moved this process forward for Medicare beneficiaries through the creation of Accountable Care Organizations (ACOs). Innovative ideas to bring together groups of providers and service suppliers with the goal of delivering seamless quality care to Medicare beneficiaries in a more cost effective way will be tested.[46] The place for the community pharmacist as a provider within an ACO is still being envisioned as this manuscript is being drafted; however, it offers yet another new opportunity for community pharmacy practice.[47]

The practice of community pharmacy has changed dramatically over the past decade. The pace of this change seems to increase as new care delivery philosophies and the organization of the healthcare system continue to evolve to address the issues of quality and cost. While a defined path for community pharmacy does not at this time exist, opportunity for utilizing the expertise of community pharmacists to ensure access to quality care related to medications remains.

The practice of health systems pharmacy

The transformation of hospitals into health systems occurred over the past 20 years because of advancement in complex medical therapies and technologies, as well as external pressures from ever changing revenue streams and restriction of resources. The traditional hospital of the past bears resemblance to the complex health systems of today and the term "hospital" is still appropriately used. The term "health system" refers to a range of services that include hospitals, hospital-based clinics, infusion centers, and hospital based outpatient departments. For the purposes of this section the two terms will be used interchangeably. Similar to health systems, the practice of pharmacy within the hospital setting has been transformed due to the increasing complexity of medication therapy and financial pressures to ensure optimum clinical outcomes with cost effective treatment, while ensuring the safe use of medications within the system. The skills and leadership that the pharmacist brings to table makes the practice of pharmacy in the health system very unique.

The health system

The health system is an organized, integrated network of relationships with different disciplines, facilities and healthcare providers, designed to improve or restore the health of a community. According to the World Health Organization (WHO), a health system consists of all organizations, people and actions whose primary intent is to promote, restore or maintain health.[48] The development of health systems began with the forerunners of early hospitals in Ancient Egyptian and Greek temples acting as centers for healing, in that they provided refuge and treatment for the sick, and also provided centers for teaching the healing arts. The first hospital on the American continent was built by the Spaniards (led by Cortez) in 1524, the Hospital of the Immaculate Conception in Mexico City. In the American colonies, a hospital was built in 1663 on Manhattan Island for sick soldiers. The first incorporated hospital in the United States was the Pennsylvania Hospital, established in 1751.

Early hospitals had a close relationship with formal religious sects and aligned with Christian doctrine. They were supported as charitable organizations, primarily for the care of the poor. As medical treatment and education developed, the public sector became more and more dependent on the services provided by hospitals. Funding sources changed from charitable contributions to government support and third party insurance companies. The medical care of the patient and their spiritual needs began to separate, in large part due to the secularization of university based education, as well as the impact of the Social Security Act (Medicare) in 1965. However, religious influences can still be seen today in American health systems. Indeed, there are health systems that are still operated by formal religious organizations and help provide care to the indigent populations who do not qualify for government support or do not have access to health plans.

The transformation of the hospital into an integrated health system generally involved the merger of different individual hospitals and the diversification of clinical services such as clinics, home health, ambulatory surgical centers, long-term care and wellness facilities. Today, according to the American Hospital Association (AHA), there are over 5700 registered hospitals in the United States.[49] Hospitals comprise private For Profit organizations owned by individuals, partnerships or corporations, private Nonprofit organizations operated by a church or other nonprofit group, and government (federal, state, and local) entities. Combined, these entities account for over 37 million admissions and over $700 billion in expenses annually.[49]

The AHA registers hospitals into four types:

1. General – providing services for a variety of medical needs and patient types
2. Specialty – providing services for patients with a specified medical condition such as cardiac, oncology, or orthopedic maladies or for specific patient populations such as pediatrics or geriatrics
3. Rehabilitation and Chronic Disease – providing care to individuals who require restorative or adjustive services
4. Psychiatric – providing services to patients who have a psychiatric related disease.

Some health systems can further be distinguished by their function beyond patient care. That function can be education, research, or public health. The health system also functions within the community as a focal point of emergency care and treatment for large numbers of victims in the event of natural disasters, catastrophic accidents, and terrorist attacks.

The patient care function at health systems is generally delivered through a structured organization of departments including acute care (i.e., emergency services, trauma, and surgical services), specialty units (i.e., cardiology, oncology, labor and delivery, neurology, intensive care units) and outpatient departments (i.e., rehabilitation, physical therapy, cardiopulmonary, dialysis, behavioral health, and dental). Non-clinical departments also contribute to the patient care function and mission of the organization by the services they provide: medical records, information services, facility maintenance, billing, quality improvement, marketing, risk management, and security. Clinical support departments provide direct and indirect patient care: laboratory services, pathology, radiology, respiratory therapy, and pharmacy.

Health system pharmacy

The transformation of pharmacy practice in hospitals is no less dramatic as the organization in which it resides, from the first hospital pharmacist, Jonathan Roberts, at the Pennsylvania Hospital in 1752 to the advanced clinical pharmacy practices in our modern health systems. Today pharmacists and pharmacy technicians work with various departments to assure the safe, efficient, and cost appropriate distribution and medication use systems. They practice as a team with physicians, nurses, and other healthcare professionals to care for the patient. Health system pharmacy has significantly grown in the latter quarter of the twentieth century. The increasing complexity of medication therapy continues to fuel the need for health system pharmacists with the skills and expertise that meet the pharmaceutical care needs of hospitals.

This transformation of pharmacy practice was accelerated by strong pharmacy leadership and support from national pharmacy professional associations, such as the American Society of Health System Pharmacists (ASHP). Starting with the landmark "Hilton Head Conference" in 1985 which cemented the need to rapidly advance clinical practice to the most recent Pharmacy Practice Model Initiative (PPMI) in Dallas, Texas in late 2010 which will continue to drive the transformation of health system pharmacy practice for the next 10 to 15 years. This continued transformation will be supported by expansion of pharmacy education and training requirements, the enhanced technical skills of the pharmacy technician, as well as the advancement of pharmacy automation.

Challenges and opportunities to improve continue to shape health system pharmacy practice. It has evolved over the years in many ways. This section will describe the historic, current state, and some of the innovations that make health system pharmacy practice unique, highlighting the following subject matter: pharmacy technicians and medication preparation, clinical practice, medication use policy, leadership, contracting and procurement, human resources, information technology, automation, and education.

Pharmacy technicians, medication preparation, and distribution systems

The role of pharmacy has historically been as supplier of the tripartite medication use system with physicians controlling the ordering and nurses the administration. Over time these standard divisions of labor have often blurred and shifted. For example, in many health systems, especially very small hospitals with less than 50 beds without 24 h pharmacy services, it is still the nurse's responsibility to prepare an intravenous dose of medication before it can be administered.[50] Nonetheless, it is the prerogative of the pharmacist and the pharmacy technician to ensure that appropriately selected medications are correctly prepared and made available for the patient. Many years ago the pharmacist was the one who actually prepared all medications for distribution. Today that is primarily the role of the pharmacy technician.

Pharmacy technician

The advancement of the pharmacist practice model into the clinical domain has been assisted to a great extent by the skilled pharmacy technician. Pharmacy technicians provide the technical support for a health system's medication preparation and distribution systems. This support allows the pharmacist to expand their focus to enhancing patient outcomes through appropriate medication management. Because individual state boards of pharmacy regulate and often specify the functions that technicians can perform under the supervision of a pharmacist, their roles vary among states. In addition, the state board may also specify the number of technicians relative to the number of pharmacists that be utilized by the pharmacy. This state to state variation has also led to differences in training, competency standards and certification requirements.

The article *Opportunities and challenges related to pharmacy technicians in supporting optimal pharmacy practice models in health systems* examined the wide variation in training and certification requirements across the United States. In 1995 the Pharmacy

Technician Certification Board (PTCB) launched the first national voluntary certification examination; however, there are still some states that have yet to require it. Although ASHP accredited technician training programs exist in colleges and technical schools, most pharmacy technicians received training, either formally or informally, on the job. The role of the pharmacy technician in most health systems is drug purchasing, preparation (compounding), and distribution with the pharmacist being responsible for direct oversight. This article states that, over the years, there have been numerous calls from many organizations to establish pharmacy technician competency standards and formalized accredited training programs leading to official certification. It further argues that if the health system pharmacy practice model is to be elevated to the level that makes it possible to meet the pharmaceutical needs of patients, this must be achieved now so that the transition can be made safely. There are many opportunities beyond the preparation and distribution of medications that involve the pharmacy technician, including obtaining medication histories, administering medications, conducting benchmark surveys, manage vaccine databases, screening electronic medical records for potential pharmacist interventions, managing medication assistance programs, and many others.[51]

Floor stock, patient prescription, and unit-dose systems

Medications are administered to hospitalized patients only upon the order of a physician (or designated allied health professional). Thus, a prescription order originates in the patient's medical record, where physicians write all the orders (prescriptions) for the patient. Because the patient's medical record, unless electronically stored, remains at the patient care area, it is essential that some means be used to transmit the prescription order from the patient area to the pharmacy. These orders are transmitted to the pharmacy usually in one of four ways:

1. The medical record has a duplicate copy so the pharmacy can obtain a carbon copy of the physician's original medication order
2. The original medication order is scanned and the image is electronically sent to pharmacy to be printed or reviewed on monitor
3. The physician writes the medication order on a separate prescription blank, commonly for home use
4. Physician inputs the order directly into a computer (Computerized Provider Order Entry or CPOE).

Once the order is received by the pharmacist, it is reviewed and if appropriate the medication is made available to the patient. This can be accomplished using different distribution systems:

- floor stock system
- patient prescription system
- unit-dose system.

In the early days of hospital pharmacy the floor stock system was the primary means that the pharmacist used to distribute medications for patient use. The pharmacist's role in those days was little more than a medication purchaser and stocker, with little involvement in the clinical review of medication orders. When a physician order was written the nurse would retrieve the medication from a supply room on the ward which was stocked by the pharmacist in bulk containers. The nurse would prepare the dose, either oral or IV, from the bulk containers and administer the dose. The pharmacist would rarely see the physician order.[52] In some cases the floor stock system is still in use today in most hospitals for drugs that are used in emergencies or for immediate patient comfort. However, the use of bulk containers to supply directly to the patient is no longer considered safe or hygienic and is therefore limited.[50] Some hospital pharmacies still supply floor stock multi-dose insulin vials to the nursing units to be used by the nurse to draw up patient-specific doses for multiple patients. Other forms of floor stock include emergency crash cart trays or other similar "kits" that are used in emergent situations. If medication is floor stocked, it is now considered safer if it is packaged as "unit dose", which will be discussed later in this section. Also to add more control, safety and accountability, automated dispensing machines (ADMs) are used.

The floor stock system evolved over time into the patient prescription system, in order to enhance safety and to promote inventory control. The patient prescription system involves the pharmacist to a greater extent in the order review. In this system the nurse transmits the order to the pharmacy and the pharmacist prepares several days of doses in a container, labeled much like an outpatient prescription. The nurse is still required to take the correct quantity of doses from the container and administer them to the patient; however, it is considered safer than the bulk floor stock system because the medications are provided for a specific patient which would help reduce drug selection errors. This method may still be in use today at some of the very small hospitals and nursing homes that do not have 24 hour and weekend pharmacy coverage and do not have the resources to purchase ADMs. It is also the method used for patient specific bulk containers or multi-dose such as lotions, aerosolized inhalers, eye or ear solutions, and some injections.

In the 1980s, the patient prescription system was largely replaced by the unit-dose system. This was done to promote patient safety and to avoid drug errors. As a result, the safest, most accepted method of dispensing medications to the hospitalized patients is the unit-dose system. This has become the standard of practice in most hospitals today and is favored by national regulatory agencies. In this system the pharmacy prepares each dose of medication ready for administration and dispenses in either a centralized medication cart-fill exchange (with the carts containing individual patient trays with a 24 hour supply) or decentralized through an ADM system. For example, tablets and capsules are labeled and dispensed as a single dose for each patient, liquids are measured into oral syringes, lyophilized injections diluted, measured accurately and transferred aseptically into sterile syringes, parenteral medication admixtures added to intravenous solutions prior to use, and oral powders and other unusual dosage forms measured and mixed appropriately. Most of these procedures involve pharmaceutical techniques called "compounding," which are a pharmacist's responsibility. Many of the drugs available today come from the manufacturer already in unit-dose form, especially oral solid medications; however, some oral liquids, topical and intravenous drugs are packaged by the manufacturer as unit dose. An option that some health system pharmacies choose to utilize is outsourcing the repackaging or compounding of unit-dose medications to third party pharmacies or compounding centers.

Compounding

Pharmaceutical compounding, once the heart of the pharmacy profession, is still a necessity in today's health system pharmacy practice. There are still many pharmaceuticals that are either not available from commercial sources or not in the appropriate dosage form. This is especially true for specialized patient populations such as pediatrics.[53] Health system pharmacy compounding includes nonsterile and sterile products and represents one of the highest risks for patient harm. The potential for human error is significant and can occur through miscalculations, missed steps, product contamination or incorrect selection of a base drug or diluent, which can lead to patient harm or death. Often these tragic, preventable deaths become headline news stories.[54–56] The risk escalates because often compounding involves the preparation of pharmaceuticals for multiple patients and even if the health system pharmacy elects to outsource a portion of its compounding service to a third party, the potential for multiple patient harm and death exists.[57]

Although there are differences in the approach and execution for compounding nonsterile or sterile products, fundamental elements that should be in place in every health system pharmacy include:

1. Comprehensive training and competency program for all personnel responsible for compounding.
2. Standard Operating Procedures (SOPs) - a detailed step by step roadmap for each different compounding category (i.e., chemotherapy infusions, neonatal oral liquids, ointments, total parenteral nutrition (TPN), intermittent infusions, etc.).
3. Compounding formulation cards or recipes especially for multiple ingredient admixtures.
4. Quality control and assurance steps–double checks, weight and color verifications, bar-code verification of base components.
5. Compounding log – documenting source containers, lot numbers, expiration dates, preparation dates, beyond use dates, internal control number,

the initials of compounding personnel, and quality control documentation.
6. Compounding reference material – published reference that supports the stability and viability of the compound or admixture.
7. Appropriate, functioning, and calibrated compounding equipment.
8. Disciplined environment – compounding personnel and their colleagues must have a sincere appreciation for the seriousness of the work they are performing. It must have the focus of their attention, without distractions. Pharmacy managers must maintain this environment by immediate coaching when at-risk behaviors or variation from SOP are witnessed.

Nonsterile compounds include products such as ointments, creams, oral liquids, and to a much lesser extent tablets, capsules and suppositories. The *United States Pharmacopeia* (USP) Chapter <795> provides a source for practice procedures and standards for nonsterile extemporaneous compounding.

Sterile compounds or admixtures include products such as IV injections, intermittent antibiotic infusions, chemotherapy infusions, pain ball pumps, TPN, cardioplegic solutions, large volume parenterals, eye drops, and so on. Compounded sterile admixtures represent the greatest risk to patient safety because there is a greater chance of significant overdoses of toxic drugs and bacterial contamination. Therefore, after growing concerns and attempts to establish self-regulated professional guidelines, the USP created the first enforceable national sterile compounding standards in 2004 called USP Chapter <797> which was later revised in 2007. This chapter establishes standards in environmental requirements and controls, personnel training and garbing, quality assurance, storage requirements, beyond use date (BUD) limitations, and SOPs for five risk categories:

1. Immediate use – for emergent situations
2. Low risk level – for simple, closed system transfers
3. Low risk level with less than 12 h BUD
4. Medium risk level – admixtures with multiple components or small volumes, batch preparations, or complex manipulations
5. High risk level – admixture originating from nonsterile ingredients or open system transfers.[58]

The USP Chapter<797> standards are enforceable by federal law through the FDA; however, most state boards of pharmacy have adopted these standards or similar standards into their state pharmacy rules and regulations. This also makes it subject to survey from accrediting organizations like the Joint Commission.

Hazardous waste disposal

One of the results of the medication preparation, distribution and administration process is left over unusable drug waste. This is generated either through remaining drug product after preparation, expired drugs that were not used, or drug residue from packages or containers after the medication has been administered to the patient. In the past these remnants were disposed of as regular landfill waste, incinerated in the hospital or simply flushed down the drain. It has been determined that some of the drugs used in the health system are considered too hazardous to the environment. The Resource Conservation and Recovery Act, enacted in 1976, defined and attempted to minimize environmentally hazardous waste. This law was largely ignored in hospitals until 2002, when Environmental Protection Agencies (EPAs) of a few states started enforcing the act by levying very large fines against hospitals that were found to be out of compliance. Enforcement has increased in other states and health system accrediting agencies, such as the Joint Commission, are now including compliance in their surveys. This has created the need for each health system to develop a pharmaceutical waste stream management system.

Compliance with the law is both complex and expensive. It requires the health system to determine if it is a small or large quantity generator of hazardous waste. This is based on the weight of acutely hazardous material, called P-List chemicals, wasted within a calendar month. The next step is to obtain an EPA identification number, then establish separate waste streams for three categories of waste:[59]

1. Commercial Chemical Hazardous Waste
   a. P Listed – Acutely Hazardous (examples: warfarin, epinephrine)
   b. U Listed – Toxic (Chemotherapy)

2. Characteristic Hazardous Waste
   a. Toxic
   b. Ignitable
   c. Corrosive
   d. Reactive
3. Non-Hazardous Waste

In order to comply, some hospitals have set up multiple color coded waste receptacles on nursing units and used the hospital's pharmacy information system to attach special codes on medications that will appear on medication administration records (MARs) or pharmacy labels directing the nurse to which receptacle the wasted drug belongs. The hazardous waste is then taken to a federally permitted hazardous waste incinerator and placed in a lined hazardous waste landfill.

Ambulatory care services

As ambulatory care activities continue to increase within the institutional setting, the health system pharmacist becomes more and more involved in providing services to these patients, either as retail oriented pharmacy services or clinical pharmacy services. The patients are often seen in clinic settings, by home care services, by hospice services, infusion centers, etc. Pharmacists practicing in ambulatory care settings have expanded many of the service concepts initiated in the hospital and the community pharmacy settings. They include special patient information brochures, patient dosing calendars, special packaging, patient education for home care, review of prescribing practices and recommendations for improvement, development of therapeutic protocols, etc. In addition, pharmacists in some clinics have collaborative practice agreements with physicians that allow the pharmacist to monitor selected patients and prescribe or adjust specific medication therapy in accordance with the agreement or protocol (e.g., anticoagulation, hypertension, asthma, diabetes). These collaborative practice agreements can be established in most states. In some states, depending on the state law, pharmacists are granted provider status for providing medication management therapy services which allows them to bill and be directly reimbursed by third party payers for those services.

Clinical pharmacy services

The practice of health system pharmacy has changed dramatically over the past 20 years. Years ago, the practice centered on preparation, compounding, and distribution of medications. Slowly, the practice of "clinical pharmacy" emerged in the 1980s. The term "clinical services" refers to the practice of providing medications to patients in the most safe, effective, and rational manner possible, while individualizing care to the recipient. Clinical services were, at that time, conducted by a select few pharmacists who typically had advanced their education with a Doctor of Pharmacy degree (beyond the Bachelor of Science Degree) and occasionally postgraduate residency training. In the mid-1990s there was a conversion of colleges of pharmacy to the Doctor of Pharmacy degree alone, eliminating the Bachelor of Science degree completely in 2004. In 1985, the American Society of Health-System Pharmacists (ASHP) conducted the Hilton Head Conference, bringing together leaders in health system pharmacy to set a future direction for the profession.[60] The result of the conference was a stronger emergence of the practice of pharmacy as a "clinical" profession. It defined the fundamental purpose of the pharmacy profession as "serving as a force in society for the safe and appropriate use of drugs."[60] Soon after, ASHP developed a standard for residency programs specializing in the clinical practice of pharmacy. Postgraduate residency programs have been steadily growing ever since. The 1993, the ASHP San Antonio Conference further established Pharmaceutical Care as the primary role of the pharmacist in serving patients.[61] In 2010, ASHP held the Practice Model Initiative Summit, defining key roles of pharmacists and technicians in ideal future practices.[62] For pharmacists who wish to attain additional recognition for their knowledge in specialty areas, the Board of Pharmaceutical Specialties (BPS) has developed a certification process to recognize areas of specialty such as nuclear pharmacy, nutrition support, pharmacotherapy, oncology, psychiatry, and ambulatory care. The BPS continues to evaluate other specialty areas for inclusion in certification.[63] Certified Geriatric Pharmacist (CGP) is another recognized opportunity for specialty recognition and is offered by the Commission for Certification in Geriatric Pharmacy.

Today, the modern practice of pharmacy often integrates the traditional distribution functions with the clinical services of the pharmacist. Health systems have either installed (or are planning to install) fully electronic medical records, which blends the prescribing, dispensing, billing, administration, and documentation functions into one computer application. Health system practitioners now have one system to access a patient's diagnosis, past medical history, laboratory values, and medication list. Computerized provider order entry (CPOE) is commonplace. Orders that are entered into the computer system by physicians must be verified or "released" by the pharmacist to appear the medication administration record (MAR). The MAR is used by nurses to schedule medication administration times and to document medication administration. While verifying physician orders, pharmacists are expected to review the following pertinent information: age, gender, weight, height, diagnosis, current medications, allergies, laboratory information, and pregnancy or lactation status. Age, gender, weight, and height are used in equations to estimate the kidney function of the patient. If the kidney function is diminished, the pharmacist may need to adjust medication doses, for those medications that are eliminated through the kidney. A diagnosis or medication indication is obtained to verify the appropriate selection of the medication for that condition. The current medication list is reviewed for any potential drug–drug interactions that may occur with the newly prescribed drug. The pharmacist will also evaluate the medications for food–drug interactions. Laboratory information is reviewed to determine the function of the kidneys and the liver. Any organ dysfunction may affect the elimination of the medication, thereby causing the potential for medication accumulation and toxicity. This is particularly important for medications that have a "narrow therapeutic index," that is, when the therapeutic dose or blood level is very close to the dose or blood level that can cause toxicity. Product selection and sterile injection preparation remain important practices in health system pharmacy.

Other common clinical activities of the health system pharmacists, either by consultation or by scope of practice policies, include the following:[64]

1. *Therapeutic Drug Monitoring* – This term generally refers to the practice of obtaining blood/serum concentration of medications, in order to maintain the drug dose in the "therapeutic range." Often the pharmacist will apply various calculations to assure that the drug reaches a "steady state" concentration that is therapeutic, but not toxic.
2. *Drug Information* – Medication therapies in health systems are growing increasingly complex and are frequently changing. The pharmacist is a valuable asset to the physician for providing drug dosing and monitoring information. In addition, the pharmacist assists nurses in scheduling medications appropriately, as well as providing medication administration guidance.
3. *Patient Care Rounds* – The act of "rounding" is becoming common, even in community hospitals. As teamwork and communication are emphasized, there is a greater need for the healthcare team to come together to discuss the multiple aspects of a patient's care. Pharmacists are an integral part of the rounding team, and evaluate drug therapy and dosing during the rounds. Pharmacists will then advise dose changes that may need to be made in the patient's drug therapy.
4. *Adverse Drug Events* – Despite medication safety efforts, medications can still cause adverse outcomes in hospitalized patients. The pharmacist has a key role in the prevention, detection, and mitigation of adverse drug events. The pharmacist can help prevent adverse events by ensuring that the patient is receiving an appropriate medication for their condition, and that the medication is given in the right dose, route, frequency, and for the appropriate duration. Pharmacists also prevent adverse events by ensuring proper administration of medications. Pharmacists can help detect adverse events by investigating any unusual circumstances, unusual prescriptions, or the administration of antidotes or reversal agents. Finally, pharmacists can help mitigate adverse events by providing ready access to any antidotes or reversal agents, and by participating in an analysis of events after the fact.

5. *Code Blue* – Pharmacists participate in "Code Blue" or resuscitation events when patients experience either a cardiac arrest or respiratory distress. The pharmacist's role is to prepare medications that may be needed during a code. Many medications used in code situations require complex calculations to determine the appropriate dose for the patient. The pharmacist can assist with these calculations to assure a therapeutic dose is used.
6. *Medication Dosing* – The health system may allow pharmacists to automatically adjust medication doses for any organ dysfunction that the patient is experiencing. Other dose modifications may be made for age or weight. In addition, the pharmacist may be able to convert a patient from an injection to an oral dosage form, if the patient is able to ingest the oral dosage form.
7. *Formulary* – Pharmacists are expected to promote adherence to the institution's formulary list of medications.
8. *Anticoagulation* – Current regulatory safety standards require that health systems have in place protocols and processes for handling high-risk drugs, including anticoagulant medications. These agents must be held within tight therapeutic control to avoid either bleeding (with an overdose) or clotting (with an underdose). These protocols are generally developed and carried out by pharmacists for medications such as heparin and warfarin. The pharmacists monitor laboratory values daily to make sure that the anticoagulant therapy is at a therapeutic level and change doses accordingly.
9. *Nutrition* – When patients cannot receive oral or enteral nutrition, parenteral (IV) nutrition is used. The sterile preparation of these products is conducted by pharmacists. There may be many chemical incompatibilities with nutritional products and the pharmacist may need to modify the nutritional formula to prevent any product inactivation. In addition, the pharmacist calculates the nutritional formula according to the amount of protein, carbohydrate, and fat that is appropriate for the patient's body weight and condition. The pharmacist calculates electrolyte, vitamin, and trace element needs for the nutritional formula.
10. *Anti-Infective Stewardship* – Pharmacists are an integral part of anti-infective stewardship teams. The Infectious Disease Society of America (IDSA) recommendations call for the thoughtful and prudent use of antimicrobial agents to avoid over exposure to patients, bacterial resistance, and secondary infections. The anti-infective stewardship team advocated by IDSA includes a pharmacist, infectious disease physicians, and infection control practitioners. The stewardship team reviews antibiotic, antiviral, and antifungal medication use in the health system daily. They will compare anti-infective use to the condition of the patient, site of infection, and culture and sensitivity results. The team then will make therapy recommendations that meet the needs of the patients, while avoiding over-exposure to unnecessary anti-infective agents. Anti-Infective Stewardship programs have been shown to be effective in reducing patient exposure to anti-infective agents.[65] Using proven anti-microbial therapies is also a Joint Commission National Patient Safety Goal.
11. *Outcomes Management* – Medicare, along with some private insurers, is increasingly basing payment to health systems on their ability to provide standard, proven therapies for certain patient conditions. These therapies are considered "core" to certain conditions. For example, each and every patient who experiences a myocardial infarction should receive low-dose aspirin, unless contraindicated, for prevention of further ischemia. These therapies are referred to a "core measures" and are being measured as a condition of participation in provision of care for Medicare patients. Pharmacists participate in compliance with core measures by assuring core therapies are received by eligible patients. The Joint Commission sets National Patient Safety Goals for health systems as a requirement for accreditation. Pharmacists participate in the achievement of National Patient Safety Goals related to medications. Examples of this include anticoagulation, medication abbreviations, drug interactions, and medication reconciliation.
12. *Managing Transitions of Care* – Managing the process of obtaining an accurate medication history of a patient upon admission to the health

system and making sure that any needed and intended medications are continued in the health system is called medication reconciliation. The term "reconciliation" is defined as "the process of making consistent or compatible." Medications prescribed in the health system should be consistent and compatible with the medications patients were taking at home, as well as with their current condition and any new medications prescribed. Patient transitions from home to health system, within the health system, and from health system back to home are considered high-risk processes. Addressing this high-risk process is a requirement of a Joint Commission National Patient Safety Goal. The list of medications must be accurate and appropriate for the patient condition, upon each transition of care. A common reason for early re-admission to the hospital is inaccurate use of medications, causing a deterioration of the patient condition or a medication adverse event.[66]

13. *Narcotic Stewardship* – A growing area of concern with the FDA, the Drug Enforcement Agency (DEA), state pharmacy boards, and the public is the misuse of narcotic medications. Pain management, hospice care, and end-of-life management with narcotic medications is a practice area that is emerging for pharmacists. Medication therapy is a primary mode of treatment for these conditions. In addition, opioid medications have a narrow therapeutic index. The role of the pharmacist in the health system is to determine therapy for chronic or acute pain upon admission to the health system, to manage acute pain that may surface during their admission (usually with injectable medications), and to stabilize therapy and convert therapy back to oral medications when the patient leaves the institution. Risk Evaluation and Mitigation Strategies (REMS) programs are commonly put into place by the FDA for opioid medications. The pharmacist has a role in REMS strategy implementation to make sure the medications are provided in a safe manner.
14. *Pharmacogenomics* – The relationship between genomes and the efficacy, elimination, and toxicities of medications is becoming more well known. Just as pharmacists evaluate organ function for their impact on elimination of medications from the body today, in the near future they will begin to evaluate the genetic code of patients in order to better predict a drug response. This prediction will be used to optimize the dose, and therefore the patient response to medications. Some health systems are currently evaluating genetic markers for drug elimination or toxicity as a routine.
15. *Medication Therapy Management Services* – Medication therapy management services (MTMS) are services that optimize therapeutic outcomes for individual patients, usually in a clinic setting. MTMSs include medication therapy reviews, pharmacotherapy consults, anticoagulation management, immunizations, and health and wellness programs. The medication therapy review is defined as a "face-to-face patient assessment and intervention as appropriate, by a pharmacist. MTMS is provided to optimize the response to medications or to manage treatment-related medication interactions or complications. MTMS includes the following documented elements: review of the pertinent patient history, medication profile (prescription and non-prescription), and recommendations for improving health outcomes and treatment compliance."[67] It is a systematic process of collecting patient-specific information, assessing medication therapies to identify medication-related problems, developing a list of medication-related problems, and creating a plan to resolve them.
16. *Documentation* – Documentation in the patient record is one of the means by which healthcare professionals communicate with one another and document care received by a patient. Pharmacists are expected to document in the patient record information such as physician consultations of the pharmacist, drug information question results, relevant drug serum concentrations and their interpretation, and patient education.

The practice of pharmacy has changed significantly in response to organizational standards, patient safety, growth of technology and informatics, and increasingly complex medication regimens.

The American College of Clinical Pharmacy defines clinical pharmacists as "someone who takes care of patients in any setting" and clinical pharmacy as "that area of pharmacy concerned with the science and practice of rational medication use."[68] As such, all pharmacists are involved in clinical pharmacy services.

Medication use policy

The practice of health system pharmacy includes collaborating with other healthcare professionals in the development of sound medication use policies. The pharmacist lends their expertise and leadership ensuring that medications used within the health system are thoughtfully considered prior to being procured, stored, prescribed and administered. Also, these steps are done safely and in the most cost effective manner while achieving the desired clinical outcome. The *ASHP Guidelines on the Pharmacy and Therapeutics Committee and the Formulary System*[69] is an excellent resource in developing sound medication use policies, including the formulary system, the role and function of a Pharmacy and Therapeutics (P&T) Committee, as well as other medication use and improvement strategies.

Formulary and formulary system

The ASHP guidelines discuss the historical development of the formulary from a basic list of medications that the military used on soldiers in the 1940s and, based in large part on published evidence of value, grew into a comprehensive tool to ensure safe, appropriate, and cost effective use of drugs in the health system.[69] The formulary of today represents the medications available for use by the health system, which have been critically assessed by the practitioners and pharmacists, as well as medication use policies, decision support tools, and system guidelines. The formulary system is the mechanism in which a formulary is established and maintained.

Pharmacy and therapeutics committee

The role of the P&T Committee is to provide oversight of medication management and manage the formulary system, including investigational drugs. The committee should meet on a regular schedule, that is, monthly or bi-monthly depending on the level of medication activity at the hospital. Optimally the membership includes a cross-sectional representation of key stakeholders of the medication use system, including pharmacists, medical staff (prescribers from different medical disciplines), nurses, and other healthcare professionals. Administrators, quality improvement personnel, and risk managers should also be present because of their supportive role in medication use. It is also common that membership include a clinical dietitian due to the use of TPN therapy and food–drug interactions. The clinical dietary department will often take advantage of the opportunity to interface with the physicians to fulfill their requirement of medical staff oversight of the health system's clinical dietary manual.

A successful P&T program relies on active physician membership because the P&T Committee represents the medical staff for medication use issues. In most health systems the actions and decisions made serve as advice and recommendations to both health system administration and the medical executive committee, where those decisions are ratified and, if structured in the medical staff by-laws, are binding to the entire medical staff. In small hospitals it is not unusual for physicians to be represented by only one or two members on P&T.

Part of the responsibility of establishing and maintaining the formulary system is deciding which medications will be added to the formulary, evaluation of medication use and outcomes within the system, monitoring and creating interventions that prevent medication errors and adverse drug reactions, development or evaluation of clinical practice guidelines as they relate to medication use, development of policies and procedures for the procurement, storage, prescribing, preparation, distribution, administration and monitoring of medications and education of health professionals on the optimal use of medications.[70]

Medication selection and review

The evaluation of medications for formulary inclusion should be an evidence-based, unbiased process using relevant scientific literature and a thorough analysis of risks and benefits to the patient. Information should be presented to the P&T committee in a formal,

standardized document, i.e. formulary monograph. ASHP guidelines suggest that the formulary document include these elements:

- Brand and generic names and synonyms
- FDA approval information, including date and FDA rating
- Pharmacology and mechanism of action
- FDA-approved indications
- Potential non-FDA-approved (off-label) uses
- Dosage forms and storage
- Recommended dosing regimens
- Pharmacokinetic considerations
- Use in special populations (e.g., children, elderly, patients with renal or liver failure)
- Pregnancy category and use during breast-feeding
- Comparisons of the drug's efficacy, safety, convenience, and costs with those of therapeutic alternatives (with evidence tables when feasible)
- If information on comparable efficacy is minimal or lacking, data on absolute efficacy (i.e., efficacy versus placebo)
- Clinical trial analysis and critique
- Medication safety assessment and recommendations (adverse drug reactions; drug–drug and drug–food interactions; specific therapy monitoring requirements; unusual administration, storage, or stability issues; and potential for medication errors, such as look-alike or sound-alike issues), and
- Financial analysis, including pharmacoeconomic assessments.[69]

As part of the medication safety assessment the FDA's Risk Evaluation and Mitigation Strategies (REMS) or MedGuide requirements should be included in the document, if they are appropriate for the facility and services provided. Other information sources that are helpful and should be considered for the review and decision include local health plan formulary status, internal data including physician prescribing and outcomes, and the experience of local recognized experts. The monograph should conclude with a recommendation to accept into formulary, reject formulary status, or accept with restrictions as to its use.

Drug reviews by the P&T committee can occur when a new drug enters the market, there is new relevant information about a drug that is already on the formulary, or as a therapeutic class review. Therapeutic class reviews should be performed regularly with the goal of reviewing the entire formulary annually. These reviews should include internal use data of existing formulary items, non-formulary drug use, new scientific evidence and relevant medication error data.

The formulary system should not, in all cases, prevent the use of agents that have not been formally approved by the P&T. There should be a policy that defines a process in which a non-formulary product may be used when medical necessity exists. P&T committees should consider an expedited review process; in this way education and safety gaps can be identified and addressed quickly.

Strategies for managing medication use

Once established as formulary the P&T Committee's responsibilities are not concluded. The P&T and pharmacy has an ongoing obligation to ensure that medications are used safely as well as economically. Several proven strategies are available for managing medication use in the health system. These include generic substitution, therapeutic interchange, IV to PO switch programs, renal dosing programs, pre-printed orders, clinical practice guidelines, and medication use evaluations.

1. *Generic Substitution* – One of the earliest strategies used in hospitals to help manage cost. There are high quality generic products available that have been determined by the FDA as bioequivalent and have been given an AB rating. Substituting less expensive generic products for branded has benefits for both the health system and the patient.
2. *Therapeutic Interchange* – The P&T Committee can create a policy that allows the pharmacist to interchange one drug that has been established to be therapeutically equivalent to the drug ordered. Therapeutically equivalent drugs possess different chemical structures but have similar therapeutic profiles. Dosing must be adjusted accordingly.
3. *IV to PO Switch Programs* – Many drugs possess similar bioavailability whether they are administered through the intravenous or oral routes. The IV route is necessary if the patient is unable

to or ordered not to take medications by mouth. There are significant cost and safety implications to switching appropriate drugs from IV to PO. Generally oral medications cost much less than their IV counterparts and the IV route subjects the patient to inherent risks, i.e., medication errors and sepsis.

4. *Renal Dosing Programs* – Policies allowing the pharmacist to automatically adjust doses of medications that are metabolized and/or eliminated through renal mechanisms in patients who have compromised renal function provide for safer therapy with fewer side effects and includes an added financial benefit. The program should specify the appropriate drugs and the specific dosing adjustment that can be made. Under the P&T protocol, when the pharmacist receives an order for that drug they check the patient's renal function and adjust the dose according to policy.

   If approved by the medical staff, via the P&T Committee, adjustments like this one and the ones mentioned above generally do not require a new physician's order. However, they should be recorded in the patient's medical record as adjustments made per P&T approved protocol. Notification should also include the patient's nurse so that they are aware of the change.
5. *Pre-printed Orders* – A useful strategy to help manage the appropriate use of medications. They can contain orders for medications, labs, nursing treatments, monitoring parameters, and other therapies all pre-printed on a physician order form. This program has multiple benefits including clear legible orders, dosing hints, guided therapy choices (based on established clinical practice guidelines), and convenience for the physician. Pre-printed orders also help the transition to computerized physician order entry. They should be reviewed by P&T on a regular basis for any necessary modifications.
6. *Clinical Practice Guidelines* – These are based on established outcomes-oriented clinical evidence. It is designed to educate the care team on the most efficacious method for treating specific conditions. National clinical practice guidelines have been developed by expert panels of clinicians for a variety of diseases and are available for the health system to use as a resource for building their own. There are many resources to obtain clinical practice guidelines. One source for clinical practice guidelines is the national guideline clearinghouse sponsored by the Agency for Healthcare Research and Quality (http://www.guideline.gov).[69] Clinical practice guidelines serve as a useful tool in developing pre-printed orders and establishing criteria for MUEs.
7. *Medication Use Evaluations* – The MUE process is a quality improvement tool for medication use. The objective is to use data to improve the use of medications in the health system for the purposes of improving clinical outcomes, reduce the potential for medication errors or adverse drug reactions or improve the financial performance of the therapy under study. It begins by establishing pre-determined utilization or outcome criteria based on the best available scientific literature or clinical practice guidelines. Observations are conducted either retrospectively or concurrently, variance from the criteria is noted, data collected, and interventions are made based on the results. In retrospective MUE studies, the data is collected and reviewed generally from patient charts or the electronic medical record and the intervention occurs some time after the event. The benefit of concurrent studies is the immediacy of improvement efforts, in that the pharmacist can screen the medication at the time of order entry or verification and the intervention can occur prior to the start of therapy. MUE activity is generally performed around problem prone, high risk or high cost medication use but can also be used to monitor the medication use policy decisions made by the P&T Committee.

Medication safety

An important duty of the P&T Committee is addressing medication safety concerns for the health system. Opportunities to address this duty include:

1. When a new drug is being submitted for formulary consideration, a thorough assessment of the drug's risks should be included in the monograph document containing potential toxicities, preparation issues, look alike/sound alike problems, and administration issues. The P&T Committee

should provide recommendations for mitigating that risk.

2. If the organization is undergoing a project that impacts medication use (e.g., smart pump implementation), there should be a proactive assessment of the risks involved. This assessment should be in the form of a failure mode and effects analysis (FEMA) which weighs the criticality of each risk element by analyzing the potential seriousness of an error, the frequency that the error might occur, and the chances of the error being caught (visibility).
3. Adverse drug event data should be routinely reviewed. This review should incorporate reports of "good catches" or events that were caught prior to reaching the patient or have the potential for causing error. Pharmacist interventions serve a very useful purpose here providing "good catch" data for the ordering component of the medication use system.
4. Targeted quality improvement projects that involve medication use. These can be identified through trending adverse drug event reports. For example: improving ADM mis-fills.
5. Medication use policies that are created by the P&T Committee should take into account potential risks or adverse consequences of that policy.
6. The P&T Committee should champion evidence based systems that prevent medication errors (e.g., smart IV pumps).
7. Continually learn about medication safety events or best practices that mitigate risks through the review of safety literature. Examples of sources include: Institute of Safe Medication Practices (http://www.ismp.org), Medwatch (http://www.fda.gov/medwatch), FDA Patient Safety News (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/psn/), and the US Pharmacopeia Patient Safety Tools and Resources (http://www.usp.org/hqi/patientSafety/resources/).

FDA MedGuides and REMS

In an attempt to improve the safety of medication use in the United States, the federal government created the requirement of MedGuides and Risk Evaluation and Mitigation Strategies (REMS). MedGuides are printed medication information that manufacturers are responsible for creating, following FDA requirements, for targeted drugs. The FDA specifies the use of MedGuides under two different laws.

- RiskMap Drug (21 CFR 208) – Considered part of labeling requirement.
- REMS Drug (Food and Drug Administration Act (FDAA) of 2007 – Considered required patient education.

MedGuides are required to be given to patients when specific targeted medications are dispensed from the outpatient pharmacy for the patient to take at home or if the medication is to be self-administered by the patient in the outpatient setting, namely the clinic. REMS are programs (strategies) developed by the manufacturer, and required by the FDA, to manage a known or potential serious risk associated with a particular drug or biological product. The law requires manufacturers to submit proposed REMS prior to product approval and, if warranted, the FDA can require post approval REMS for established products. Examples of strategies include:

- Medication guides
- Communication plans for healthcare professionals
- Elements to assure safe use (ETASU)
- Special training or certification for prescribing or dispensing
- Limited dispensing (specified pharmacy)
- Special monitoring
- Use of patient registries
- Implementation system – mechanism(s) to assure components of the ETASU are followed.

From the health system perspective MedGuides pertain primarily to the outpatient setting; however, inpatients and inpatient pharmacies can be impacted by REMS. Certain drugs are only made available through a selected pharmacy provider which can cause delays due to ordering and shipping. This can cause some difficulty in providing the continuum of care to the patient.

Medication safety officer

The Medication Safety Officer (MSO) or similar title is a fast growing specialty area of practice in the health system for one who is focused on the safe

use of medications across the organization. Although suited for the expertise of a pharmacist, in some cases the role might be filled by a registered nurse or even a physician. If a pharmacist, it is important to remain an unbiased resource for nursing, physicians and administration. Some MSOs report to the director of pharmacy, others to hospital administrators or quality/risk managers.

Although the MSO is involved in quality-related improvement strategies and programs for the safe use of medications, the job description can vary from system to system depending on reporting structures. Some of the responsibilities could include:

- Providing support to the P&T Committee on issues related to safe medication use
- Leading the health system's medication safety committee or team
- Identifying and leading the implementation of best medication practices
- Development of standard operating procedures and training tools
- Conducting educational programs regarding medication safety
- Encouraging medication event reporting and providing report analysis and trending
- Identifying and/or leading quality improvement projects involving medication safety
- Serving as an internal safety consultant by rounding in all areas where medications are used, assesses current state and makes recommendations for improvement
- Participating in the health system root cause analysis (RCA) program when a significant medication misadventure occurs, determining where all the risks exist and developing medication safety plans to address them for the entire health system
- Reviewing external information resources such as journal articles, alerts, and safety bulletins. Creating a medication safety library and sharing pertinent information with pharmacy, nursing, physicians, and administrators
- Keeping medication safety issues in front of associates with newsletters, alerts, notices, and so on
- Working with senior leadership to ensure that there is a strategic priority placed on medication and patient safety.

The position of MSO is a recent development in health systems due to the increased interest in patient safety over the past 10 years. There were not many opportunities for formalized training. Generally these individuals developed themselves through reading, attending conferences, being mentored by safety leaders, participating on medication safety panels, etc. Today there are more formalized medication safety training programs including accredited residency and fellowship programs. A new professional association called the American Society of Medication Safety Officers (ASMSO) has been created to assist in professional development and to help establish resource networks.

Leadership

The health system or hospital is an organization of people, each one of whom has their own individual mind filled with their own individual thoughts, goals, expectations, ideas, personal problems, and personalities. The people also have responsibilities to the organization that make it possible achieve the outcomes necessary to keep doing what the organization is designed to do, in this case, improve the health of the community it serves. That way it can obtain enough financial reward so that it can continue to do what it is designed to do, whether that responsibility is to clean a recently vacated room so that it can be ready for the next patient or be the CEO of the entire organization. Each is important to the success of the organization and leadership makes it happen, and good leadership makes it happen well even through challenging times.

Many definitions exist for the term leadership. One source defines leadership as "(1) establishing a clear vision, (2) sharing that vision with others so that they will follow willingly, (3) providing the information, knowledge, and methods to realize that vision, and (4) coordinating and balancing the conflicting interests of all members or stakeholders. A leader comes to the forefront in case of crisis, and is able to think and act in creative ways in difficult situations."[71] John Maxwell's definition is briefer: "leadership is influence – nothing more, nothing less."[72] The ability to influence others is clearly the key to leadership, and the ability to create and share

a vision that others will want to follow by providing them with rationale for change and demonstrating a caring attitude to their welfare are tools for creating influence. Leaders are able to adapt to change and inspire others to commit to follow.

Managers may be leaders, but there is a clear distinction between leading and managing people. A manager makes sure things get done, SOPs are followed, and variances are corrected. They make sure the work schedule is complete and posted, that quality controls are in place and functioning correctly. Managers bring value to the organization by being good at getting people to do what they are supposed to do and maintaining the status quo in day to day operations. Leaders observe trends, identify needs, create direction, communicate passion, and inspire others to follow. Covey[73] makes the distinction clear in his analogy of two types of lumberjacks. A manager lumberjack is great at making sure saw blades are kept sharp, workers are felling trees at the appropriate rate to make quota, and OSHA requirements are adhered to, while the leader lumberjack climbs the tallest tree, surveys the landscape and yells down to the manager "Hey, we're in the wrong forest, we need to be 25 miles north of here!" Leaders focus on getting people to commit to the right goal, while managers concentrate on getting people to move toward a goal.[74]

Leadership is not always about titles and positions. In all organizations there are those leaders who are in the formal position to lead, from the CEO to the director of pharmacy. These are individuals in position of authority, and have a greater potential to influence others because they have greater access to information, resources, and contact with other leaders. White[75] calls these individuals "big L" leaders. Then there are those who are not in an official role as a leader, who do not possess the title or authority, yet they clearly can influence those around them. In some cases they can be very powerful leaders. White[75] calls these "little L" leaders. One of the skills of a successful "big L" leader is to recognize, influence and tap into those "little L" leaders to help drive initiatives. The CEO of a health system can create a passion within the organization to improve services and throughput, establish goals and priorities, and support his subordinates in reaching those goals by providing resources, that is, patient throughput consultants, whereas a solitary housekeeper can inspire other housekeepers through their actions and commitment to excellence by turning an empty patient room around quickly, because they know that is their contribution to moving the organization closer to its goal of improved throughput.

Health system leadership

The health system has an organized leadership structure. The ultimate accountability belongs to a governing board, usually called the Board of Directors or Board of Regents, who delegates responsibilities to the CEO or president including: fulfilling the mission, strategic planning, selection of competent personnel including the medical staff, control of health system funds, and supervision of the physical plant. The governing board generally has several committees that assist in fulfilling its role, such as:

- the executive committee
- committee dealing with personnel appointments, especially the medical staff
- finance committee
- public relations committee.

The CEO hires subordinates to assist him or her in carrying out their responsibilities. Depending on size and complexity of the health system, there could be more than one layer of administrators. These administrators, in turn, hire a leader for each department, including a nursing service, blood bank, physical medicine, business office, housekeeping, and pharmacy. These leaders are responsible for strategic planning, hiring, control of funds (i.e., budget) and operations of their individual departments.

The medical staff have a different leadership structure due to the independent status of some of the physicians. Generally there is a medical executive board which is supported by various medical staff committees that take care of the requirements of the medical staff: credentialing, peer review, medical education, quality, P&T, and so on. There are also department level leaders that are generally broken down into therapeutic categories, namely cardiology, transplant, and oncology.

Pharmacy leadership

The head of the pharmacy department is the pharmacy director. If they are head of several hospital pharmacies in a system their title may be system director, executive or senior director. The director's responsibilities include leading overall pharmacy operations and clinical services, human resource management (selecting, developing, and coaching pharmacy staff), initiating quality improvement programs, creating and revising pharmacy policy and procedures, financial management (budgeting, billing, and revenue), and maintaining regulatory compliance. Depending on the size and complexity they may be assisted by managers, supervisors, clinical leaders, and so on.

Historically the pharmacy director was limited only with the operations within the four walls of the pharmacy department. The pharmacy was seen as a revenue department back when fee-for-service reimbursement was the norm. This is no longer the case and the pharmacy director can no longer remain inside the pharmacy. The challenges of today's limited resources, economic downturns, dwindling reimbursement, pay-for-performance programs, focus on quality and medication safety, and increasingly regulatory mandates demand that the head of pharmacy take an active role as a health system leader.

Medications now take up a large portion of the overall health system expense. In some larger health systems this could be $30 million or more.[76] Billing for medications has also become increasingly difficult and complicated with regulatory requirements for Medicaid and Medicare programs. Corporate compliance laws place legal accountability for the financial practices on the health system and its leadership, including the pharmacy director. This increase in responsibility and accountability on the head of pharmacy services is out of balance with the title "pharmacy director."

Health systems have identified key areas that are strategic to the success of the organization and have placed leaders in "chief" roles. For example, there are chief financial officers, chief medical officers, chief nursing officers, chief information officers, and chief compliance officers. Recognizing the impact and scope of medication use in the health system, the role of chief pharmacy officer has developed over the past 10 years.[77] This position allows the pharmacy leader to have a seat at the executive leadership table of the health system, giving them direct access to the chief executive officer or chief operating officer, provide input to system decisions and the ability to impact strategic planning. Thus the CPO has access to more information and resources and a greater opportunity to influence more people, making it possible to drive larger, more far reaching medication use improvement initiatives.

Strategic planning and goals

The pharmacy leader recognizes opportunities for improving the practice of pharmacy at their organization, understands the shifting health care environment, the challenges faced by the health systems, and innovations in pharmacy technology. They use this information to create a vision for pharmacy services that stretches beyond boundaries of current practice. Thomas Edison once said "a vision without execution is hallucination."

Strategic planning and goal setting are necessary elements to turn daydreams into reality. The health system executive team uses strategic planning and goal setting to establish the map and the milestones of the organization's vision. It sets priorities and direction for others to follow, sometimes linking them to accountability measures and pay incentives. In some organizations some form of formal planning is required of each department head following an established template. If this does not exist the pharmacy leader must establish his or her own method of strategic planning and goal setting.[78]

Before establishing a strategic plan the pharmacy leader will begin with a vision of what pharmacy services will need to look like in the future in order to meet the needs of the patient and the health system. He or she will use available information about the future direction of pharmacy practice, i.e. the Pharmacy Practice Model Initiative (PPMI) and external trends and changing laws in health care, such as reimbursement tied to quality outcomes, the establishment of accountable care organizations (ACOs), and patient centered medical homes.

ACOs were established by the Patient Protection and Affordable Care Act (PPACA) of 2010. It is a model for delivering health care services. To qualify for special reimbursement, doctors and hospitals must establish a network that would provide the

entire healthcare needs of a Medicare population of patients for 3 years. If the health system desires to form an ACO the pharmacy has an opportunity to contribute by providing pharmacy services along the entire continuum of care. A similar model, patient centered medical home, is a physician-coordinated team of care providers who work together to provide all of the healthcare needs of the patient. The pharmacist is uniquely qualified to participate on this team. For example, they could manage medication therapy in chronic conditions, helping to optimize outcomes and reduce utilization costs.[79]

Recognizing the importance of creating a shared vision with the pharmacy staff, the pharmacy leader involves not only pharmacy leadership, but also the "little L" leaders in his or her staff to develop a strategic plan for the pharmacy department that incorporates both long term and short term goals. In order to influence and gain the support of health system administrators, it is important for the pharmacy leader to tie pharmacy's goals into the goals of the health system. For example, it may be a health system goal to reduce the number of hospital re-admissions from the emergency department by a certain percentage. The pharmacy leader can demonstrate the effectiveness of placing a pharmacist in the emergency department and reducing re-admission rated by educating patients on targeted medications and providing follow-up compliance phone calls. In this way the pharmacy can contribute to achieving a health system goal as well as achieve a goal of improving pharmacy services.

Performance improvement

It should be the goal of each pharmacy leader to establish a program that continually reviews the current medication use system and identifies areas that are in need of improvement. This can be identified through direct observation and measurements, customer feedback, employee feedback, medication event reports or data retrieved through information systems. These could be internal pharmacy only issues, such as pharmacy STAT order turnaround time or involve other disciplines such as medical staff or nursing, such as the anticoagulation management program.

Once a gap in performance is identified the pharmacy leader should employ an improvement program to address it. There are several formalized performance improvement models available and health systems usually adopt a particular methodology, establish resources and reporting structures, and require leaders to use them. Some of performance improvement methodologies include: Six Sigma, Lean, and PDCA.

Six Sigma is a method used to improve quality by identifying and removing defects in a particular process and eliminating variability. There are a specific steps and statistical tools used to achieve improvements and these generally require intense training and resources to implement and maintain in a health system. Six Sigma refers to the statistical value in the manufacturing industry where the output of a process yields three defects in a million products. Some Six Sigma improvement strategies have been blended into the Lean method for performance improvement. In Lean, the idea is to identify a particular value stream or process and remove wasted steps in the workflow, creating less variation and optimum output. Lean also requires specialized training and significant commitment from the organization to implement; however, the gains from these methodologies can be significant.

PDCA is an established performance improvement management process in use in many health systems. PDCA stands for Plan, Do, Check, Act. The planning step usually involves identifying stakeholders, creating an improvement team, understanding the current process and quality gaps, developing an improvement intervention and appropriate measures of success, then implementing the intervention (Do). Check involves collecting the data and determining if successful or where further improvements can be made. Act is the action of taking that information and applying it to the process. PDCA can be done over and over again, as in a cycle, making incremental improvements as refinements are made. It is often called the rapid cycle improvement program.

Regulatory and accreditation

Because healthcare has become recognized by the public as a right and because the government is a major funding source for heath systems, it stands to reason that health systems would be highly regulated including health system pharmacy practice. These include

governmental agencies and accrediting bodies. Some of the governmental agencies include:

- Food and Drug Administration (FDA) – safety, efficacy, labeling of medications
- Drug Enforcement Administration (DEA) – controlled substance laws
- Occupational Safety and Health Administration (OSHA) – hazardous materials
- National Institute for Occupational Safety and Health (NIOSH)
- Centers for Disease Control and Prevention (CDC) – infection control issues
- Office of Inspector General (OIG) – protection of integrity of government programs; conducts audits, investigations, inspections, and other functions
- Environmental Protection Agency – pharmacy waste stream management
- Office for Civil Rights (OCR) – Portions of the Health Insurance Portability and Accountability Act of 1996 (HIPAA)
- State Boards of Pharmacy – licensure requirements for individuals and pharmacies. Enforces the rules and regulations of the state's pharmacy practice act.[80]

In order to participate in the federal Medicare programs and receive federal funds, health systems must be certified by Centers for Medicare and Medicaid Services (CMS) and adhere to the Conditions of Participation (CoP), which are standards established by CMS to ensure quality and protect the health and safety of Medicare and Medicaid recipients. Health systems can be inspected by a state health agency for compliance to CoP or they voluntarily receive accreditation through an accrediting body that has received deeming authority by CMS. Deemed status indicates that the healthcare organization has met relevant Medicare requirements. There are three organizations with deeming authority: The Joint Commission (TJC), Healthcare Facilities Accreditation Program (HFAP), and Det Norske Veritas Healthcare's (DNV) National Integrated Accreditation for Healthcare Organizations (NIAHO^{SM}).[80]

The Joint Commission is the primary accrediting body for hospitals and health systems. TJC establishes a set of performance expectations, called standards, that are regularly revised and enhanced. They have also created the National Patient Safety Goals (NPSGs) that address specific patient safety concerns. TJC performs unannounced surveys about every 3 years and accreditation is for 3 years.

The American Osteopathic Association's (AOA) Healthcare Facilities Accreditation Program (HFAP) accredits primarily osteopathic healthcare facilities, but is not limited to just those hospitals. HFAP also have compliance standards and the accreditation cycle is for 3 years.

Det Norske Veritas Healthcare's National Integrated Accreditation for Healthcare Organizations (NIAHO) integrates CMS Condition of Participation with International Organization for Standardization (ISO) 9001 Standards. NIAHO works closely with the health system to develop and implement a Quality Management System. The accreditation cycle is for 3 years.[80]

Contracting and procurement

Group purchasing organizations

An integral function of the pharmacy department is the contracting for medication purchases and procurement of medications. Most hospitals join Group Purchasing Organizations (GPOs) or buying groups to take advantage of volume based discounts.[81] In a network of hospitals, a uniform contract can be negotiated for all members of the network. The GPO may also negotiate performance-based contracts with individual drug companies. In a performance-based contract, the hospital or network is rewarded for buying a higher percentage from a drug company, as compared to that company's competitor. For example, two drug companies may produce similar medications for a health condition. Typically, the two competing medications will be in the same drug class and have similar chemical structures (such as angiotensin receptor blockers (ARBs) as an example). Because the two drugs have similar chemical structures and clinical indications, the hospital can designate them as similar enough to be interchangeable. Efficacy and outcomes data must support this interchangeability. As such, the companies may offer the hospital a discount incentive to move the utilization towards their product, thereby creating a favorable market share. "Market share" is

Table 11.1 An example of an ARB market share incentive program

Utilization tier	Market share percentage	Price discount
Tier 1 discount	50	3%
Tier 2 discount	75	5%
Tier 3 discount	90	7%

the amount of utilization of a medication divided by the utilization of that medication plus other "like" medications (as defined by the contract) An example of an ARB market share incentive program is depicted in Table 11.1.

In this example, the higher the market share of this medication compared to its competitor, the higher the discount.

Wholesaler

Although contracting services are provided by the GPO, the warehousing and delivery of medications to the hospital site is accomplished by a wholesaler. Most hospital pharmacies obtain all of their contract pharmaceuticals through a single wholesaler. This system is known as the prime-vendor system and allows the hospital to work primarily through one company.[81] In this manner, multiple purchase orders are eliminated and ordering is further facilitated through computer systems. Although using a prime-vendor system is desirable, it is also useful to develop a relationship with a secondary wholesaler, in the event that the prime vendor cannot meet the hospital's needs. Most hospitals order electronically on a daily basis. Typically, the pharmacy department will have personnel dedicated to this activity, usually a pharmacy buyer. Deliveries are usually received the same day. The goal of daily ordering is to maintain a just-in-time inventory at the hospital site, reducing product expiration and waste. An ideal inventory "turn" rate is 10 to 20 times annually. The prime vendor will usually provide useful utilization reports to the hospital that can be used for trending and cost savings analysis. A snapshot of high cost utilization is obtained through an 80/20 report. Which depicts the 20% of medications used that typically account for 80% of the institution's expenditures. Typically, the 80/20 report consists of such agents as chemotherapy, blood products, biologic agents, and antibiotics.

Annual or semi-annual inventories should be taken as a check on the theoretical inventory record maintained by pharmacy.[81] For high-cost medications or medications of abuse, a more frequent inventory should be done to discover any shrinkage that is occurring. Medications such as narcotics, steroids, blood enhancing products or erectile dysfunction products are targets for theft and re-sale. Special precautions and more frequent inventories of these agents should be done.

The pharmacy will, in general, take advantage of generic medication availability. Certain high-risk medications with unreliable or variable bioavailability may require purchase of a brand-name medication. The wholesaler will assist in determining a preferred product list in the purchasing system, so that buyers know which medication products should specifically be purchased. Some products may need to be purchased directly from the manufacturer. Other products may be available only through a limited distribution by the manufacturer. Biopharmaceutics are medications developed using existing DNA from human or other biologic source. Examples of biopharmaceutics includes blood factors, hormones, growth factors, interferons, interleukins, and monoclonal antibodies. Because the manufacture of biopharmaceutics is a complex process, generic biopharmaceutics, or "follow-on biologics" usually do not exist. Companies attempt to replicate biopharmaceutics; these generic-like products are not identical to the original products, and are termed "biosimilars."[82] For very high-cost medications, usually biologics for chronic conditions, patients may receive assistance with purchase through a Pharmaceutical Manufacturer Patient Assistance Program, to have all or part of the purchase priced paid.

Using the utilization reports available from the wholesaler, the pharmacy department will target certain drugs or drug classes where there is an opportunity for cost savings. Cost savings programs may be related to operation changes, clinical or utilization changes or contract changes. Operational changes in the pharmacy can lead to product cost savings. Re-packaging products at a reduced price, splitting

tablets, batching sterile product preparation, and reusing returned product are all ways to save costs from an operational perspective. Using therapeutic interchange programs, changing injections to oral medications when possible, using pharmacist monitored dosing programs, and changing physician prescribing practices are all ways of achieving drug cost savings through changes in clinical utilization of medications. Finally, generic medications, performance-based contracts, and consistent buying practices are all ways of achieving drug cost savings through the contracting process.[81]

Drug shortages

Drug shortages are emerging as a significant burden for health system pharmacies.[50] There are many reasons for this. Keeping "just-in-time" inventories leads to minimal product on hand. When one product experiences a shortage, there may not be enough on hand to meet the patient needs. The majority of raw materials for drug manufacture comes from outside the United States. If political unrest or a natural disaster befalls the country of the raw material origin, it has the potential to lead to a drug shortage. Industry mergers can lead to product shortages. A drug manufacturer may decide to discontinue production of a medication, putting the entire burden of demand on another company. The FDA cannot require a company to produce a drug and the company may decide the product line is no longer profitable. Manufacturing difficulties or regulatory citations are major reasons for drug shortages. If a manufacturing plant is not meeting regulatory production standards, the plant may need to close while repairs or process changes are put into place. This is the most common reason for current medication shortages. Drug shortages have the potential to cause therapy delays or cancellations, procedure delays or cancellations, adverse drug events, and rising costs of medications. Health systems are particularly affected by drug shortages of injectable medications.

Drug shortages impact on almost every process in the hospital. The hospital will need to determine an appropriate replacement for the unavailable drug. The replacement drug should be selected based on common FDA-approved indications, drug class, chemical structure, side effect potential, and route of administration. Physician communication needs to take place to inform physicians of the shortage and the appropriate replacement therapy. Prescribing processes, including the electronic medical record are impacted. Drug selection and standard order sets need to be changed in the electronic medical record. Pharmacy distribution processes may need to be changed as a result of a drug shortage. The preparation may include changes in dilution, solution, labeling, expiration, and stability. Nursing administration process may be affected by a drug shortage. A nurse may not be familiar with the new product that is provided by the pharmacy, and what its indication is. Dilution and infusion or injection requirements may be different for the replacement drug. Communication of these requirements on the labeling is essential. Finally, monitoring of the drug effects may change as a result of drug shortages. Although one agent may need dose adjustments for renal failure, another may not. Laboratory monitoring for therapeutic effect and for adverse effects may be different with the new drug. All of these aspects must be taken into consideration when responding to a drug shortage.[83]

As a result of the emergence of drug shortages, obtaining medications from outside sources or from compounding pharmacies has become more common. The Director of Pharmacy and buyers need to make sure that the outside sources are reliable and reputable. Use of compounding pharmacies that do not employ good manufacturing processes has led to patient deaths. Quality assurance is a top priority when evaluating a compounding pharmacy. When obtaining medications from outside sources, the Director or buyer should require a "pedigree" or chain of ownership document from any sources with which they are unfamiliar.[84] Inadequate storage conditions and inappropriate expiry can be problems with pharmaceuticals obtained from unfamiliar sources.

The contracting and procurement functions of a pharmacy are paramount to the provision of care in health systems. Buying contracted products, receiving these products, maintaining inventory controls, ensuring product integrity, and controlling costs are all a part of the contract and procurement process. Drug shortages lead to alteration in processes and deserve careful attention to avoid therapy delays and cancellations, or adverse patient events.

Human resources

Human resources (HR) management in health system pharmacy includes a broad range of functions. The successful operation of a hospital pharmacy department requires strength in numerous critical HR functions such as the recruitment, hiring, and continuous training of staff. The practice of pharmacy in hospital environments has become very complex. This complexity only continues to increase. Issues such as increased patient acuity, increased involvement of pharmacists in clinical decision making, the manufacturing, prescribing, distribution, administration, and monitoring of very complex drug therapies such as immune modulators, have all changed the scope of pharmacy practice as well as the skills needed to support pharmacy services. Pharmacy technicians have also advanced along with the development of the pharmacist's practice. Higher functioning roles for pharmacy technicians (e.g., tech-check-tech[85,86]) and the further development and integration of pharmacy technology have also driven the types of individuals needed for hire by hospitals.

Regulatory impact on pharmacy roles

National pharmacy standards and most state laws require that a pharmacist provide oversight of all aspects of drug management.[87] Pharmacists are licensed by State Boards of Pharmacy to practice pharmacy. Traditional tasks requiring a pharmacist's license include functions such as the review and approval of prescriptions or orders written by licensed independent practitioners (e.g., physician, nurse practitioner, physician assistant), as well as the final check on drug products prior to dispensation and administration.

States vary widely on how pharmacy technicians are recognized. Some states require licensure, others require registration, certification or proof of the completion of a pharmacy technician training program. Other states do not require any licensure, certification, or registration. A few states minimally acknowledge the role of the pharmacy technician. Technicians perform many traditional distributive or operational task such as pouring, counting, labeling, profiling, adjudicating claims, stocking, and so on.[88]

Recruitment

In the early 2000s a severe pharmacist shortage created a significant demand for pharmacists and also resulted in significant increases in pharmacist salaries. In response, many states and private schools started new schools of pharmacy. From 2000 to 2009, the number of pharmacy schools increased from 78 to 92.[89] During this same period, numbers of graduates increased by 50% (7176 to 10 764 graduates). By February, 2011 there were 104 accredited schools of pharmacy. By the late 2000s a change in the national economy, driven by faulty mortgage loans, resulted in a slowdown in the demand for pharmacists and technicians in most urban areas.

Recruitment of pharmacy staff largely depends on the unique needs of the position, as well as the supply and demand of the types of skills that potential employees possess for the position. Also affecting the recruitment of staff are location of the practice site, size of the hospital pharmacy, acuity of the patients, and relative importance of the needed position. Internal development of staff and promotion is one option for filling open positions. If staff promotion is not an option, pharmacies may utilize a broad range of recruiting tools including:

- Advertisements in professional journals, newspapers, state professional society newsletters, and electronic bulletin boards,
- Personnel placement services provided by national or state professional societies
- Oral and written recommendations from colleagues. Some organizations offer a "finder's fee" for hires that result from an employee referral
- Personal discussion or correspondence with potential candidates
- Recruitment visits to colleges of pharmacy or to facilities that conduct technician-training programs
- Professional recruiting firms, which typically charge the organization a percentage of the position's annual salary. In addition, recruitment advertising companies offer access to a list of job seekers for a fee
- Familiarizing students with the organization by offering summer jobs or participating in college of pharmacy experiential rotations

- Tuition assistance programs for students in exchange for future work commitments
- A "prospect list" of individuals applying for previous job openings, which can often be supplied by the human resources department
- Internet-job-site postings
- Community job fairs and local or state welfare-to-work programs
- Organization-sponsored events such as continuing education sessions, award presentations, or community outreach programs.[90]

Many organizations will recruit technicians from technician training programs which range from 6 to 24 months. Other organizations may offer on-the-job instruction to help train individuals lacking prior technical experience. Some technical schools offer an Associate of Science (AS) degree. The American Society of Health System Pharmacists has recommended that employers hire pharmacy technicians that have completed an ASHP-accredited pharmacy technician training program and are certified by the Pharmacy Technician Certification Board (PTCB).[87] If technicians are not certified they should receive this certification within 24 months of employment.

Work schedules

Pharmacies in larger hospitals remain open 24 hours a day and 365 days a year. As a result, scheduling becomes much more complex in these organizations. Smaller hospital pharmacies may be open for limited hours throughout the week or may have no pharmacist or technician at all. Depending on the size of the organization, a broad range of staff with varying skills may be needed. These skills may include, but are not limited to, dispensing, clinical drug knowledge, sterile product preparation, billing, information systems and technology, medication safety, operational effectiveness, medication use process, formulary management, and compliance, to name a few.

Services offered by a hospital pharmacy are usually arrived at through agreements between the pharmacy, hospital administration, nursing, and medical staffs. These services are based as much on the needs of patient care in the hospital as it is based on the supply of staff. When scheduling staff, much effort is placed on providing consistent and highly reliable levels of service given the numbers of staff available. Staffing in this manner produces a much more reliable pharmacy service and minimizes errors. Cross-training staff to work in more than one area also extends the ability of a pharmacy department to maintain a constant level of service regardless of absences, planned or unplanned (e.g., vacation, sickness, FMLA). Some states mandate that a licensed pharmacist review medication orders prior to dispensation or be available to answer drug information questions. In isolated areas, where pharmacist resources are limited, this may be performed remotely by a pharmacist working on behalf of a telepharmacy service. Staffing agencies are another option considered when pharmacist and technician staffing needs exceed the ability of a hospital pharmacy to supply them.

Non-traditional work schedules have become more prevalent in the hospital pharmacy workforce, especially for pharmacists. This has become an important factor in the retention of highly qualified pharmacists in an era of pharmacist shortages and in the creation of less desirable shifts (e.g., night shift). The need for staffing flexibility has been compounded by an aging pharmacist workforce. More than one-third of practicing pharmacists are 60 years of age or older. In addition, the number of women practicing pharmacy also continues to increase, also having an impact on adjustable schedules. In 2009, 46.4% of the pharmacist workforce was female vs. 31.3% in 1990. In addition, a larger number of women work part time than do men (29.8% versus 18.4%, 2009).[91] Creative schedules have included: seven days on seven days off (10 hours per night), four 10-hour shifts, offering part-time work at the discretion of the employee, job sharing in which one full time position is covered by two or perhaps three pharmacists.[92]

Performance planning

Performance planning is another important aspect of pharmacy human resources management. The best performance planning systems are provided in a structured way such that the strengths and weaknesses of an individual are identified. These strengths and weaknesses are usually reviewed in both the behavioral and job function domains. As an outcome, goals and objectives are developed with the intent

to challenge the individual in a positive way to grow professionally. Professional growth is a lifelong pursuit in pharmacy. Many state boards of pharmacy require pharmacists to obtain continuing education (CE) hours as a mechanism to ensure that continued learning occurs. Similarly, the PTCB also requires annual CE hours for pharmacy technicians. Another form of continued learning is continuing professional development (CPD). The principles of CPD can be summarized as follows:[93]

- CPD is a systematic, ongoing, cyclical process of self-directed learning
- CPD includes everything that practitioners learn that enables them to be more effective as professionals
- CPD includes the entire scope of the practitioner's practice and may include activities both within and outside the usual work setting
- CPD can strengthen the partnership between the practitioner and his or her organization, so as to meet the development needs of both
- Practitioners are responsible for their own professional development. The organization can have a role in helping practitioners meet the developmental needs related to job performance.

Information technology and automation

Information technology and automation significantly impact the delivery of hospital pharmacy services. Almost all pharmacy services are supported in some way by these systems. The impact of technology on pharmacy services has also resulted in the need for pharmacists to develop skills and in many cases specialize in this practice area in order to optimally support these systems.

Pharmacy distributive services are usually high volume, include tasks that should be consistently repeated with precision, and whose output will result in the administration of a medication to a patient. Due to the number of opportunities for medication errors and drug diversion in the medication use process, many companies have developed automated systems to ensure the accurate dispensation and administration of medications as well as prevent diversion.

Pharmacy related automation is represented by a wide variety of systems. They include: robots (cart-fill, IV and syringe compounding, retail prescription vial fill, and delivery), automated dispensing machines (ADMs), carousels, drug repackaging/bar-coding machines, and IV infusion smart pumps, to name a few.

Numerous information systems in hospitals and health systems include drug data. These systems range from pharmacy practice specific information systems such as the inpatient and outpatient pharmacy information systems, to systems that affect the workflow of other practitioners and the care of patients (e.g., electronic medication administration record (eMAR), computerized provider order entry (CPOE), and electronic health records (EHRs)). In addition, drug library databases are also found within smart infusion pumps, drug utilization benchmarking databases, ADMs, and drug repackaging/bar-coding machines. Pharmacy drug data are equally important within financial systems such as the charge data master (CDM) for hospital financial billing.

Pharmacy informatics

Pharmacy informatics has been defined as "the use and integration of data, information, knowledge, technology, and automation in the medication use process for the purpose of improving health outcomes."[47] With the significant growth in pharmacy information systems, automation, and other related technologies, pharmacy informatics has become a specialty field of practice much like what has happened for pharmacy practice in clinical areas of specialization. Pharmacy informaticists come from a wide variety of backgrounds and include professionals ranging from non-clinical information technology programmers and project managers, to pharmacy technicians and pharmacists. Although there are a few training and residency programs, most individuals in this field have "knowledge of computer systems, medication-use processes, safety issues, clinical management of medications, drug distribution, and administration, and have developed extensive expertise in using technology to support these activities."[47] Pharmacy informaticists develop programming requirements, oversee medication databases and clinical decision-support systems,

resolve system issues, assess and design information technology so as to avoid errors, and utilize clinical data to improve patient outcomes.[94]

Pharmacy information systems have greatly evolved over the decades. However, in general pharmacy information systems should perform the following activities:

- Inpatient and outpatient order entry, management, and dispensing
- Inventory and purchasing management
- Reporting (utilization, workload, financial)
- Clinical monitoring
- Manufacturing and compounding
- Intervention management
- Medication administration
- Connectivity to other systems (pharmacy automation, CPOE, EHR, financial, etc.)
- Pricing, charging, and billing.[95]

Pharmacy information systems have been and continue to be the leading clinical medication systems for performing such tasks as identifying drug–drug interactions, avoiding drug–food interactions, drug–disease state monitoring, and detecting overdosing or under-dosing of medications, to name a few.

Computerized provider order entry (CPOE)

As a profession, pharmacists have adopted technology at a much faster rate than other clinical professions. Physician adoption of information systems such as CPOE have taken much longer. During the late 1990s and early 2000s, adoption of CPOE became more prevalent as data began to show that CPOE utilization possibly prevented mediation errors. This momentum was spurred with the publication of the 1999 Institute of Medicine (IOM) report *To Err is Human*.[96] The report indicated that between 44,000 and 98,000 Americans potentially die each year due to hospital based medical errors and recommended CPOE as one possible solution.

The advent of CPOE has been important for the advancement of pharmacy practice, improvement of pharmacy services, and the prevention of medication errors. CPOE has resulted in time savings through the efficient communication of medication orders directly to the pharmacy. This has avoided the countless hours of delay during which paper orders would remain in a chart prior to being found and sent to pharmacy. Likewise, medication order legibility has improved, virtually eliminating errors associated with poor handwriting because CPOE has the ability to standardize the medication ordering process and communicate textual information. Whereas CPOE has been useful in the hospital environment, the process of sending electronic prescriptions to outpatient/retail pharmacies (e-Prescribing) has also improved communication in the ambulatory environment.

Electronic health record (EHR)

An EHR is an "electronic record of health-related information on an individual that can be created, gathered, managed, and consulted by authorized clinicians and staff across more than one health care organization."[97] The data contained within the EHR are inclusive of medication (prescribing, dispensing, administration, monitoring). EHRs are seen as important tools in improving the quality of care provided to patients.[98] However, in one study, only 18% of physicians reported having an EHR.[99]

To promote the rapid adoption of EHRs, Congress passed in 2009 the Health and Information Technology for Economic and Clinical Health (HITECH) Act. The bill "allocates approximately $44,000 for each practicing clinician and between $2 million and $10 million for each hospital that qualifies as a 'meaningful' user of EHRs."[100] The Act requires information systems to demonstrate electronic prescribing, the ability to share health data between providers and hospitals, and quality reporting.

Electronic medication administration record (eMAR)

With the development of pharmacy information systems, pharmacies were able to preserve and update patient medication profiles electronically instead of maintaining handwritten medication lists. The ability to maintain such lists of medications within the pharmacy information system also led to the practice of pharmacy printing the "profiled" medication lists for use as MARs. Through clinical system integration and real-time electronic communication, MARs are

now being provided in a completely electronic format (eMAR). This has allowed caregivers such as nurses to immediately view ordered medications on a computer. The eMAR can also be used to communicate location of products, provide administration information, and document medication administration.

Automated dispensing machines (ADMs)

ADMs have been rising in prominence for several decades. They are decentralized and located in various areas such as hospital patient care units, surgical suites, procedural areas, emergency departments, and clinics. ADMs are similar to automated teller machines (ATMs). However, instead of money, ADMs ensure controlled access to medications by requiring users to provide personal identification in order to access the contents. Most of these systems utilize bio-identification or fingerprint technology for controlling medication access.

ADMs can charge and credit patients for medications removed on their behalf or returned if not administered. Some ADMs are used for the floor-stocking of medications. In this scenario, while access to medications is still controlled, any medication may be removed for any patient. This particular option is more commonly utilized in procedural, emergency or outpatient environments. The use of "profiled" medications is considered to be a much safer methodology for medication management within ADMs. This option is more commonly used in hospital patient care units and only allows the removal of medications that have been reviewed and approved by a pharmacist. Products of high abuse potential such as controlled substances may also be tightly controlled by requiring users to provide an accurate count of the medication prior to removal. ADMs support medication inventory management including placing orders for wholesaler replenishment based on the inventory on hand. In cases where medications are needed urgently, certain medications where permitted can be accessed via an "override" function. This option is discouraged because it bypasses pharmacist review.

Bar code medication administration (BCMA)

BCMA is the application of bar-coding technology to the medication administration process in order to improve the accuracy and therefore safety during the act of medication administration. The concept is similar to that utilized by numerous other industries (grocery stores, delivery companies, aviation, etc.) to ensure highly accountable, safe services. In 2009, a survey conducted by the American Society of Health-System Pharmacists concluded that 27.9% of hospitals were utilizing BCMA.[64]

"BCMA assures that the 'five rights' are confirmed – right patient, right medication, right dose, right time, and right route."[101] In one study, the researchers found a 41.4% reduction in medication errors through the utilization of BCMA. The authors also found a 50.8% reduction of potential adverse drug events (excluding timing errors) as well as a reduction of transcribing errors from 6.1% on non-BCMA units to 0.0% on patient care units that used the technology.[102] However, just the presence of bar coded medications will not prevent errors. Users must also follow the proper procedures for the use of the BCMA system. Workarounds have included scanning the medication outside of the patient's room, scanning a patient bar code not attached to the patient, and confirming administration before administration occurred.[103]

One major challenge for hospital pharmacies is the fact that not all unit–dose medications provided by manufacturers are barcode ready. In organizations committed to BCMA, this requires pharmacies to find vendors who may repackage unit-of-use items into bar-coded packaging. Alternatively, hospital pharmacies may purchase bar code packaging equipment to overwrap already unit-dosed items or to prepare unit–dose packaged medications from bulk containers. Bar-coding equipment is also available to place bar-coded flags or stickers on vials, ampules, and syringes. Pharmacies that maintain these types of systems must also develop rigorous systems of quality assurance to prevent the introduction of mislabeled products.[104]

Other technologies

The use of IV Robotics for the preparation of sterile products is an emerging area of pharmacy technology.[105] This technology is offered by a limited number of vendors and provides pharmacies with an alternative to manually prepared IV medications. IV

robotics support the preparation of sterile products within an enclosed sterile ISO class 5 environment. These robots can fill both syringes and IV bags and utilizes a "combination of bar codes, images, and weight checks to ensure that the appropriate medication is used and dispensed based on patient-specific needs."[106]

Also growing in strength of use is the application of smart infusion pumps. Although infusion pumps have been around for years, the application of clinical data at the point of care in the form of drug libraries is a more recent development. These libraries provide clinical support in the form of soft and hard stops to guide the safe administration of intravenous medications. Many of these systems also support bar code technology that allows the pump to access the patient's medication profile. This ensures that the correct medication and dose are being administered at the right rate and allows for auto programming of the pump to ensure that pump programming errors are avoided. Errors have been seen with these systems when the drug library has been bypassed, alerts are overridden or independent double checks are not followed.[106]

Hospital pharmacies have begun using carousel dispensing technologies (CDT). This technology utilizes the concept of a rotating carousel with shelves for drug storage. The user of the system remains stationary while the requested medication is brought to the user. These systems have been shown to improve operational efficiency, reduce error rates associated with dispensing requests, decrease inventory carrying costs, and minimize space required for drug storage. These systems are also capable of self-replenishment by placing orders directly with wholesalers based on decremented inventory. CDT is utilized for dispensing STAT doses, first doses, ADM replenishment, and filling clinic orders. Most of these systems utilize barcode and pick-to-light technologies in which product selection can be highlighted and verified to support accuracy.[107,108]

One tenet of technology and automation in healthcare is that these tools and systems would support the delivery of care in a safe and effective manner. Many of those improvements (e.g., legibility, timeliness, accuracy of dispensation) have been seen. However, there is an increasing body of work that is also reflective of errors that may be facilitated through the use of these systems. One study demonstrated that CPOE facilitated 22 types of medication error risks.[109] Another 62-hospital study utilized a simulation tool to assess the safety of decision support and determined that 53% of the medication orders processed by clinical information systems would have resulted in fatalities.[110] As a result, many hospitals have implemented systems for conducting readiness assessments and have limited initial implementation of technologies and information systems to "pilot" areas in order to minimize the impact of new systems until all potential sources of error have been limited, isolated or resolved.

Education and training

Health system pharmacists are commonly involved in the education of doctor of pharmacy students, health professionals, patients, and pharmacy residents.

Hospital practice experience

The Accreditation Council for Pharmacy Education (ACPE) for doctor of pharmacy programs requires two types of experiential training for pharmacy students. The first type is called an introductory pharmacy practice experience (IPPE). The IPPEs should begin early in the curriculum, be interfaced with didactic course work that provides an introduction to the profession, and continue in a progressive manner leading to entry into the advanced pharmacy practice experiences.[111] These introductory experiences must be at least 300 hours total and occur over the first 3 years of the professional curriculum. IPPEs occur in either institutional or community settings, and may allow the pharmacy student to assume direct patient care activities. IPPEs are conducted by qualified pharmacist preceptors who are licensed in the United States. As such, it is common for the health system pharmacists to be involved in providing IPPEs. Activities typical for an IPPE in the health system include observation of surgical procedures, shadowing a pharmacist on duty, conducting projects, attending staff meetings, joining physician rounds, and participation in the dispensing pharmacy. Some unique aspects of health system pharmacy that do not necessarily exist in the community setting include the presence of

an electronic medical record, automated dispensing machines, physician rounds, sterile products preparation, and bar-code medication administration.

The Advanced Practice Pharmacy Experiences or APPEs, occur during the last professional year after all didactic courses are completed.[111] The APPEs must be at least 1440 hours (36 weeks) in length. Advanced practice experiences meet specific goals and objectives and meet competencies in community pharmacy, hospital or health system pharmacy, ambulatory care, and inpatient/acute care general medicine. Health system participation in the provision of APPEs ranges from 63 to 100% of hospitals, with an average of 78% of health systems providing this type of student experience.[112] Of these sites, an average of 78% also provide experiential education to physicians, nurses, and other allied health professionals. Pharmacists in these settings typically will provide medication education to other health professionals, as well.

Modern pharmacy practice models focus on patient safety, continuity of care, and patient education.[15] A pharmacist therefore may provide education to patients regarding proper use of their medications. Medication related education, along with medication therapy management can improve patient outcomes and reduce costs of care.[113] Elements of patient education regarding medications include proper drug, dose, frequency, indication for use, potential side effects, and how to handle missed doses. In addition, the pharmacist can provide special instructions for techniques used to deliver medications that are inhaled, absorbed through the skin or injected. In addition to providing education, providing a patient discharge plan that includes follow-up by a pharmacist for high risk patients can reduce hospital readmissions.[114]

Residency programs

Pharmacy residency training has undergone an evolution over the past 80 years. The first health system residencies, called "hospital pharmacy internships" were established in 1927. Early residencies focused on operational aspects of pharmacy, as well as leadership.[115] As drug manufacturers continued to refine the development and packaging of medications, the profession could focus less on product preparation and more on clinical aspects of patient care. Medication therapies became more complex and the profession learned how medications were absorbed, distributed, metabolized, and excreted differently in various patient populations. The application of clinical knowledge became more common in the pharmacy profession. The American Society of Health-System Pharmacists developed an accreditation standard for residency training in clinical pharmacy practice. Since then, the number of postgraduate students seeking residency positions has grown steadily. There are a number of reasons for this growth in residency programs and applicants. Medication therapies have grown more complex over the years, as the population ages. People are living longer with chronic diseases. The number of colleges of pharmacy has grown, increasing the pool of applicants for residency positions. This growth has also increased the competition for residency positions. Finally, national organizations have advocated for residency training as a prerequisite for health system pharmacy practice. Residency programs have been recognized by some organizations as essential to future growth and innovation in practice.[116] Residents allow organizations an extra set of hands to "try out" new ideas and new ways of doing things. A resident's natural curiosity as a new practitioner will motivate pharmacists to maintain medication knowledge and competency in the profession. Residents can serve as pharmacist "extenders," providing pharmacy services in areas that had not been served prior to the residency program. Finally, residents can assist with the education of pharmacy students, nurses, physicians, and other health professionals.

Well over half of health system pharmacists are involved in the training and education of health professionals. In US hospitals, this number approaches 80%.[112] Health system pharmacists are involved in the education of pharmacy students, physicians, nurses, other health professionals, patients, and pharmacy residents.

Conclusion

The practice of health system pharmacy continues to evolve as the medication therapies become more complex. Regulatory requirements remain prevalent in the health system environment. The use of technology and technicians will bring the pharmacist's expertise closer to the patient, in order to facilitate

optimal use of medications. The automation of some of the distribution processes has allowed pharmacy technicians a greater role in managing the medication use process. Although the pharmacist is still accountable for overall supervision of the prescription process, their roles are growing at a faster rate in areas such as clinical pharmacy, drug policy, medication safety, performance improvement, transitions of care, and informatics. Most health systems are involved in training future pharmacists and future leaders of the profession.

Pharmacy practice in industry: potential roles for pharmacists

Modern pharmaceutical education endows pharmacists with a broad background of scientific, technical, and clinical knowledge associated with state-of-the-art medications. Pharmacists have a comprehensive understanding of drugs, dosage forms, delivery systems, therapeutics, administration, clinical effects, healthcare settings, patient needs, outcomes, and associated expertise. While most pharmacists utilize this background in some form of community practice,[117,118] their expertise is particularly suited for the work within the pharmaceutical and related industries. Pharmacists have numerous opportunities to utilize all aspects of their diverse education in professional practice in industry, and to do so in a significant, meaningful, and personally rewarding way.

The healthcare industry encompasses a wide variety of specific companies of varying size and capabilities. Pharmaceutical and related companies may be large multinational corporations or may be small virtual enterprises. The scope of products manufactured and distributed by these companies is broad and diverse. Companies may manufacture small molecule and biotechnology products, medical devices, diagnostic reagents, dietary supplements, cosmetics, and other products. Collectively these products contain great numbers of individual drugs, reagents, and other ingredients in a variety of traditional and evolving delivery systems.

Pharmacists are involved in the manufacturing, testing, and support of these products in many ways during the product life cycle. They may work in technical areas such as chemistry, manufacturing, and control functions; in clinical research, analysis, marketing and other business functions; and other supportive functions such as regulatory affairs, legal affairs, and patents. Pharmacists with additional education are able to utilize their total education in industry positions. For example, many pharmacists have biology, chemistry, engineering, or business degrees prior to receiving their pharmacy degree. Other pharmacists pursue advanced degrees such as PhD, MPH, MS, JD, MBA, or other specialized training after receiving the PharmD. Advanced education in project management, industrial science, and other disciplines provides further personal development and specialized skills used in industry. Pharmaceutical practice in industry provides opportunities for fulfilling careers for all of these individuals.

Pharmacists in government

Current challenges on access, safety, quality, and cost in healthcare coupled with increasing healthcare workforce shortage as well as the recent enactment of the Affordable Care Act on March 23, 2010 offer significant opportunities for pharmacists and pharmacist-delivered patient care services. New and exciting possibilities for advanced pharmacy practice and careers are offered in government sectors, with the federal sector offering the broadest range of opportunities.

The trend toward systems of managed care administration has set into motion several initiatives that have reformed the provision of healthcare in the United States. Although commitments and action steps at the end of the last century sought to reduce the overall size of the federal establishment, it became clear at the beginning of this century that certain parts of that establishment designed to protect against terrorism needed expansion. The effect of changes in the federal sector will be spread over several years. It can be anticipated that federal-sector health systems will be extremely dynamic through the turn of the century and beyond.

Pharmacists and the profession of pharmacy are at the crossroads of healthcare with many opportunities available for the creation of new forms of practice. Nowhere is this truer than in the federal sector, which offers numerous opportunities for innovation through

novel clinical service delivery models, research, and in policy and regulatory mechanisms. It used to be true that pharmacists practicing within the several federal services were not the highest paid practitioners in the profession. However, changes due to federal legislation providing for a sign-on bonus, special pay, loan repayment, and board certified pay for pharmacist officers have made practicing pharmacy in federal services competitive with the private sector. Pharmacist officers and federal civil service pharmacists also enjoy a benefits package that is generally more supportive of personal and family needs than is in the private sector in terms of leave and medical benefits. In addition, pharmacists desiring to practice advanced forms of clinical activities usually find greater fulfillment in federal practice than in most of the private sector as there are greater capacity with a variety of practice settings and unique inter-professional practice environments in the federal sector. Federal uniformed service also offers the unique opportunity to pursue a career in which one's seniority and retirement program remain intact throughout one's career moves. Those pharmacists oriented toward patient care and public health find a particularly rewarding form of practice in federal service. Finally, even if pharmacists do not choose a full-time federal career, there are ample opportunities for part-time and intermittent federal service throughout the nation.

Pharmacists and public health

Public health is a societal effort to protect, promote, and restore the public's health.[119] It is a combination of sciences, skills, and beliefs that are directed to the prevention of diseases, maintenance of a healthy life, and improvement of the health of all the people through collective or social actions. It is concerned with threats to health based on population health analysis. The population in question can be as small as a handful of people or as large as all the inhabitants of several continents (e.g., during a pandemic). The dimensions of health can encompass "a state of complete physical, mental and social well-being, and not merely the absence of disease or infirmity," as defined by the WHO; http://www.who.int.[120] Public health incorporates the interdisciplinary approaches of epidemiology, biostatistics and health services. Environmental, community, behavioral, and occupational health are other important subfields.

The focus of public health intervention is to improve health and quality of life through the prevention and treatment of disease and other physical and mental health conditions, through surveillance of cases and the promotion of healthy behaviors. The programs, services, and institutions involved emphasize the prevention of disease and the health needs of the population as a whole. Public health activities change with changing technology and social values, but the goals remain the same: to reduce the amount of disease, premature death, and disease-produced discomfort and disability in the population. Public health is thus a social institution, a discipline, and a practice. The Institute of Medicine defines the mission of public health as "fulfilling society's interest in assuring conditions in which people can be healthy."[121]

Consultant pharmacy practice

Consultant pharmacists come from a variety of pharmacy practice backgrounds. Rooted in the community pharmacy tradition, consultant pharmacists are expert clinicians in geriatric pharmacotherapy, adept practitioners of pharmacy systems management, enterprising business leaders, and integral members of the geriatric interdisciplinary team. Consultant pharmacists possess a unique position and an important history in the development of pharmacy practice in America. To understand consultant pharmacy requires an appreciation of the sweeping legislation enacted by Lyndon Johnson in the 1960s. Intrinsically linked to the enactment of Title XVIII and Title XIX of the Social Security Act, consultant pharmacy was created out of a basic unmet need – to improve medication management in nursing homes.

Nuclear pharmacy practice

Nuclear pharmacy, also referred to as radiopharmacy, is the specialty practice of pharmacy that focuses on the safe and efficacious use of radioactive drugs. Radioactive drugs, referred to as radiopharmaceuticals, constitute a special class of drugs according to the Food, Drug, and Cosmetic Act (FD&C Act).

The FDA, in Title 21 of the Code of Federal Regulations (CFR), defines a radioactive drug as a drug that exhibits spontaneous disintegration of unstable nuclei with the emission of nuclear particles or photons and includes any nonradioactive reagent kit or nuclide generator intended for use in the preparation of any such substance. Similarly, the British and European Pharmacopoeias define a radiopharmaceutical as any medicinal product which, when ready for use, contains one or more radionuclides (radioactive isotopes) included for a medicinal purpose. From these definitions, it is apparent that a radiopharmaceutical consists of both a drug component and a radioactive component. The drug component is responsible for localization in specific organs or tissues. The radioactive component is responsible for the emission of gamma rays for external detection in diagnostic imaging and/or particulate radiation for radionuclide therapy. Radioactive *in vitro* diagnostic kits for radioimmunoassays and brachytherapy sources for radiotherapy implants are classified by the FDA as devices, in contradistinction to radiopharmaceuticals, which are classified as drugs.

A distinctive feature of radiopharmaceuticals, in contrast to traditional drugs, is their lack of pharmacological effects. Radiopharmaceuticals are employed as tracers of physiological functions. Their small amounts of mass produce negligible effects on biological processes, while their radioactivity allows noninvasive external monitoring or targeted therapeutic irradiation. The ratio of radioactivity to mass is termed "specific activity." Accordingly, radiopharmaceuticals typically have a high specific activity (i.e., abundant radioactivity per small amount of mass).

Some radiopharmaceuticals are simply salts of radioisotopes of elements (e.g., I-131 sodium iodide, Tl-201 thallous chloride, Sr-89 strontium chloride), but most radiopharmaceuticals consist of radioactive atoms attached to, or incorporated into, other drug molecules that serve to carry the radioactive atoms to the intended tissues or organs. Some radiopharmaceuticals are manufactured and commercially marketed by pharmaceutical companies in their final, ready-to-use dosage forms. Due to their short half-lives, however, most radiopharmaceuticals require preparation of the final product either on-site, such as in a hospital's nuclear pharmacy or nuclear medicine department (in some nuclear medicine departments, radiopharmaceuticals are prepared by Nuclear Medicine Technologists, working under the supervision of an authorized user Nuclear Medicine physician or nuclear pharmacist), or in a local commercial nuclear pharmacy that then delivers the finished products to surrounding hospitals and clinics.

Radiopharmaceuticals can be categorized as either diagnostic or therapeutic. Diagnostic radiopharmaceuticals are intended for use in the diagnosis and/or monitoring of various disease states. Relatively small radiation doses are delivered in diagnostic nuclear medicine procedures, similar in magnitude to radiation doses from diagnostic X-ray procedures roughly corresponding to the same organ system (see Table 11.2). Examples of diagnostic radiopharmaceuticals include Tc-99m medronate (MDP) (in practice, most radiopharmaceuticals are referred to by common names, such as abbreviated chemical names, rather than by nonproprietary drug names established by the United States Adopted Names Council (USAN)) for bone imaging procedures,Tc-99m macroaggregated albumin (MAA) for lung imaging procedures, and I-123 sodium iodide for thyroid imaging procedures (see Table 11.3). Therapeutic radiopharmaceuticals, conversely, are intended for use in the treatment of various disease states. Relatively large radiation doses are purposefully delivered to cause localized radiation damage, similar in magnitude to radiation doses from teletherapy (external beam irradiation). A common example of a therapeutic radiopharmaceutical is I-131 sodium iodide for treatment of hyperthyroidism or thyroid cancer (see Table 11.4).

Radiopharmaceuticals are employed in the discipline termed "nuclear medicine." Nuclear medicine may be a separate unit or found as a part of radiology. In some situations, limited groups of radiopharmaceuticals may also be employed in specialty practices, such as radiation oncology, cardiology, or endocrinology. In a diagnostic nuclear medicine procedure, the radiopharmaceutical is administered to the patient most often by IV injection, although sometimes by oral, inhalation, or other routes. The localization, disposition, and/or clearance of the radiopharmaceutical is then determined by detection of the gamma radiation emitted from the radionuclide. Conventional

Table 11.2 Radiation doses for selected nuclear medicine and X-ray imaging procedures*

	Effective dose		Effective dose
Nuclear medicine procedure	**(mrem)**	**X-ray procedure**	**(mrem)**
Bone scan	422	Spine series	347
Gastric emptying scan	35	Barium meal	300
Infection scan	665	CT abdomen/pelvis	1400
Liver scan	278	CT liver	790
Perfusion brain scan	688	Head CT	210
Perfusion lung scan	163	CT chest	930
PET scan, FDG	703	CT chest/abdomen/pelvis	1800
Renal scan	518	Intravenous pyelogram	250
Thyroid scan, I-123	326	CT neck	480

* Data from RADAR (Radiation Dose Assessment Resource), http://www.doseinfo-radar.com/RADARHome.html.

nuclear medicine imaging employs a "gamma camera," which detects gamma radiation in two dimensions and produces "planar" images. Single Photon Emission Computed Tomography (SPECT) refers to the special case when a gamma camera rotates around the patient and detects individual gamma rays through a series of angles. These data are then processed by a computer to create images of three-dimensional slices. Positron Emission Tomography (PET) refers to the detection of annihilation photons, subsequent to emission of positrons by certain radionuclides. PET scanners are constructed as solid rings of detectors that employ coincidence detection of the annihilation photon pairs. These data are then processed by a computer to create images of three-dimensional slices.

Normal versus abnormal images vary, depending on the procedure. For example, a normal image with a radiopharmaceutical designed to be phagocytized by the liver will appear as a rather uniform uptake and distribution of the radiopharmaceutical throughout the liver. A space-occupying lesion, such as a tumor, lacks phagocytic cells, so it does not concentrate the radiopharmaceutical. Thus, the image of the liver will show a "cold" area (i.e., an area with less radioactivity than the surrounding normal liver; Fig. 11.1). The opposite effect is noted in the case of a radiopharmaceutical designed to localize in areas of the bone metastases. Excessive amounts of the radioactivity will occur in the area of the metastatic lesion, in comparison to the surrounding normal bone. This is termed a "hot" spot on the image (Fig. 11.2).

The radionuclides used for radiopharmaceuticals employed in diagnostic nuclear medicine studies have short half-lives. Half-life is defined as the time it takes for one-half of the radioactive atoms to undergo radioactive decay with emission of their characteristic radiation. For example, technetium Tc-99m has a physical half-life of 6.0 hours (Fig. 11.3). The shorter the half-life, the lower is the total number of atoms necessary for the production of a given unit of activity and, hence, the higher the specific activity, compared with a longer half-life radionuclide. Simply stated, the atoms for a short-half-life radionuclide do not exist very long before emitting their radiation. This allows a patient to receive an extremely small mass of radionuclide, which provides a high degree of safety for the patient, while allowing the nuclear medicine

Table 11.3 Diagnostic radiopharmaceutical products* commercially available in the United States in 2011 and their common uses

Albumin, iodinated I 125 (I-125 RISA) injection	Determination of plasma volume
Albumin, iodinated I 131 (I-131 RISA) injection	Determination of plasma volume
Ammonia N-13 injection	Myocardial perfusion imaging
Fludeoxyglucose F-18 (F-18 FDG) injection	Brain, heart, and tumor imaging
Gallium citrate Ga-67 injection	Tumor and infection imaging
Indium In-111 capromab pendetide injection†	Imaging of prostate cancer
Indium In-111 chloride sterile solution	Radiolabeling of peptides and antibodies
Indium In-111 ibritumomab tiuxetan injection†	Non-Hodgkin's lymphoma imaging
Indium In-111 oxyquinoline (In-111 oxine) sterile solution	Radiolabeling of leukocytes
Indium In-111 pentetate (In-111 DTPA) injection	Imaging of cerebrospinal fluid flow
Indium In-111 pentetreotide injection†	Imaging of somatostatin receptors on tumors
Iodine I-131 tositumomab injection	Non-Hodgkin's lymphoma imaging
Iobenguane I-123 (I-123 MIBG) injection	Imaging of neuroendocrine tumors
Ioflupane I-123 injection	Imaging of dopamine transporters in brain
Iothalamate sodium I-125 injection	Determination of glomerular filtration rate
Rubidium chloride Rb-82 injection	Myocardial perfusion imaging
Sodium chromate Cr-51 injection	Determination of red cell volume
Sodium fluoride F-18 injection	Bone imaging
Sodium iodide I-123 capsule	Thyroid imaging
Sodium iodide I-131 capsule	Thyroid uptake measurement, thyroid imaging
Sodium iodide I-131 oral solution	Thyroid imaging
Sodium pertechnetate Tc-99m injection (Tc-99m TcO_4^-)	Thyroid, salivary gland, blood pool imaging
Technetium Tc-99m albumin aggregated injection (Tc-99m MAA)†	Lung perfusion imaging
Technetium Tc-99m bicisate injection (Tc-99m ECD)†	Cerebral perfusion imaging
Technetium Tc-99m disofenin injection (Tc-99m DISIDA)†	Hepatobiliary imaging
Technetium Tc-99m exametazime injection (Tc-99m HMPAO)†	Cerebral perfusion imaging
Technetium Tc-99m mebrofenin injection (Tc-99m BRIDA)†	Hepatobiliary imagng

(continued overleaf)

Table 11.3 *(continued)*

Technetium Tc-99m medronate injection (Tc-99m MDP)†	Bone imaging
Technetium Tc-99m mertiatide injection (Tc-99m MAG3)†	Kidney imaging
Technetium Tc-99m oxidronate injection (Tc-99m HDP)†	Bone imaging
Technetium Tc-99m pentetate injection (Tc-99m DTPA)†	Kidney, lung ventilaiton imaging
Technetium Tc-99m pyrophosphate (Tc-99m PYP)†	Bone, myocardial infarct, blood pool imaging
Technetium Tc-99m labeled red blood cells injection (Tc-99m RBCs)†	Blood pool imaging
Technetium Tc-99m sestamibi injection (Tc-99m MIBI)†	Myocardial perfusion, breast tumor imaging
Technetium Tc-99m succimer injection (Tc-99m DMSA)†	Kidney imaging
Technetium Tc-99m sulfur colloid injection†	Liver/spleen and gastric emptying imaging
Technetium Tc-99m tetrofosmin injection†	Myocardial perfusion imaging
Thallous chloride Tl-201 injection	Myocardial perfusion imaging
Urea C-14 capsule	Breath test for *H. pylori* infection
Xenon Xe-133 gas	Lung ventilation imaging

* Proper name (common name).
† Approved product exists in kit form.

Table 11.4 Therapeutic radiopharmaceutical products* commercially available in the United States in 2011 and their common uses

Iodine I-125 3-iodo-4-hydroxybenzenesulfonate (HBS)*	Intracavitary brachytherapy of brain tumors
Iodine I-131 tositumomab injection	Treatment of non-Hodgkin's lymphoma
Samarium Sm-153 lexidronam pentasodium injection (Sm-153 EDTMP)	Palliation of painful bone metastases
Sodium iodide I-131 capsule	Treatment of hyperthyroidism, thyroid cancer
Sodium iodide I-131 oral solution	Treatment of hyperthyroidism, thyroid cancer
Strontium chloride Sr-89 injection	Palliation of painful bone metastases
Yttrium Y-90 chloride sterile solution	Radiolabeling of ibritumomab tiuxetan
Yttrium Y-90 ibritumomab tiuxetan†	Treatment of non-Hodgkin's lymphoma
Yttrium Y-90 microspheres§	Intravascular brachytherapy of liver tumors

* Proper name (common name)
† Approved product exists in kit form.
§ Radioactive device, rather than a radioactive drug.

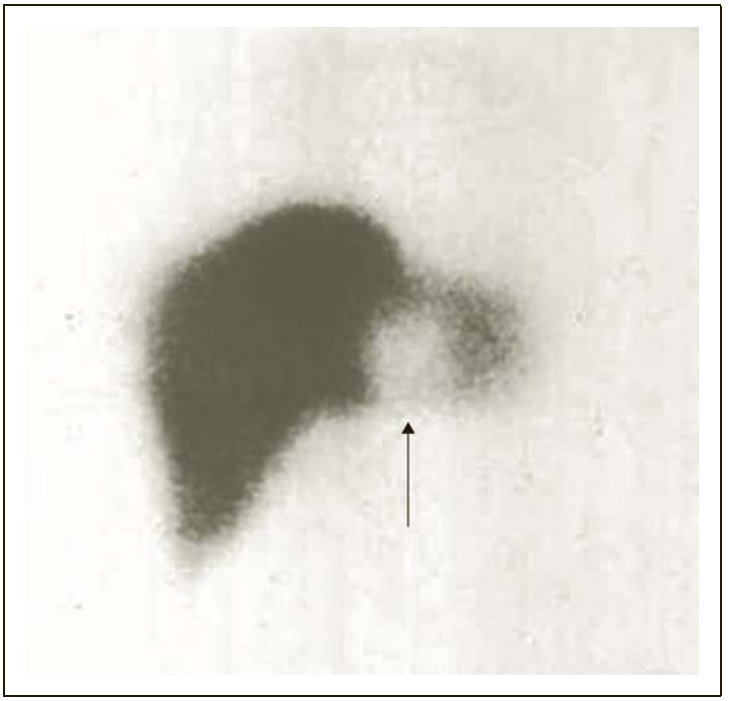

Figure 11.1 A hemangioma is exhibited as a cold spot (arrow) relative to surrounding normal liver uptake on a Tc-99m sulfur colloid liver scan.

procedure to be conducted satisfactorily. A rapid rate of decay and, thus, frequent radiation emission is further desirable for the efficient performance of these procedures, since the gamma camera must "see" a certain number of gamma rays to obtain sufficient data to create the desired image.This half-life, based on radioactive decay, is also referred to as "physical half-life." Because radiopharmaceuticals administered to patients undergo biologic elimination, there is also a drug excretion half-life referred to as "biologic half-life." Hence, a radiopharmaceutical administered to a patient undergoes both radioactive decay and biologic elimination, so its overall "effective half-life" is equal to [(physical half-life) × (biologic half-life)] ÷ [(physical half-life) + (biologic half-life)].

Because the radionuclides commonly employed in radiopharmaceuticals have short half-lives, most radiopharmaceuticals must be prepared on the day of use. This is accomplished most frequently with the aid of a nonradioactive reagent kit and radioactivity obtained from a radionuclide generator. The reagent kit is usually a multi-dose vial that contains the compound (ligand) to be labeled (i.e., attachment of the radionuclide to the compound) and other components necessary to accomplish the labeling process and allow administration of the final product. The radionuclide generator most often employed is the technetium generator. The radionuclide technetium Tc-99m is produced by the decay of molybdenum Mo-99. Molybdenum-99 has a half-life of 6 hours and allows the generation of Tc-99m over a period of 1 to 2 weeks. The Tc-99m is separated from the Mo-99 by passing a sterile saline solution through an ion-exchange column containing the Mo-99 and the Tc-99m that has been generated. The Mo-99 remains on the column, whereas the Tc-99m, in the chemical form of sodium pertechnetate, elutes from the column and is collected in a sterile vial. Aliquots of this eluate are then used to prepare radiopharmaceuticals with the reagent kits.

Quality-control issues are important in this process. The possibility of the presence of Mo-99 in the eluate must be determined, because this radionuclide has a longer half-life, emits a more damaging form of radiation (beta), and is in the wrong chemical form. The purity of the desired compound must also

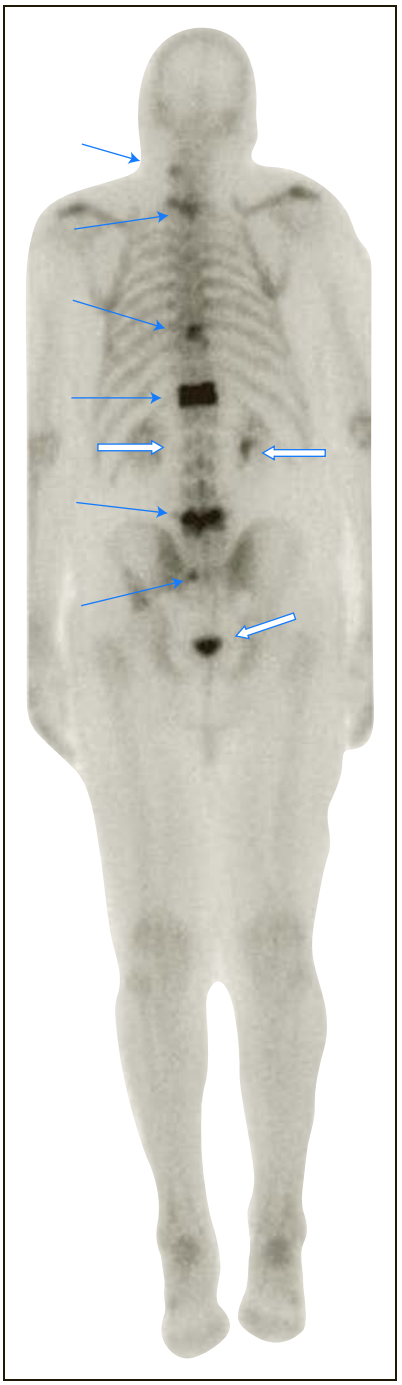

Figure 11.2 Multiple metastases to the bone from primary breast cancer are exhibited as "hot" spots (arrows) relative to surrounding normal bone uptake on a Tc-99m medronate bone scan. Kidneys and urinary bladder are also seen (open arrows), due to normal excretion into the urine.

be determined following preparation of the radiopharmaceutical with the sodium pertechnetate and a reagent kit. This is usually accomplished using paper or thin-layer chromatography procedures. A specified percentage of the radioactivity must be incorporated in the specified compound (i.e., the radiopharmaceutical). If a significant fraction of the radioactivity remains as sodium pertechnetate, the radiopharmaceutical product will not distribute in the body as expected and might cause confusion or even an improper diagnosis.

A few radiopharmaceuticals are employed in the treatment of disease, most often certain cancers. Like diagnostic radiopharmaceuticals, these compounds are designed to localize in the diseased tissue. However, these radiopharmaceuticals emit particulate radiation, typically beta particles, that deposit their energy in a localized area with the intent to destroy cells in the diseased tissue.

Perhaps the best known approach to therapy with a radiopharmaceutical involves the use of radioactive iodine, I-131, administered as sodium iodide to the patient. The I-131 is taken up by the thyroid gland and incorporated into thyroid hormones. Whereas small, diagnostic dosages of I-131 produce negligible biological damage, the beta radiation emitted by large, therapeutic dosages of I-131 destroys thyroid tissue. Depending on the disease state, hyperthyroidism or thyroid cancer, the amount of radioactive iodide given to the patient varies considerably. The usual dosage ranges for treatment of hyperthyroidism (partial destruction) and thyroid carcinoma (total destruction) are 140 to 370 MBq (4 to 10 mCi) and 3700 to 5550 MBq (100 to 150 mCi), respectively. In contrast, less than 1 MBq (a few microcuries) of I-131 is given for diagnostic purposes. This is an important consideration when counseling a patient regarding the use of radioactive iodine for diagnostic procedures.

One of the more recent developments in oncologic nuclear medicine is the use of monoclonal antibodies labeled with a gamma-emitting radionuclide for diagnostic imaging and with a beta-emitting radionuclide for subsequent therapy. For example, ibritumomab, the parent murine monoclonal antibody of the widely used chimeric antibody rituximab, selectively binds to the CD20 antigen found on the surface of B-lymphocytes and lymphatic tumor cells.

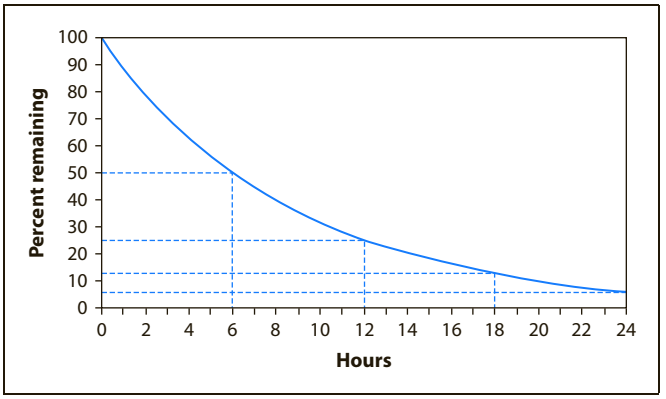

Figure 11.3 Radioactive decay of Tc-99m demonstrating its half-life of 6 hours.

When radiolabeled with gamma-emitting In-111, ibritumomab tiuxetan is used for imaging in patients with non-Hodgkin's lymphoma; when radiolabeled with beta-emitting Y-90, ibritumomab tiuxetan is used for subsequent radioimmunotherapy of non-Hodgkin's lymphoma in these same patients.

As described, radiopharmaceuticals constitute a unique and specialized category of drugs. Similarly, individuals who handle radiopharmaceuticals need to possess a unique and specialized body of knowledge and skills. Specifically, nuclear pharmacy practitioners must have specialized training in several areas, including nuclear physics, radiation detection instrumentation, radiochemistry, and radiation protection. An experiential component of this training in a practice setting is essential as well. The level of knowledge and experience necessary, as well as services provided, vary with the practice site. The majority of nuclear pharmacists practice in a commercial nuclear pharmacy. Most practitioners in this setting have a first professional degree, whereas nuclear pharmacists in an institutional site have commonly obtained an advanced degree (e.g., MS). The basic functions are similar; however, the pharmacist in the larger hospital may be more involved with clinical service, investigational products, and teaching. The pharmacist in a commercial nuclear pharmacy inherently spends considerable time preparing and dispensing radiopharmaceuticals, since one pharmacy services a dozen or more different hospitals and clinics.

Home infusion pharmacy practice

The provision of home care has existed since the late 1800s, when societal concerns regarding immigration, industrialization, and infectious diseases generated the need for visiting nurses. Early home care services primarily consisted of midwife and nursing assistance for births, and the care of influenza and tuberculosis patients. This early form of home care paved the way for the development of alternate site healthcare. The term *home care* generally refers to community-based nursing and hospice services provided to patients in their homes. The term includes a wide variety of services provided outside the confines of the hospital, as outlined in Table 11.5. The National Association for Home Care and Hospice (NAHC) estimates that 12 million Americans receive home care from over 33,000 providers.[122,123] In 2009, $103.2 billion was spent on home healthcare and durable medical equipment, accounting for 4% of the total US national healthcare expenditure.[124]

Since the early 1990s, home healthcare has become the fastest growing segment of healthcare. In 1999, the US Supreme Court rendered a decision in *Olmstead v. L.C.*, affirming the Americans with Disabilities Act of 1990, which "increased pressure on federal and state programs to deliver advanced health care services to patients at home."[125]

The dramatic increase in the alternate site healthcare market has largely occurred due the nationwide effort to control healthcare costs. During the

Table 11.5 Types of home care services

- Homemaker Services (e.g., cleaning, cooking for the homebound)
- Personal Care Services (e.g., bathing, dressing)
- Durable Medical Equipment (e.g., walkers, oxygen, hospital beds)
- Home Respiratory Care (e.g., respiratory therapy, nebulizers)
- Medical Devices and Supplies (e.g., glucometers and glucose test strips)
- Skilled Nursing Services
- Physical Therapy
- Occupational Therapy
- Speech/Language Pathology
- Medical Social Work
- Hospice Care
- Pharmacy Services (e.g., infusion therapies, inhalation therapies, clinical monitoring)

Data from: Lima HA. *Pharmacy Practice News* 1999; (July) 33, and National Association for Home Care and Hospice. Basic Statistics About Home Care, 2010. Available at: http://www.nahc.org/facts/10HC_Stats.pdf (accessed July 1, 2011).

1980s, the US healthcare system underwent dramatic changes. In particular, with the introduction of diagnosis-related groups (DRGs) as a cost-control measure, home care offered a cost-effective alternative following the post-acute hospital stage.[122] Driven by heightened emphasis on cost-effectiveness and cost-containment, technological advances have been developed that enabled the safe and effective administration of complex treatments in the home, including home infusion therapy.

Home infusion is an important component of the home care industry and accounts for approximately $9 to $11 billion annually. This service provides therapies to patients in their homes or alternate settings, such as ambulatory infusion clinics. Home infusion therapy involves the prolonged intermittent or continuous parenteral administration of pharmaceutical products (e.g., medications, nutrients, or other solutions) most often delivered intravenously, subcutaneously, intramuscularly, or epidurally. Commonly prescribed home infusion therapies include: antibiotics, antifungals, parenteral nutrition (PN), pain management, hydration, chemotherapy, immune globulins, corticosteroids, inotropics, blood clotting factors, other intravenous drugs, as well as enteral nutrition.[122,126] According to the ASHP *Minimum Standard for Home Care Pharmacies*,[127] a home care pharmacy is one that provides primarily, if not exclusively, home infusion products and related monitoring services.

Currently, approximately 1000 pharmacy organizations nationwide provide infusion therapy services. These pharmacies include local, regional, and national pharmacy organizations that are independently owned, publicly traded, or affiliated with hospitals, health systems, home health agencies, retail pharmacies, retail pharmacy chains, or durable medical equipment suppliers.[126] Home nursing services may be provided by the infusion pharmacy to ensure proper patient and caregiver training, and to monitor the clinical care of the patient in the home. Alternatively, home nursing services required for the safe provision of home infusion therapy can be provided by a qualified home health agency.

Home infusion pharmacy services differ dramatically from most retail pharmacy operations. While retail pharmacies primarily dispense oral medications, infusion pharmacies must have the equipment necessary to safely prepare and store sterile parenteral preparations. This includes: laminar flow hoods or isolators and clean room complexes to reduce the risk of microbial contamination, modified storage areas for certain drugs, and additional compounding equipment and supplies for the sterile preparation of parenteral drugs. In addition to sterile preparation expertise, home infusion pharmacists must have the knowledge and commitment to provide pharmaceutical care within an interdisciplinary team to a broad cross-section of patients treated in their homes and in alternate site settings.[128] A summary of home infusion pharmacists' responsibilities is outlined in Table 11.6.

Specialty pharmacy

Specialty pharmacy is a unique pharmacy practice that has its origins in the home infusion practice setting. Although an accepted industry standard and FDA definition are lacking, specialty pharmaceuticals were originally defined as those products produced by recombinant DNA technology (biotech drugs) and administered via injection.[129] Early specialty drugs

Table 11.6 Home infusion pharmacist responsibilities

- Preadmission Assessment
- Initial Assessment
- Product, Devices, and Ancillary Supply Selection
- Care Plan Development
- Patient Education and Counseling
- Clinical Monitoring
- Communication with Patient, Caregiver, Nurse, Dietitian, and Prescriber
- Coordination of Drug Preparation, Delivery, Storage, and Administration
- Precautions for Employee and Patient Safety
- Home Care Record Documentation
- Adverse Event Reporting
- Performance Improvement Activity Participation
- Policy and Procedure Development and Implementation
- Legal, Regulatory and Accreditation Compliance
- Training, Continuing Education and Competence

Data from: ASHP Guidelines on the Pharmacist's Role in Home Care. *Am J Health-Syst Pharm* 2000; 57:1252–7.

were used to treat complex genetic conditions including: cancer, hemophilia, hepatitis C, multiple sclerosis, and pulmonary hypertension. However, specialty drug dosage forms have expanded and can include high-cost oral, injectable, infused, and inhaled biotech drugs, and are sometimes called biologicals or biologics. The newer specialty pharmaceuticals are targeted to more common chronic conditions such as rheumatoid arthritis and asthma. Many specialty drugs are not biologics and conversely, many biologic drugs are not considered specialty drugs. Insulin is a biologic but is not considered a specialty drug. Many specialty drugs are orphan drugs or are used to treat diseases for which there are no other available treatments. An increasing amount of specialty drugs on the market today and in the FDA pipeline can be taken orally. Specialty drugs require intensive "therapy management" by health professionals due to a high incidence of adverse effects and compliance issues that require dosage adjustments and monitoring. Characteristics of specialty pharmaceuticals are listed in Table 11.7.

Specialty medications typically require "high-touch" services in the forms of distribution, administration, or patient management: all of these factors add costs for the purchaser or consumer. In fact, one universally accepted characteristic of specialty pharmaceuticals is their high cost. Recombinant insulin does not fit the definition of a specialty pharmaceutical, but interferon beta-1a (Avonex®), a $17,000+-a-year product used to treat multiple sclerosis (MS) that requires a refrigerated chain of distribution, clearly does.[131] The US Centers for Medicare and Medicaid (CMS) will put a drug on its specialty tier if the monthly cost of the drug exceeds $600.[132] This cost is misleading because most specialty medications cost well over $1,000 per month for one drug. Consider the multiple

Table 11.7 Characteristics of specialty pharmaceutical[130]

High cost
Developed using biotechnology/recombinant technology
Requires specific, detailed patient education on administration of the drug
Administered as a self-injectable
Office-administered injectable or self-infused
Administered orally (often as a monoclonal antibody)
Requires special handling, such as refrigeration storage, inventory, or distribution
Limited distribution
Used to treat complex genetic diseases that require special monitoring and therapy management
Often times, is an orphan drug used to treat rare diseases
Requires high-touch service model, complex care and continuous patient management
Used in the treatment of specific diseases including but not limited to:
Crohn's disease
Growth hormone deficiency
Hemophilia, von Willebrand disease and other bleeding disorders
Hepatitis C
Hereditary angioedema
HIV/AIDS
Immune disorders
Lysosomal (metabolic) storage disorders (LSDs)
Multiple sclerosis (MS)
Neuroimmunological disorders (e.g., CIDP, Guillain Barré)
Oncology
Pulmonary arterial hypertension (PAH)
Psoriasis
Respiratory syncytial virus (RSV)
Rheumatoid arthritis (RA)
Transplant
Not managed under traditional outpatient prescription drug benefit

Adapted from [129,130]

medications a hepatitis C or an HIV/AIDS patient may take where monthly costs can exceed $4,000. Traditionally, specialty drugs are used to treat relatively small numbers of patients who have rare, chronic and oftentimes genetic or orphan diseases. These drugs require special handling and clinical monitoring and are very expensive, ranging from $10,000 to over $250,000 per year.

Pharmacists in academia

Pharmacists in academia, like other academicians, have responsibilities in the categories of teaching; scholarly/research activity; patient care; and service to their department, college, and/or university. Within most colleges of pharmacy, there are faculty members in tenure-track positions and those in non-tenure-track positions, whereas some colleges are non-tenure granting institutions only. The choice to pursue a given academic appointment track is based on the individual's preference to focus on a specific aspect of academia, as well as the university's expectations of that faculty member. That is, some individuals may prefer the classroom setting focusing on teaching, whereas others prefer involvement in patient care and service. Tenure-track faculty are expected to be more productive in the area of scholarship, with less time devoted to patient care than non-tenure-track faculty.[133] According to the AACP, for colleges that do offer both tracks of academic appointments, 53% of pharmacy faculty are either tenured or are in a tenure-track position.[134] When considering the discipline of pharmacy practice as a whole, where the vast majority of individuals are pharmacists, 34% of these faculty members are tenured or in tenure-track positions.

However, the majority (65%) of pharmacy practice faculty members are in contractual, non-tenure-track positions.[134] These tracks are often defined as "clinician-educator" positions, where individuals may have an annual contract agreement or "rolling" agreements of various time length (e.g., 4 year renewal). The number of non-tenured faculty, including clinical faculty members, continues to rise. During the 1991–1992 academic year, 22% of all faculty members were in non-tenure-track positions, compared to 42% of faculty members in such positions in 2004–2005.[135] In 2010–2011, 47% of pharmacy faculty members were in non-tenure-track positions.[134] This rise in non-tenured faculty most likely reflects the increasing curricular need for academicians with expertise in clinical arenas, such as critical care, infectious diseases, internal medicine, cardiology, oncology, and other practice disciplines.

Typically, departments and divisions in colleges of pharmacy have guidelines for promotion and tenure, as well as guidelines for promotion of non-tenure-track faculty. A level of excellence is expected in primary categories (e.g., teaching, scholarly/research activity, patient care, service) to support promotion and tenure of a given faculty member. With respect to teaching, the "teaching load" may be calculated in different ways (e.g., lecture contact hours, student credit hours: course credit hours multiplied by the number of students in that course). For pharmacy practice faculty, the number of weeks precepting students per year are also included. Of note, most pharmacy faculty (tenured and non-tenured) may not have been "taught to teach." Thus, they require professional development support from their institutions to gain experience in pedagogy and scholarly activity. A few of these faculty members may have had teaching requirements or experiences in their graduate school or residency programs, which gives them some formal teaching experience prior to taking a faculty position.

Professional practice or patient care responsibilities necessary for promotion may include evidence of substantial commitment to pharmaceutical care (e.g., time commitment and duration of service), leadership in practice policy and protocol development, participation in activities to ensure the optimal use of medications, publication of scholarly articles concerning professional practice, efforts to maintain professional competence, and presentations of educational programs. A faculty member's workload may constitute all of the aforementioned metrics, as well as other institution-specific requirements.

Evaluation of scholarly/research activity may include the number of manuscripts a faculty member publishes annually in peer-reviewed journals and/or in other professional publications. Other types of publications that may be considered scholarly include books, book chapters, and continuing professional education articles, among others. Research efforts in the realm of scholarly activity include the number

of federal and/or non-federal grants submitted and approved/funded, as well as grant dollar amounts. Scholarly activity also includes presentations made (e.g., "podium/poster presentations" at meetings, invited lectures, and continuing professional education presentations at the local, state or national level).

The service component of a faculty member's responsibility would include university and school committee work, as well as other types of professional and community service (e.g., advising student organizations, holding leadership positions in a professional organization). Typically, pharmacists' service to the profession, in academia, means participating in intra- and inter-professional organizations (e.g., the American Pharmacists Association (APhA), the American Society of Health-Systems Pharmacists (ASHP), American Associations of Colleges of Pharmacy (AACP), the American College of Clinical Pharmacy (ACCP), and the American Public Health Association (APHA), among others). Further, academic pharmacists may hold many leadership positions in these organizations. This provides a critical link between professional organizations and academia.

Those pharmacists in academia on tenure-track appointments, like other academicians, strive for promotion and tenure over a 6-year period and typically apply for promotion with tenure at the time of advancement from the rank of assistant professor to the rank of associate professor (e.g., the 7th year). Once the rank of associate professor is achieved, the pharmacist academician may strive to attain the highest academic rank of "full professor," which acknowledges a national and international reputation through continued outstanding teaching, scholarly/research activity and service for their contributions to their specific discipline, and continued professional growth. These individuals are recognized nationally or internationally for their expertise. There is no defined time frame to be promoted from associate to full professor.

Similar teaching, scholarly activity, and service expectations exist for non-tenure-track faculty members. However, requirements, as far as the number of items in each category, are scaled down for these individuals, to account for the additional patient care/clinical responsibilities. These pharmacy clinician-educators in academia are also heavily involved in experiential education and responsible for teaching the student to apply basic science and clinical knowledge to pharmacy practice.[136] A study published in 2002 investigated faculty member commitment to the categories of teaching, scholarly activity, service, and patient care for tenure-track individuals versus non-tenure-track individuals in pharmacy practice departments (Table 11.8).[133]

Table 11.8 Responsibilities for pharmacy practice faculty in tenure and non-tenure tracks

Discipline	Tenure track	Non-tenure track
Number of weeks per year precepting students	26 + 9.4 (n = 48)	34.1 + 6.8 (n = 49)
Number of clerkship students per year	12.1 + 6.0 (n = 47)	16.5 + 6.3 (n = 47)
Number of didactic hours taught per year	34.8 + 23 (n = 47)	29.5 + 24 (n = 47)
Number of peer-reviewed articles published per year	1.7 + 1.3 (n = 48)	0.6 + 0.7 (n = 48)
Number of committees assigned to per year	2.2 + 0.9 (n = 48)	1.8 + 0.9 (n = 48)

n, Number of pharmacy practice departments responding.[133]
(From Glover ML, Deziel-Evans L. Comparison of the responsibilities of tenure versus non-tenure track pharmacy practice faculty. *Am J Pharm Ed* 2002; 66: 388–391.)

Nutrition in pharmacy practice

Diet and nutritional status are the foundations of good health and well-being. Nutrition consists of a complex system of macronutrients, vitamins, minerals and fluids that are essential for growth and development. Many chronic diseases such as osteoporosis, cancer, and coronary artery disease have dietary associations. Health-care practitioners need to be aware of the importance of proper nutrition in disease prevention and the interrelationships of the biochemical roles of nutrients and their impact on deficiency states and disease processes.

Nutrients and associated substances

In both general and specialty practice pharmacists in a variety of settings are called upon to care for patients

requiring nutrient-related interventions. Nutrition is rarely the primary problem for these patients; rather an underlying disease process, condition or therapeutic regimen compromises nutrition status or results in outright nutrient deficiencies. For other patients preventative care and disease risk reduction may be the goal. In either case *nutritional pharmacotherapy* represents an integration of the principles of pharmacotherapy with the pharmaceutical sciences and clinical nutrition. It involves the evaluation and implementation of the best therapeutic plan for the patient in which dietary supplements, enteral nutrition, or parenteral nutrition may be necessary. This is built on a longstanding history of using food, containing traditional nutrients and associated bioactive substances, to manage human conditions. In recent years more attention has been given to the specific aspects of the diet that not only prevent deficiencies but also can be used to prevent chronic disease, augment growth and development, and treat select disorders of health. It is valuable to appreciate that nutrients and associated substances may be delivered in fresh foods, processed and fortified foods, dietary supplement products, medical foods, and drugs. With the exception of food these are all pharmaceutical preparations.

Nutrients and associated substances found in foods or pharmaceutical "delivery systems" are physiologically active substances. The chemical structure and structure–activity relationships of individual nutrients are no different than any other natural or synthetic drug. In fact the kinetic behavior of some nutrients is more complex than that of many drugs. Nutrient bioavailability can vary greatly with the delivery vehicle and dosage form. Additionally nutrient absorption, distribution, and elimination will vary with an individual's nutrition status. Dietary supplement products may contain nutrients or associated substances as the sole ingredient, but more often are included in multi-ingredient products. The latter sometimes combine nutrients with botanical and other non-nutrient ingredients. Meal replacement formulas and medical foods intended for patients unable to consume adequate nourishment orally are additional delivery vehicles for nutrients and associated substances. Some nutrients are found as drug products – in oral and parenteral dosage forms. These nutrient-containing products are often intended for specific disorders. Parenteral nutrients can be combined to form a parenteral nutrient admixture used to support patients unable to otherwise take or assimilate nutrients through the gastrointestinal tract.

There exists a nutrition continuum from health to disease, across the life cycle, in which pharmacists have become involved based on their knowledge set and clinical opportunity. Even many inherited metabolic disorders require close attention with nutrient manipulation. Particularly in the field of nutrition, where misinformation may endanger the health of individuals, consumers must be provided opportunity to learn to make sound decisions regarding their health and nutrition status. Pharmacists can be involved in educating patients on various aspects of nutrition, screening patients for poor nutrition status, suggesting referral to other healthcare providers for more specific needs, and managing therapeutic regimens that contain dietary supplements, enteral nutrition, or parenteral nutrition. Furthermore, depending on the setting, pharmacists may be involved in clinical or basic research that involves nutrients and associated substances. Pharmacists can be involved to varying degrees in helping consumers and patients alike with preventive strategies as well as therapies involving nutrients.

Veterinary pharmacy

Scope of veterinary pharmacy practice

In 1977, a survey of agricultural sector veterinarians[137] demonstrated the need for pharmacist involvement in veterinary medicine and recommended the establishment of a veterinary pharmacy specialty that required specialized education and examination for licensure. More than three decades after this recommendation, the Board of Pharmaceutical Specialties (BPS) does not yet recognize veterinary pharmacy as a pharmacy specialty practice. However, veterinary pharmacy certainly qualifies for consideration in light of BPS's overriding concern to "ensure that the public receives the level of pharmacy services that will improve a patient's quality of life."[138] BPS's stated concern does not characterize patients as being limited to the human species, and society expects a competent performance from pharmacists when providing pharmaceutical care for all family members, human

or otherwise. As human reliance on animals increases (e.g., companionship, service, research, food, agribusiness, and entertainment), most pharmacists will eventually find themselves providing some degree of pharmaceutical care and drugs to a non-human patient. Many pharmacists have devoted a large portion, if not all, of their professional practice to providing pharmaceutical expertise and specialized skills to caring for animals. Pharmacists desiring to effectively participate in animal care have many career options. The current scope of veterinary pharmacy practice includes, but is not limited to, veterinary academia, veterinary specialty referral centers, community and online (Internet) pharmacies, the pharmaceutical and agricultural industry, and governmental public health and regulatory sectors.

Veterinary teaching hospitals

The most well-established practice of veterinary pharmacy resides in veterinary academic teaching hospitals. Pharmacists in these roles provide expertise in areas of service (drug selection, distribution, and control), teaching (didactic, incidental exchanges, client counseling, in-service education, and continuing education programs for pharmacists and veterinarians), and research (clinical trial development and administration, compounded preparation quality assurance, adverse drug reaction and medication error reporting, publication of articles in scientific and professional journals, and drug information query requests). A typical day for a veterinary teaching hospital pharmacist involves rounding with clinical faculty, house officers, and students; preparing and delivering lectures for veterinary, pharmacy, and veterinary technology students; providing drug utilization review and therapeutic interventions; maintaining hospital pharmacy operations (inpatient and outpatient drug distribution, preparing sterile and nonsterile compounds, admixture of intravenous and chemotherapeutic therapies); and engaging in a variety of incidental teaching and consultative activities with students, veterinary practitioners, and animal owners.

Veterinary specialty referral centers

Increasingly, veterinary specialty referral centers are employing veterinary pharmacists. Interventions by these pharmacists have a direct and positive impact on patient care, patient well-being, and practice revenue.[139] Some veterinary pharmacists in these settings are species specialists and are noted for their expertise and skills in providing pharmaceutical care for a single species, such as pharmacists caring for horses in exclusively equine veterinary practices. A typical day for a veterinary specialty referral center pharmacist involves many of the distributive and consultative duties that are performed by the veterinary teaching hospital pharmacist but with less emphasis on teaching or research.

Community pharmacy

One of the most rapidly growing areas of veterinary pharmacy practice is in the community pharmacy setting. When the Animal Medicinal Drug Use Clarification Act of 1996 codified the extra-label use of human drugs in animals, veterinarians began prescribing more and more human drugs for use in animal patients. As a result, pharmacists in chain and independent pharmacies were presented with an unprecedented number of prescriptions for animals. The professional rewards of helping animals combined with the financial rewards of cash-paying customers caused community pharmacists to focus more on the animal prescription market. Independent pharmacies began collaborating with veterinarians to provide compounded preparations for animal patients, and large retail chains began allowing pets into the discounted generics plans traditionally offered for human prescriptions. The result has been the emergence of several veterinary-only pharmacies catering solely to animal patients, and most recently, veterinary-only online pharmacies are beginning to become more prevalent.

Industry (pharmaceutical, agricultural)

Pharmacists with veterinary expertise are also valuable to the animal health industry. Because of their unique training that combines pharmacological expertise, clinical decision making, and marketing skills, pharmacists with specialized veterinary training make excellent professional representatives for the veterinary pharmaceutical industry. They can easily explain the pharmacodynamics and clinical advantages of new drugs to veterinarians and can serve as consultants for adverse event monitoring and reporting. Veterinary pharmacists also serve a role in research and

development in the veterinary pharmaceutical industry and design and oversee pre- and post-marketing clinical trials for veterinary drugs. Many veterinary pharmacists also possess an expertise in livestock animal medicine and are contracted by producers to consult in areas of medication management, specialized compounding, and avoidance of drug residues in the tissues of food-producing animals. As pharmacists are well trained in pharmacokinetic principles, they are able to collaborate with producers to predict drug depletion profiles for therapeutic agents used in food-producing animals.

Government sectors (FDA, CDC, NIH, disaster relief)

Veterinary pharmacists are also impacting the governmental and regulatory sectors. The Center for Veterinary Medicine of the Food and Drug Administration (FDA CVM) employs many veterinary pharmacists in areas of compliance, surveillance, adverse event reporting, and medication error prevention. The Centers for Disease Control and Prevention (CDC) also employ veterinary pharmacists who are charged with overseeing the distribution and use of biological agents and drugs used to prevent or treat rare diseases that are zoonotic between animals and humans. The National Institutes of Health (NIH) employ a veterinary pharmacist responsible for providing drugs, compounds, and consultation for research animals in NIH funded protocols. This pharmacist focuses his/her efforts on minimizing the stress that drug administration can cause to research animals, and has developed combination drug dosage forms and transmucosally absorbed drugs for nasal and buccal administration.

Veterinary pharmacists also serve on disaster relief teams. These specially trained pharmacists are parts of multidisciplinary teams of veterinarians, veterinary technicians, and pharmacists. Regional teams of disaster relief veterinary professionals remain on alert and are deployed to stricken areas to provide triage, care, and treatment for displaced and injured animals. One of the largest deployments of a Veterinary Medical Assistance Team (VMAT) was during the hurricane Katrina recovery in 2005 and involved many veterinary pharmacists.

Extemporaneous prescription compounding

Historically, pharmaceutical compounding was the beginning of pharmacy and has been an integral part of pharmacy practice throughout its history. This is demonstrated by some definitions and references to pharmacy, including:

- Pharmacy is the art or practice of preparing and preserving drugs and of compounding and dispensing medicines according to the prescriptions of physicians.[140]
- Pharmacy is (1) the art or practice of preparing, preserving, compounding, and dispensing drugs or (2) a place where medicines are compounded or dispensed.[141]
- Pharmacy is the science, art, and practice of preparing, preserving, compounding, and dispensing medicinal drugs and giving instructions for their use.[142]
- And thou shalt make it an oil of holy ointment, an ointment compounded after the art of the apothecary; it shall be an anointing oil.[143]
- Even today, the definitions of pharmacy include the preparation of drugs.[144,145]

The heritage of pharmacy, spanning some 5000 years, has centered around the provision of pharmaceutical preparations for patients. Pharmacists are the only healthcare professionals that possess the knowledge and skill required for compounding and preparing medications to meet the unique needs of patients. The responsibility of extemporaneously compounding safe, effective prescription preparations for patients who require special care is fundamental to the pharmacy profession.

The nineteenth century saw more consistency in compounding formulations through the establishment of the *United States Pharmacopeia* (USP). In the twentieth century, it has been estimated that a broad knowledge of compounding was still essential for 80% of the prescriptions dispensed in the 1920s. The middle part of the century did not see an end to the art and science of compounding, but it did give way to newer technology, allowing for manufactured products. In the latter part of the century,

a broad knowledge of compounding was still essential. In the twenty-first century, a broad knowledge of compounding is essential and will become even more so with more individualized medication prescribed in the field of biologics.[140]

The pharmaceutical industry began to take over the production of most medications used by the medical profession. In many ways, this has provided superior service, new methods, and a vast array of innovative products that could not have been provided on a one-on-one basis. Research and development have been the hallmarks of pharmaceutical manufacturers. However, the very nature of providing millions of doses of a product requires the dosage forms (e.g., capsules, tablets, suppositories) and doses (individual strengths of each dose) be limited and results in a one-sided approach to therapy. In the twenty-first century, it is no longer economical for a pharmaceutical company to manufacture a product in several doses or in several dosage forms to meet the needs of the entire range of patients receiving therapy. Marketing strategies determine the majority of patient needs, but the very nature of the process cannot meet all patient needs.

We must also recognize that some individuals and their healthcare needs do not fall in the windows of theoretical dosage strength and dosage forms and that large-scale manufacturers cannot cost-effectively tailor-make a medication for a handful of patients and meet the ever-changing needs of a given patient, disease state, or institution. The skills of pharmacists practicing compounding fill this gap to meet individualized needs. By this assessment, the pharmacist may, through understanding of the principles of compounding and recognition of their skill level in working *secundum artem*, recommend therapy be provided that is not provided by the pharmaceutical industry but that is individualized for a specific patient's needs at a specific time.

Compounding has always been a basic part of pharmacy practice; the drugs, dosage forms, and equipment or techniques used are the variables. Pharmacists possess knowledge and skills that are unique and not duplicated by any other profession. Pharmacy activities to individualize patient therapy include compounding and clinical functions. Either function in the absence of the other results in placing pharmacy in a disadvantaged position. It is important to use a pharmacist's expertise to adjust dosage quantities, frequencies, and even dosage forms for enhanced compliance. All pharmacists should understand the options presented by compounding.

Pharmaceutical compounding is increasing for a number of reasons, including the availability of a limited number of dosage forms for most drugs, a limited number of strengths of most drugs, home healthcare, hospice, the non-availability of drug products/combinations, discontinued drugs, drug shortages, orphan drugs, new therapeutic approaches, and special patient populations (e.g., pediatrics; geriatrics; bioidentical hormone replacement therapy for postmenopausal women and andropause in men; thyroid patients; pain management; dental patients; environmentally and cosmetic sensitive patients; sports injuries; limited distribution system drugs; and veterinary compounding, including small, large, herd, exotic, and companion animals).

Newly evolving dosage forms and therapeutic approaches suggest that compounding of pharmaceuticals and related preparations, specifically for individual patients, will become more common in pharmacy practice. Compounding pharmacy is unique, as it allows the compounding pharmacist to use much of their scientific, mathematics, and technology background to a fuller extent. Compounding pharmacists develop a special and unique relationship with the patients they serve. They work hand-in-hand with physicians to solve problems not addressed by commercially available dosage forms.

In institutional healthcare environments there is quite a bit of batch production of sterile and nonsterile preparations performed to meet individual patients' needs or prescribers' clinical investigational protocols. Many institutions are now outsourcing some of their compounding to specialty pharmacies specially equipped to address changing patterns of drug therapy. Some of this results from the impact of the new USP standards enhancing the facility, equipment, personnel, and process requirements.

The compounding pharmacist

Pharmacists are unique professionals: well trained in the natural, physical, and medical sciences and sensitized to the potential tragedy that may result from a single mistake that may occur in the daily practice

of their profession. Pharmacists have developed the reputation of being available in the local community to interact with patients, provide needed medications, and work with patients to regain or maintain a certain standard or quality of health, as well as just being there in time of need.

Pharmacy is a complex mixture of different practices and practice sites. No longer is pharmacy simply community pharmacy or hospital pharmacy. Pharmacy is diverse and offers many opportunities for those willing to look around, find their niche, and practice pharmacy to meet the needs of their own community of patients. Most compounding pharmacists appear interested and excited about their practices. In fact, many pharmacists intimately involved in pharmaceutical care have now realized the importance of providing individualized patient care through the preparation of patient-specific preparations. Compounding pharmacy is not for everyone, but, as it grows, it will provide for an increasingly significant number of pharmacists the excitement and fulfillment of using their innovative and creative skills to help solve patient problems.

As mentioned, pharmaceutical compounding requires the use of training in mathematics, science, and technology more than some of the other practices of pharmacy. It has been stated that:

"The sciences are what support pharmacy's expertise in drug distribution and drug use. Recent history leads one to question whether we in the profession, and some in pharmaceutical education, recognize and appreciate the contribution that the pharmaceutical sciences have made and continue to make to the pharmacy profession and health care. The pharmaceutical sciences are what make us unique. They provide us the special value that we bring to the bedside. No other health professional is capable of bringing to the pharmacotherapeutic decision-making table such concepts as pH, particle size, partition coefficient, protein binding, structure-activity relationships, economics, and epidemiology. The pharmaceutical sciences, combined with pharmacy's infrastructure, including pharmaceutical education, are what make the pharmacist an indispensable participant on the health care team."[146]

And what area of pharmacy practice has the opportunity of using the scientific education and training as much as pharmacists involved in individualizing patient care through extemporaneous compounding? The pharmaceutical sciences, especially chemistry and pharmaceutics, serve as the foundation for pharmacists' ability to formulate specific dosage forms to meet patients' needs.

Definitions

Pharmacy is united in the sense that pharmacists have a responsibility to serve their patients and compound an appropriately prescribed preparation in the course of their professional practice. It is the right and responsibility of pharmacists to compound medications to meet the specific needs of patients. Pharmacists are ultimately responsible for the integrity of the finished preparation compounded under their immediate supervision.

Compounding has been defined by the USP as: the preparation, mixing, assembling, altering, packaging, and labeling of a drug, drug-delivery device or device in accordance with a licensed practitioner's prescription, medication order, or initiative based on the practitioner/patient/pharmacist/compounder relationship in the course of professional practice. Compounding includes the following:

- Preparation of drug dosage forms for both human and animal patients
- Preparation of drugs or devices in anticipation of prescription drug orders based on routine, regularly observed prescribing patterns
- Reconstitution or manipulation of commercial products that may require the addition of one or more ingredients
- Preparation of hazardous drugs or devices for the purposes of, or as an incident to research (clinical or academic), teaching, or chemical analysis
- Preparation of drugs and devices for prescriber's office use where permitted by federal and state law.[147]

Compounding may hold different meanings to different pharmacists. It may mean the preparation of oral liquids, topical creams/ointments, and suppositories; the conversion of one dose or dosage form into another; the preparation of select dosage forms from bulk chemicals; the preparation of intravenous admixtures, parenteral nutrition solutions, pediatric

dosage forms from adult dosage forms; the preparation of radioactive isotopes; the preparation of cassettes, syringes, and other devices with drugs for administration in the home setting; or compounding for animal patients.

There are two different types of compounded prescriptions, including the extemporaneous and the batch prepared. The extemporaneous prescription is one that is unexpected or one the pharmacist may expect to receive on a fairly routine basis on a small scale. The batch prepared prescription is one in which multiple identical units are prepared as a single operation in anticipation of the receipt of prescriptions. There may be some benefits to quality, if preparation protocols are on file or standardized preparations are established based on stability, to decrease medication errors.

Finally, the USP uses the term "preparation" for a compounded drug dosage form or dietary supplement or a device to which a compounder has introduced a drug. The term "product" is used to describe a manufactured pharmaceutical dosage form.

Evaluating the need

When considering whether to compound a prescription, one might wish to consider the following questions:

1. Is a product commercially available in the exact dosage form, strength, and packaging?
2. Is the prescription rational, concerning the ingredients, intended use, dosage, and method of administration?
3. Am I qualified to prepare this prescription by education, skill development, and expertise?
4. Do I have the proper equipment, supplies, and chemicals or drugs?
5. Is there documentation for assigning a beyond-use date for the prescription preparation, or do I use the guidelines delineated in USP Chapters <795> and <797>, *Pharmacy Compounding – Nonsterile Preparations* and *Pharmacy Compounding – Sterile Preparations*, respectively?
6. Is there an alternative by which the patient will receive a benefit?
7. Will this compounded preparation satisfy the intent of the prescribing physician and meet the needs of the patient?
8. Is there a bona fide prescriber–pharmacist–patient relationship?
9. Does the patient have the necessary storage facility, if required, to assure potency of the preparation until its beyond-use date?
10. Can I perform the necessary calculations to compound the preparation formula?
11. Am I willing to complete the necessary documentation to compound the preparation?
12. Is there a literature reference that might provide information on use, preparation, stability, administration, etc.?
13. How long will the patient be using the preparation, and what is the expected duration of therapy consistent with an appropriate beyond-use date? Alternatively, should the preparation be compounded in small quantities and dispensed to the patient in short time intervals?
14. Can I do some basic quality control to check the preparation prior to dispensing (e.g., capsule weight variation, pH, visual observations, smell)?
15. Am I assured of ingredient identity, quality, and purity?
16. What procedures do I have for investigating and correcting out of specifications preparations?
17. Are the physical, chemical, and therapeutic properties of the individual ingredients consistent with the expected properties of the ordered drug preparation?[148]

Evaluating the feasibility of batch compounding

The following questions may be considered prior to batch compounding activities:

1. Will the processes, procedures, compounding environment, and equipment used to prepare this batch produce the expected qualities in the finished preparation?
2. Will all the critical processes and procedures be carried out exactly as intended for every batch of the compounded preparation to produce the same high-quality preparation in every batch?
3. Will the finished preparation have all the qualities as specified, on completion of the preparation and packaging of each batch?
4. Will each batch retain all the qualities within the specified limits, until the end of the labeled

beyond-use date (i.e., is it chemically, physically, and microbiologically stable?)

5. Can I monitor and trace the history of each batch, identify potential sources of problems, and institute appropriate corrective measures to minimize the likelihood of their occurrence?
6. Do I have a program of potency testing in place?[148]

Pharmacists who perform batch compounding should be capable and willing to do so properly, particularly when performing sterile compounding. Trends indicate that more batch compounding may occur in more pharmacies in the future.

Economic considerations

There are, at least, two different economic considerations in making the decision to compound prescriptions; these include (1) pharmacist compensation and (2) healthcare costs.

Pharmaceutical compounding is a cognitive service; hence, cognitive services reimbursement is justified. In the same manner as a surgeon uses cognitive, technical, and manipulative skills, so does the pharmacist use cognitive, technical, and manipulative skills in extemporaneous compounding to meet individualized patient needs. The pricing of a compounded prescription should include consideration for pharmacodynamic and pharmacotherapeutic decision making, formulation expertise, time, reimbursement of materials, and the use of facilities and equipment. Compounding prescriptions can be attractive professionally and financially. Historically, it has been said that compounding is an act whereby the professional and scientific knowledge of a pharmacist can find its expression. For those pharmacists dedicated to doing a quality job in compounding, the professional, psychological, and financial rewards can be substantial.

Compounding prescriptions can be a way of lowering the cost of drug therapy. In some cases, it is less expensive for the pharmacist to prepare a specific prescription for the patient, which may mean the difference between the patient actually obtaining the drug or doing without it. If compounding a prescription results in a patient being able to afford the drug therapy, it must be considered. In hospitals, it is less expensive to prepare an intravenous admixture for administering multiple drugs as compared to involving nursing time to administer multiple single drugs.

Another example concerns the economic use of expensive drug products. Some drug products are expensive and may have short shelf-lives. If a patient does not need the entire contents of a vial or dosage unit, in many cases, the remaining drug product is discarded and wasted. However, there are numerous instances in which the pharmacist can divide the commercial product into smaller, usable units, store it properly, and dispense the required quantity on individual prescriptions. Compounding can include the repackaging of drug products into smaller packages suitable for patient use.

Another obliquely related economic question can be addressed regarding the commercialization of compounded preparations. Over the years, it has been interesting to note that many compounded preparations, eventually, become commercially manufactured products. Examples include:

- Fentanyl Lozenges
- Minoxidil Topical Solution
- Nystatin Lozenges
- Clindamycin Topical Solution
- Dihydroergotamine Mesylate Nasal Spray
- Buprenorphine Nasal Spray
- Buffered Hypertonic Saline Solution
- Erythromycin Topical Solution
- 17P-Hydroxyprogesterone Caproate Injection
- Testosterone Topical Gels
- 4-Aminopyridine Capsules (Fampridine)
- Nitroglycerin Rectal Ointment
- Colchicine Injection

as well as numerous other dermatological and pediatric oral liquids and some premixed intravenous solutions. It is inevitable that a very stable, compounded preparation will become a manufactured product, when it becomes economically profitable for a pharmaceutical manufacturer to produce it.

Compounding factors

Stability

One key factor in compounding prescriptions is stability. The more common types of stability of which compounding pharmacists should be aware are

chemical, physical, and microbiological. Whereas commercially manufactured products are required to possess an expiration date, compounded preparations are assigned a beyond-use date. There are numerous sources of information that can be used for determining an appropriate beyond-use date, such as chemical companies, manufacturers' literature, laboratory data, journals, and published books on the subject. Most pharmacists prepare or dispense small quantities of compounded preparations and recommend storage at room, cool, or cold temperatures.

The standards published in the USP 35/NF 30 Chapter <795>, Pharmacy Compounding – Nonsterile Preparations, explain that: "In the absence of stability information that is applicable to a specific drug and preparation, the following maximum beyond-use dates are recommended for nonsterile compounded drug preparations that are packaged in tight, light-resistant containers and stored at controlled room temperature unless otherwise indicated; and for sterile preparations for which a program of sterility testing is in place."

For nonaqueous formulations

The beyond-use date is not later than the time remaining until the earliest expiration date of the active pharmaceutical ingredient (API) or 6 months, whichever is earlier.

For water-containing oral formulations

The beyond-use date is not later than 14 days, when stored at controlled cold temperatures.

For water-containing topical/dermal and mucosal liquid and semisolid formulations

The beyond-use date is not later than 30 days.

These maximum beyond-use dates may be exceeded, when there is supporting valid scientific stability information directly applicable to the specific preparation (e.g., the *same* drug concentration range, pH, excipients, vehicle, water content).[147]

The standards published in the USP 35/NF 30 Chapter <797>, Pharmacy Compounding – Nonsterile Preparations, for beyond-use dates relate the beyond-use date to the risk level of the compounded sterile preparations (CSPs).

For low-risk preparations

In the absence of passing a sterility test, the storage periods cannot exceed the following time periods, provided that, before administration, the CSPs are properly stored and are exposed for not more than 48 hours at controlled room temperature, for not more than 14 days at a cold temperature, and for 45 days in solid frozen state between −25°C and −10°C.

For medium-risk preparations

In the absence of passing a sterility test, the storage periods cannot exceed the following time periods, provided that, before administration, the CSPs are properly stored and are exposed for not more than 30 hours at controlled room temperature, for not more than 9 days at a cold temperature, and for 45 days in solid frozen state between −25°C and −10°C.

For high-risk preparations

In the absence of passing a sterility test, the storage periods cannot exceed the following time periods, provided that, before administration, the CSPs are properly stored and are exposed for not more than 24 hours at controlled room temperature, for not more than 3 days at a cold temperature, and for 45 days in solid frozen state between −25°C and −10°C.

Quality control

One of the fastest growing and most important areas of pharmaceutical compounding is that of quality control. Quality must be built-in to the preparation from the beginning steps to evaluating the final preparation. USP 35/NF 30 Chapter <1163> Quality Assurance in Pharmaceutical Compounding has been newly revised and is official. The chapter discusses the composition of a quality assurance program that should include, at least, the following nine separate but integrated components: (1) training; (2) standard operating procedures (SOPs); (3) documentation; (4) verification; (5) testing; (6) cleaning, disinfecting, and safety; (7) containers, packaging, repackaging, labeling, and storage; (8) outsourcing, if used; and (9) responsible personnel.

There are several quality control tests that can be done within the pharmacy, and others can be sent to a contract laboratory. The following quality control tests can be considered for the respective dosage forms:

1. *Oral and Topical Liquids (solutions, suspensions, emulsions)* – Weight/volume, pH, specific gravity, active drug assay, globule size range, rheological properties/pourability, physical observation (color, clarity), and physical stability (discoloration, foreign materials, gas formation, mold growth)
2. *Hard Gelatin Capsules* – Weight–overall average weight, weight–individual weight variation, dissolution of capsule shell, disintegration and/or dissolution of capsule contents, active-drug assay, physical appearance (color, uniformity, extent of fill, locked), and physical stability (discoloration, changes in appearance)
3. *Ointments, Creams, and Gels* – Theoretical weight compared to actual weight, pH, specific gravity, active drug assay, physical observations (color, clarity, texture–surface, texture–spatula spread, appearance, feel), and rheological properties
4. *Suppositories, Troches, Lollipops, and Sticks* – Weight, specific gravity, active drug assay, physical observation (color, clarity, texture of surface, appearance, feel), melting test, dissolution test, and physical stability
5. *Parenteral Preparations* – Weight/volume, physical observation, pH, specific gravity, osmolality, assay, color, clarity, particulate matter, sterility, and pyrogenicity.

Compounding support

Numerous agencies, companies, and organizations are available to assist pharmacists in compounding. Information, chemicals, supplies, and equipment are readily available. Chemical and supply companies have increased in size and number in recent years, and many provide information on compounding, incompatibilities, and stability. Specialty compounding organizations have developed over recent years and provide full-line services and products to the compounding pharmacist. Many national and international organizations provide continuing professional education programs in both nonsterile and sterile compounding.

These entities provide services to compounding pharmacists, ranging from selling a complete line of compounding supplies to providing only chemicals or compounding aids. Others offer additional services to include formulas, as well as consulting expertise by telephone or via the Internet. This service can assist in the process of compounding a particular preparation that may be difficult.

Training and experience

Pharmacists involved in upgrading and enhancing the traditional aspects of extemporaneous compounding need to keep current with all the new tools of their trade, retrieve the old from storage, and put in a bit of practice using their scientific background and techniques, before they will be comfortable in exhibiting their skills.

Because there is an expectation that pharmacists can compound, there is a need that pharmacists be able to compound. Due to the decrease in instruction in compounding pharmacy in colleges of pharmacy, graduating pharmacists may not feel comfortable in their ability to compound. They can be advised to seek training, if their practice may encompass compounding activities. The need for pharmaceutical compounding training and experience is addressed by short courses, continuing education, increased curricular requirements, and apprenticeships. Additional training areas for compounding are needed to provide the experience needed to compound prescriptions accurately and safely. Many pharmacists who compound become actively involved in the practicums and rotations of the colleges of pharmacy in their respective states.

Only properly educated and trained pharmacists should be involved in pharmaceutical compounding. If pharmacists wish to compound, they should participate in continuing professional education programs designed to properly train them, including the scientific basis and practical skills necessary for sound, contemporary compounding.

The practice of pharmacy is regulated by individual state boards of pharmacy. Pharmacy compounding is inherent in the practice of pharmacy; hence, it is governed in the United States by the state boards of pharmacy. Compounding is a part of the "practice of pharmacy" and is not a "product," consequently, traditional compounding does not come under the direct auspices of the FDA. Also, the FDA considers all compounded medications as "non-approved." Actually, there are many common medications on the

market that have never been FDA-approved, including the pre-1938 drugs, as well as any drug product that has been altered in any way not described in the labeling. Other examples of non-FDA-approved drugs include all intravenous admixtures and extemporaneous pediatric and geriatric formulations, and cancer cocktails, as well as others.

Equipment

The equipment needed will be determined by the type and extent of the services one provides. Many pharmacies already have clean air environments (e.g., laminar air flow hoods, isolation barrier systems) in which aseptic compounding of sterile solutions is performed. These same units can be used to compound other sterile preparations, such as eye drops. A balance, preferably electronic, is essential. Ointment slabs (i.e., pill tiles), along with spatulas of different types and materials, should be purchased. A few mortars and pestles (i.e., glass, ceramic, plastic, disposable) and some glassware should be secured. It may not be necessary to buy a roomful of equipment, but one should purchase what is needed to start the service and should build on it as the service grows and expands to different arenas.

Much of the equipment used today in compounding has changed. Today, electronic balances are used more often than torsion balances; micropipets are commonplace; and ultrafreezers are sometimes required in addition to standard refrigerator freezers. This area is constantly changing, and the compounding pharmacist should be aware of the available technology to prepare accurate and effective prescriptions. Becoming acquainted with the local representative for a laboratory supply company is helpful.

Environment

A separate area for traditional compounding is recommended, rather than simply cleaning off a small area of the dispensing counter. The compounder needs a clean, neat, well-lit, and quiet working area. If aseptic compounding is considered, a clean air environment (e.g., laminar air flow hood, isolation barrier system) should be used. The actual facility used depends on the level and volume of compounding done.

Formulas

Consistency of compounded preparations is important. Formulas should be developed or obtained and tried, to assure that each time an extemporaneous preparation is prepared the methods used, ingredients added, and the order of steps is documented. This accomplishes three things. First, it provides the methodology for each person involved or requested to provide such service the information necessary to do so properly. Second, it provides consistency from batch to batch. Third, if the preparation does not turn out the way expected, a stepwise methodology exists for reviewing and determining what happened and what revisions and improvements are needed.

Chemicals and supplies

If one is going to prepare a topical preparation, a vehicle (e.g., cream, ointment, gel) and the active pharmaceutical ingredients (e.g., either finely ground product from an available tablet or injection or pharmaceutical-grade chemicals) would be required. One needs proper dispensing containers for the medication. In short, a relationship with providers that carry chemicals and supplies is important.

Pharmacists have been using raw chemicals and other materials for prescription compounding throughout history. In the past, these chemicals and materials have been obtained from natural sources, raw materials, and household ingredients. Today, compounding pharmacists use chemicals from various reliable commercial sources, depending on their availability.

Some chemical companies place a disclaimer on their chemicals for various reasons, including, but not necessarily limited to:

1. The companies do not want to be required to provide complete labeling of the materials as required by the Food Drug and Cosmetic (FD&C) Act; consequently, they state they are not to be used as drugs. This exempts the companies from having to comply with the FD&C regulations.
2. The source of the chemicals may not be companies meeting current Good Manufacturing Practices; consequently, when the drugs are repackaged,

only selected information concerning the level of potency, impurities, and other miscellaneous characterization data is provided.

3. The disclaimer is to protect the companies from the use of their supplies, without the full compendial-type testing, as required by the FDA for drug ingredients for manufacturing.

Historically, the FD&C Act has not applied to chemicals used for pharmaceutical compounding, but it does apply to chemicals used for manufacturing. The selection of the chemical source for compounding is a judgment call on the part of pharmacists. When selecting a supplier of compounding chemicals, certificates of analysis should be obtained and reviewed for purity and impurities, as part of the decision-making process.

Chapter <795> Pharmacy Compounding–Nonsterile Preparations in USP 35/NF 30 is summarized here as follows:[147]

A USP, NF, or Food Chemicals Codex (FCC) substance is the recommended source of ingredients for compounding all drug preparations. If that is not available, the use of another high-quality source, such as analytical reagent (AR) or certified American Chemical Society (ACS) grade, is an option for professional judgment. If the substance is not an official preparation or substance, additional information, such as a certificate of analysis, should be obtained by the pharmacist to ensure its suitability.

A manufactured drug product may be a source of active ingredient. Only manufactured drugs from containers labeled with a batch control number and a future expiration date are acceptable as a potential source of active ingredients. When compounding with manufactured drug products, the pharmacist must consider all ingredients present in the drug product relative to the intended use of the compounded preparation. There are issues when compounding with commercial products, however.

USP standards for pharmaceutical compounding require the API be present in an amount equal to 90.0 to 110.0% of the label. This can pose a problem, when compounding using commercially manufactured products, due to the variation in allowable strengths by USP dosage form monographs (and overfills) or from the standards set in the individual New Drug Approval (NDA).

Compounding using manufactured products can place the pharmacist in a situation in which the final preparation may not be in compliance with the USP standards. The pharmacist has no way of knowing what the actual allowable range of the API may be in the manufactured product or of its actual analyzed potency. It may be 90.0 to 110.0%, or it may be 80.0 to 120.0%, or even a broader or different range. If the pharmacist does not know what the "actual" potency of the API is in the commercial product, then there is a possibility that the compounded preparation will be outside the allowable USP standards. Obviously, in many clinical situations, this variation will not be significant, but it is important nonetheless. This situation occurs in all practice sites and involves both nonsterile and sterile compounding.

In recent years, "compounding kits" have become commercially available in which the ingredients for a specific compounded preparation are pre-weighed and each individual kit contains the necessary supplies for compounding. The kits are labeled with instructions to the pharmacist for compounding the preparation. For busy pharmacies, these kits can save time.

In summary, it is the responsibility of the pharmacist to select the most appropriate quality of chemical for compounding, beginning with the USP/NF as the first choice and, if this is not available, then descending the list of purity grades (Table 11.9), using professional judgment and discretion. A certificate of analysis for the chemicals should be obtained and kept on file in the pharmacy for these selected chemicals.[147,149]

Compounding information sources

Numerous sources are now available for compounding information, including books, journals, pamphlets, brochures, and electronic media. Some of these reference sources should be accessible by compounding pharmacies, including the following:

Pharmacy and medical libraries

Compounding databases

http://www.CompoundingToday.com

Table 11.9 Description of chemical grades

Grade	Description
Technical or commercial	Indeterminate quality
CP (Chemically Pure)	More refined, but still of unknown quality
USP/NF	Meets minimum purity standards; conforms to tolerances set by the USP/NF for contaminants dangerous to health
ACS reagent	High purity; confirms to minimum specifications set by the Reagent Chemicals Committee of the American Chemical Society
Analytical reagent	Very high purity
HPLC	Solvents purified for use in high-performance liquid chromatography (HPLC); very high purity
Spectroscopic grade	Very high purity
Primary standard	Highest purity; required for accurate volumetric analysis (for standard solutions)

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United States Pharmacopeia 35/National Formulary 30. United States Pharmacopeial Convention, Rockville, MD, 2012.

Journals

Australian Journal of Hospital Pharmacy
Canadian Journal of Hospital Pharmacy
European Journal of Hospital Pharmacy
International Journal of Pharmaceutical Compounding
Journal of the American Society of Health-System Pharmacists
Lippincott's Hospital Pharmacy
Pharmacy Times
Secundem Artem
The Annals of Pharmacotherapy
US Pharmacist
Pharmaceutical manufactures
Package insert information

Compounding types

Ambulatory-care compounding

If individuals can walk, they are considered mobile or ambulatory (i.e., not bedridden). Consequently, most pharmacists are involved in ambulatory care, and most ambulatory patients are outpatients. Actually, the term can also be applied to homecare patients and even institutionalized patients who are mobile. One general characteristic of ambulatory patients is that they are responsible for obtaining their own medication, storing it, preparing it (if necessary), and taking it.[150] It seems almost incongruous that in healthcare today, as we become more aware that patients are individuals, respond as individuals, and must be treated as individuals, that some healthcare providers appear to be grouping patients into categories. They are grouped in categories for treatment, for reimbursement from a third party, or for determining

levels of care in managed-care organizations and using fixed-dose products provided by pharmaceutical manufacturers that are available because the marketing demand is sufficiently high to justify their manufacture and production. Why should the availability or the lack of availability of a specific, economically profitable, commercially available product dictate the therapy of a patient?

Pharmacists have an opportunity to extend their activities in patient care as the emphasis continues to shift from inpatient care to ambulatory care. Ambulatory care, however, is so diverse and involves so many disciplines that it is sometimes difficult to understand, and it changes rapidly. Also, ambulatory care could encourage a team approach to health improvement, prevention, health maintenance, risk assessment, early detection, management, curative therapy, and rehabilitation.[151] Ambulatory care offers various opportunities for individualizing patient care through pharmaceutical compounding. In fact, it is the area in which most compounding pharmacists practice.

Pharmacists' roles in ambulatory care patients can include, among others:

1. Dispensing
2. Compounding
3. Counseling and compliance enhancement
4. Minimizing medication errors
5. Disease state management
6. Therapeutic drug monitoring
7. Minimizing expenditures.[150–152]

Most reimbursement for ambulatory patients comes from dispensing the product or the compounded preparation. Little financial consideration is given to counseling, minimizing medication errors, compliance enhancement, and therapeutic monitoring. However, these activities are important, and they all should be performed. Due to the unique nature of compounded medications, counseling is an absolute must for these patients.

From this discussion of the activities of ambulatory care pharmacists, it should be evident that extemporaneous compounding is a vitally important in ambulatory patient care.

Institutional pharmacy compounding

The ever-present responsibility of the healthcare industry is to provide the best available care for the patient, using the best means to do so, and providing that care in a conducive environment. This must be sufficiently economical to not put the institution in jeopardy of being unable to continue to provide the services to the community they serve. This requires cooperation on the part of the institutional administration, the medical staff, and the employees (nurses and pharmacists, in particular, as regards to medication usage) and must involve the patient. One of the effective means by which institutions can meet these challenges is to consider expanding extemporaneous compounding services within the institutional pharmacy. Pharmaceutical care and pharmaceutical compounding can provide cost savings to the institution, while providing needed options to the physician through problem-solving approaches and stimulating the institutional pharmacist through new challenges that allow the expression of both his or her skills and his or her art.

Institutional pharmacists have always been actively involved in compounding, or producing medications for the patient. Daily intravenous (IV) therapy is provided through compounding of medications. Antibiotic piggybacks, TPN solutions, IV additives, and many others are calculated, compounded, dispensed, and then administered by the nursing staff daily. The preparation of pediatric dosage forms has also been an area of extensive activity in some hospitals.

To assist institutional administrators in supporting the provision of extemporaneous compounding services, they should be aware that:[153]

1. The patients' needs are better served
2. The economic implication is favorable to the institution, or at least no less favorable than other alternatives
3. The provision of such alternative care improves and does not detract from the image of the institution for the purpose of public relations
4. Making such services available enhances the abilities of the physician to meet the patients' specific needs
5. The services fall within regulatory guidelines
6. The pharmacy staff is capable of performing such services.

Members of the institutional staff are constantly reading journal articles and are aware of innovative

thought and practice by their peers. When physicians become aware of the skill, availability, and awareness of pharmaceutical compounding and that they can have almost any medication they need, in the form and strength they need for a specific situation, they request it more often. As the institutional pharmacy staff demonstrates their expertise and problem-solving skills, the medical staff consistently depends upon them.

Guidelines are essential in determining any changes within an institutional pharmacy. Policies and procedures must be written to indicate the types of services made available. The two most important aspects to consider when making both the decision and the guidelines are:[153]

1. Keep intact the triad relationship. The medical staff (physician), the hospital staff (pharmacist and nurse), and the patient should all be informed of the decision to approach patient care by the use of institutionally compounded products. The patient is already aware that much of this occurs in the preparation of their TPN solutions or their IV antibiotic piggybacks. Patient awareness that the institution has recognized a special need they might have and that the institution is going the extra mile to meet those needs enhances public relations. The patient, recognizing that he or she is being treated as an individual, is receiving treatment benefit that may have a placebo effect in enhancing their improvement, especially when handled in a caring manner.
2. Do not overstep one's bounds. When products are commercially available to meet the needs of the institution, the patient, and the physician, use them. When the physician desires a pharmaceutical that is different for any number of reasons than anything commercially available, then one should consider extemporaneous compounding.

In consideration of meeting patient specific needs, the institutional pharmacist must look at various modalities as potential solutions. When traditional institutional processes and procedures are not meeting the patient's need, extemporaneous compounding should be a consideration. Improving outcomes and getting patients well and out of the institution as quickly as possible should be the end goal. Individualized dosage forms, dosage strengths, and alternative routes of administration can often help attain these goals. There are many easily accessible organizations specializing in helping meet these needs. The public relations aspect of meeting these needs may enhance community support. Improving outcomes assists the medical staff, by allowing them to spend their time dealing with new problems, as hospital pharmacy meets the challenge of past problems. Nursing and pharmacy have the enhanced opportunity to use the skills they have developed and to provide opportunities for pharmacy to have more patient involvement and job satisfaction. Due to some cost considerations in meeting the new USP compounding standards, some hospitals outsource part of their compounding activities. In evaluating an outsourcing pharmacy, the institutional pharmacy needs to confirm that the outsourced facility is USP Chapter <795> and <797> compliant.

Veterinary compounding

Veterinary compounding is necessary for many reasons. For example, with multiple species, ranging from small to large, it would be impossible to practice effective medicine without compounded preparations. Treating exotic species, small and large animals (birds to whales; land and aquatic), and animals with cancer requires compounding. There is no ideal anesthetic drug, which has led veterinarians to devise anesthetic combinations, inducing good-quality anesthesia with minimal risk to the animal. Compounding is essential for safe and effective veterinary anesthetic practice. Veterinarians are called on to anesthetize elephants, gorillas, tigers, ostriches, sharks, horses, cows, and poisonous snakes, among others.

Other reasons veterinary compounding is necessary include:

1. The necessity for multiple injections in the absence of a compounded multi-ingredient preparation
2. Rapid changes in management and disease problems in veterinary medicine
3. Problems associated with the treatment of large numbers of animals with several drugs within a short period
4. Cost-prohibitive factors associated with the large volume of some large-volume parenterals required for animals

5. The need for previously prepared antidotes for use in cases of animal poisoning.

Veterinary compounding will continue to exist in the future for the same reason it does now: to fulfill therapeutic needs in veterinary medicine.[154]

Nuclear pharmacy compounding

Nuclear pharmacy is a specialty practice of pharmacy that is a patient-oriented service and embodies the scientific knowledge and professional judgment required for improving and promoting health through assurance of the safe and efficacious use of radioactive drugs for diagnosis and therapy. Radioactive drugs, commonly referred to as radiopharmaceuticals, are a special class of drugs regulated by the FDA. They are unique in that they contain an unstable nuclide (radioactive nuclide) as a part of the compound designed to localize in an organ or tissue. Since radiopharmaceuticals are radioactive, the Nuclear Regulatory Commission, or a similar state agency, is heavily involved in regulatory matters relevant to radiopharmaceuticals.

A nuclear pharmacist is expert at preparing (compounding) radiopharmaceuticals with Tc-99m sodium pertechnetate and reagent kits. The kits are multiple dose vials, containing the compound to be labeled with the radioactive nuclide Tc-99m to create the radiopharmaceutical. The contents within the vial are sterile and pyrogen free, as is the Tc-99m sodium pertechnetate. Most radiopharmaceuticals are administered intravenously, so a nuclear pharmacist must be proficient at maintaining aseptic conditions during compounding.

Today, there are several hundred commercial, centralized nuclear pharmacies providing a significant fraction of radiopharmaceuticals used in nuclear medicine procedures.[155]

Regulations and guidelines

The documents of special importance in providing guidelines and standards for pharmaceutical compounding are the USP 34/NF 29 chapters:

Chapter <795> Pharmacy Compounding – Nonsterile Preparations
Chapter <797> Pharmacy Compounding – Sterile Preparations
Chapter <1163> Quality Assurance in Pharmaceutical Compounding

The following are summaries of USP Chapters <795>, Pharmacy Compounding – Nonsterile Preparations and <797> Pharmacy Compounding – Sterile Preparations.[147]

USP Chapter <795> Pharmacy Compounding – Nonsterile Preparations

This material in this section is divided into (1) Introduction, (2) Definitions, (3) Categories of Compounding, (4) Responsibilities of the Compounder, (5) Compounding Process, (6) Compounding Facilities, (7) Compounding Equipment, (8) Component Selection, Handling, and Storage, (9) Stability Criteria and Beyond-Use Dating, (10) Packaging and Drug Preparation Containers,(11) Compounding Documentation, (12) Quality Control, (13) Patient Counseling, (14) Training, and (15) Compounding for Animal Patients.

Introduction

The Introduction explains the purpose of the chapter, which is to provide compounders with guidance on applying good compounding practices for the preparation of nonsterile compounded preparations for both humans and animals. The chapter also provides general information to enhance the compounder's ability to extemporaneously compound preparations of acceptable strength, quality, and purity.

Definitions

The Definitions section defines how certain terms are used in the chapter and includes terms, such as active pharmaceutical ingredient, added substances, beyond-use date, component, compounder, compounding, hazardous drug, manufacturing, preparation, stability, and vehicle.

Categories of compounding

The chapter defines three categories of compounding: Simple, Moderate, and Complex. Simple is making a preparation that has a USP compounding monograph or appears in a peer-reviewed journal article with specific details and stability data for that formulation,

as well as reconstituting or manipulating commercial products that require the addition of one or more ingredients as directed by the manufacturer. Moderate includes making a preparation that requires special calculations or procedures to determine quantities of components per preparation or per individualized dosage units or making a preparation for which stability data is not available. Complex compounding is making a preparation that requires special training, environment, facilities, equipment, and procedures to ensure appropriate therapeutic outcomes.

Responsibilities of the compounder

This section states that the compounder is responsible for compounding preparations of acceptable strength, quality, and purity, along with other requirements. It goes further to detail ten General Principles of Compounding.

Compounding process

This section is a step-by-step presentation on the compounding process to ensure uniformity of activities in preparing each formulation.

Compounding facilities

This section discusses the standards for the facility. It must be adequate and appropriate for the compounding activities performed, and the area should be separate from other functions that occur in the pharmacy and maintained in a clean and sanitary condition.

Compounding equipment

Equipment used must be of the appropriate design and capacity for the preparations being compounded. There should be procedures for its selection, purchase, storage, cleaning, maintenance, and calibration, as well as procedures to minimize any mix-ups and cross-contamination.

Component selection, handling, and storage

The sources of the ingredients were previously covered in this chapter. Also included are 11 guidelines that must be followed when selecting, handling, and storing components for compounded preparations.

Stability criteria and beyond-use dating

This section was previously discussed in this chapter.

Packaging and drug preparation containers

Containers and closures used in packaging compounded preparations must meet USP requirements. They shall be of a suitable clean material that does not alter the quality, strength, or purity of the compounded drug preparation.

Compounding documentation

Compounding Documentation describes the Formulation Record, the Compounding Record, Standard Operating Procedures and the Material Safety Data Sheets and how they are used.

Quality control

Quality Control is included to ensure the accuracy and completeness of the compounding process. Compounded preparations must meet the USP/NF standards, and the pharmacist should review each procedure in the compounding process as a final check.

Patient counseling

This section explains that, at the time of dispensing, certain details need to be discussed with the patient, including the proper use, storage, and evidence of instability of the compounded preparation(s).

Training

A discussion of the steps that should be included in a detailed training procedure is presented, along with a discussion of what is important, and the training and evaluation of personnel requirements is presented.

Compounding for animal patients

Compounding standards apply to those preparations that are compounded for animal patients, just as they do for human patients. Because animals are different, a discussion of some of the considerations is presented.

USP Chapter <797> Pharmacy Compounding – Sterile Preparations

USP Chapter <797> involves procedures and requirements for compounding sterile preparations (CSPs). This chapter is divided into the following sections: (1) Introduction,(2) Organization of this Chapter, (3) Definitions, (4) Responsibility of Compounding Personnel, (5) CSP Microbial Contamination Risk

Levels, (6) Personnel Training and Evaluation in Aseptic Manipulation Skills, (7) Immediate-Use CSPs, (8) Single-dose and Multiple-dose Containers, (9) Hazardous Drugs as CSPs, (10) Radiopharmaceuticals as CSPs, (11) Allergen Extracts as CSPs, (12) Verification of Compounding Accuracy and Sterility, (13) Environmental Quality and Control, (14) Suggested Standard Operating Procedures (SOPs), (15) Elements of Quality Control, (16) Finished Preparation Release Checks and Tests, (17) Storage and Beyond-Use Dating, (18) Maintaining Sterility, Purity, and Stability of Dispensed and Distributed CSPs, (19) Patient or Caregiver Training, (20) Patient Monitoring and Adverse Events Reporting, (21) Quality Assurance (QA) Program, (21) Abbreviations and Acronyms, and (22) Appendices.

Introduction

The objective of this chapter is to describe conditions and practices to prevent harm, including death, to patients that could result from improperly compounded sterile preparations. It lists five conditions that might occur and includes nonsterility, excessive bacterial endotoxins, variability in intended strength of the correct ingredients, unintended chemical and physical contaminants, and ingredients of inappropriate quality. The standards in this chapter are intended to apply to all persons who prepare CSPs and in all places CSPs are prepared.

Organization of this chapter

This chapter is organized to facilitate the practitioners understanding of the accuracy and quality practices involved in preparing CSPs. In addition to the main sections, there are five appendices to assist the practitioner.

Definitions

This section contains 29 definitions applicable to the compounding of sterile preparations.

Responsibility of compounding personnel

This section discusses the various procedures, requirements, and performance responsibilities of those involved in compounding sterile preparations. Compounding personnel are responsible for ensuring CSPs are accurately identified, measured, diluted, and mixed and are correctly purified, sterilized, packaged, sealed, labeled, stored, dispensed, and distributed. The section lists 14 objectives that must be achieved by supervisory compounding and dispensing personnel.

CSP microbial contamination risk levels

Included is a discussion on the various risk levels determined by the corresponding probability of contaminating a CSP with (1) microbial contamination and (2) chemical and physical contamination. Three risk levels are identified: Low, Medium, and High, along with examples of each. The characteristics described for each level are intended as a guide to the breadth and depth of care necessary in compounding. The section discusses the conditions, personnel and process requirements, examples, and quality assurance associated with each risk level. The beyond-use dates associated with each level are also described.

Personnel training and evaluation in aseptic manipulation skills

This section describes the requirements for training personnel involved, as well as how these individuals are validated in aseptic manipulations using media-fill challenge testing.

Immediate-use CSPs

This is a new category, intended for situations in which emergency or immediate patient administration of a CSP is required. Since this is an exempt category, there are six listed requirements that must be met to utilize it.

Single dose and multiple dose containers

The "use times" of single and multiple dose containers are described, along with whether or not the multiple-dose containers contain preservatives.

Hazardous drugs as CSPs

The requirements for compounding with hazardous drugs are described. It details their storage, handling, preparation, and the use of newer technology to allow safer handling of these drugs. Also discussed are activities involving containment and disposal.

Radiopharmaceuticals as CSPs

These general comments refer to USP Chapter <823> Radiopharmaceuticals for Positron Emission Tomography – Compounding and some of the technology

used in this type of compounding. In addition, some requirements related to equipment and facilities are discussed.

Allergen extracts as CSPs

Allergen extracts are single dose or multiple dose intradermal or subcutaneous injections that are CSPs and may be exempt from the CSP requirements, if 11 different conditions described in this section are met.

Verification of compounding accuracy and sterility

Verification of compounding accuracy standards, methods of sterilization, and depyrogenation are discussed in this section. Sterilization by filtration, autoclaving, and dry heat are described.

Environmental quality and control

Environmental Quality and Control presents discussions on critical site exposure, clean rooms, barrier isolators, facility design, primary engineering controls, viable and nonviable environmental sampling testing, personnel requirements, cleaning and disinfecting the compounding area, personnel cleansing and garbing, personnel training and competency evaluation of garbing, aseptic work practices and cleaning/disinfection procedures and action levels, and documentation and data evaluation.

Suggested standard operating procedures (SOPs)

Twenty-three suggested SOPs are presented, but the compounding pharmacy must have SOPs written to cover every significant activity in the pharmacy.

Elements of quality control

Quality control standards are presented for sterile and nonsterile ingredients, devices, and equipment. This section also discusses the training and performance evaluation program for those involved in aseptic compounding activities.

Finished preparation release checks and tests

This section describes physical inspection, compounding accuracy checks, sterility testing, bacterial endotoxin (pyrogen) testing, and identity and strength verification of ingredients.

Storage and beyond-use dating

Storage and beyond-use dating provides background and rationale for the determination of beyond-use dates for CSPs. The beyond-use dates for CSPs are associated with the end-preparation testing for these preparations, as well as the monitoring of controlled storage areas. It also discusses beyond-use dating for proprietary bag and vial systems, as well as monitoring controlled storage areas to ensure that potency is retained throughout any storage time.

Maintaining sterility, purity, and stability of dispensed and distributed CSPs

This section discusses both sterile preparations for institutional use and packing and transporting CSPs. Topics included are packaging, handling and transportation, administration, education and training, and storage in locations outside CSP facilities (i.e., in patients' homes). This section also discusses redispensed CSPs involving returned and unopened preparations.

Patient or caregiver training

Detailed topics are provided that should be a part of a training program to ensure the patient or caregiver understands and complies with the many special and complex responsibilities involving the storage, handling, and administration of CSPs.

Patient monitoring and adverse events reporting

Explanations are provided for monitoring patients and any adverse events that might occur, including the establishment of SOPs for reporting these events.

Quality assurance (QA) program

The Quality Assurance section describes the standard of a formal program intended to provide a mechanism for monitoring, evaluating, correcting, and improving the activities and processes involved with CSPs.

Abbreviations and acronyms

This section describes the abbreviations and acronyms used in this chapter.

Appendices

There are five different appendices used to assist in understanding and implementing these standards in compounding pharmacies.

Other compounding-related USP chapters

There are two additional General Chapters in the USP/NF, prepared specifically for pharmacy compounding: Chapter <1160> Pharmaceutical Calculations in Prescription Compounding and Chapter <1163> Quality Assurance in Pharmaceutical Compounding.[156]

USP Chapter <1160> Pharmaceutical Calculations in Prescription Compounding

This chapter is provided as a reference and review of pharmaceutical calculations that may be used in compounding pharmacies.[147] It discusses topics, such as weighing, buffer solutions, dosage calculations, percentage concentrations, specific gravity, dilution and concentration, potency units, reconstitution, alligation, molar, molal and normal concentrations, milliequivalents and millimoles, isoosmotic solutions, flow rates in intravenous sets, temperature, and others related to pharmaceutical compounding.

USP Chapter <1163> Quality Assurance in Pharmaceutical Compounding

This chapter is designed to provide compounders with information related to establishing a quality assurance program in their facility. It discusses (1) Training, (2) SOPs, (3) Documentation, (4) Verification, (5) Testing, (6) Physical testing of dosage units, (7) Weight assessment, (8) Microbiological testing, (9) Cleaning, disinfecting, and safety, (10) Containers, packaging, repackaging, labeling and storage, (11) Outsourcing, (12) Responsible personnel, and (13) Summary.

Other applicable chapters

Numerous other General Chapters in the USP/NF are related to compounding and directly impact it, such as Chapters <1151> Pharmaceutical Dosage Forms, <1176> Prescription Balances and Volumetric Apparatus, <1219> Stability Considerations in Dispensing Practice, and <1231> Water for Pharmaceutical Purposes.

Model State Pharmacy Act and rules of the National Association of Boards of Pharmacy (model act)

The National Association of Boards of Pharmacy (NABP) *Good Compounding Practices Applicable to State Licensed Pharmacies (Appendix B), Model Rules for Nuclear/Radiologic Pharmacy and Model Rules for Sterile Pharmaceuticals* are other documents designed to apply to the compounding of drugs by state-licensed pharmacies. Some state boards of pharmacy use it as a model, and others use the USP chapters integrated into their regulations.

NABP good compounding practices applicable to state licensed pharmacies

The different subparts and their titles include:

1. Subpart A – General Provisions and Definitions
2. Subpart B – Organization and Personnel
3. Subpart C – Drug Compounding Facilities
4. Subpart D – Equipment
5. Subpart E – Control of Components and Drug Product Containers and Closures
6. Subpart F – Drug Compounding Controls
7. Subpart G – Continuous Quality Improvement Program
8. Subpart H – Labeling Control of Excess Products
9. Subpart I – Records and Reports.

NABP model rules for sterile pharmaceuticals

The different parts and their titles include:

1. Part 1 – Purpose and Scope
2. Part 2 – Definitions
3. Part 3 – Policy and Procedure Manual
4. Part 4 – Physical Requirements
5. Part 5 – Records and Reports
6. Part 6 – Delivery Service
7. Part 7 – Disposal of Cytotoxic and/or Hazardous Wastes
8. Part 8 – Emergency Kits
9. Part 9 – Cytotoxic Drugs
10. Part 10 – Patient Education and Training
11. Part 11 – Quality Assurance/Compounding and Preparation of Sterile Pharmaceuticals
12. Part 12 – Pharmacist Care Outcomes.

Special considerations in extemporaneous compounding

General considerations in compounding various dosage forms are discussed in chapters contained in *Remington Part 5: Pharmaceutical Dosage Forms:*

Manufacturing and Compounding.[157] However, there are aspects of compounding that should be discussed to compound preparations that are of acceptable strength, quality, and purity, including

1. Compounding with hydrates and solvates
2. Compounding with inorganic salts
3. Compounding with salts
4. Compounding with esters
5. Compounding with aliquots
6. Compounding with "potency-designations" active ingredients
7. Compounding with commercial products.

It is important to know the purity and form of all ingredients used in compounding, especially of APIs. Is the quantity of drug per dosage unit calculated on the anhydrous or hydrated form and, if so, which hydrated form? Is it calculated on the "base" or the "salt" form of the drug; or, on the "base" or the "ester" form? Some drugs are either obtained as an "aliquot" or a "dilution" or are prepared as aliquots or dilutions to be later weighed or measured for compounding purposes. Also, a number of drugs are available with labeled potency designations; for example, Gentamicin Sulfate USP "has a potency equivalent to not less than 590 mcg of gentamicin per mg, calculated on the dried basis."

Sources of information that can be used to determine the "form" of the drug (base, salt, or ester), if it is commercially manufactured, would be the commercial products, the USP/NF monographs, etc. For example, Albuterol Sulfate Tablets USP, are based on the "albuterol" content (present as the sulfate form). The USP states "Albuterol Tablets USP contain an amount of albuterol sulfate equivalent to not less than 90.0% and not more than 110.0% of the labeled amount of albuterol ($C_{13}H_{21}NO_3$)."

Diphenhydramine Hydrochloride Capsules USP, are based on the total molecule (i.e., diphenhydramine hydrochloride). The USP states "Diphenhydramine Hydrochloride Capsules USP contain not less than 90.0% and not more than 110.0% of the labeled amount of diphenhydramine hydrochloride ($C_{17}H_{21}NO.HCl$)."

Compounding with hydrates and solvates[158]

Concerning whether or not a drug is a hydrate, a solvate, or just contains some amount of water, common sources would be the USP/NF, Certificates of Analysis, and looking at the chemical structure or empirical formula of the drug (for solvates and hydrates).

An example of a USP/NF monograph is shown in Fig. 11.4. It is apparent that this is a hydrate. The more molecules of water present in the molecule, the more of the chemical that must be weighed to obtain the actual active drug. An example of a Certificate of Analysis is shown in Figure 11.5.

As a drug example that is available with different amounts of water, let us look at different forms of dexamethasone.

- Dexamethasone contains less than 0.5% of its weight in water
- Dexamethasone acetate has one molecule of water of hydration and contains between 3.5 and 4.5% of water; the anhydrous form contains less than 0.4% water
- Dexamethasone sodium phosphate contains a sum of water and alcohol that may be up to 16.0%.

Another example is Lidocaine Hydrochloride. Lidocaine hydrochloride occurs as a monohydrate and as the anhydrous form. The water content may be between 5.0 and 7.0%.

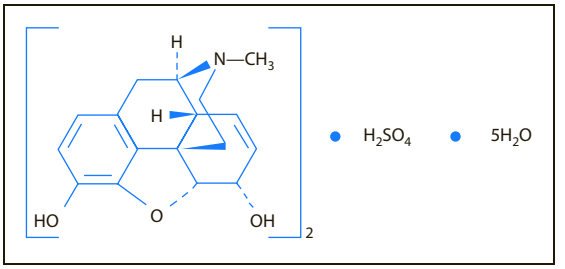

Figure 11.4 USP 35/NF 30 monograph chemical structure for morphine sulfate.

CERTIFICATE OF ANALYSIS

Morphine Sulfate, USP — CAS 62111-15-0

$(C_{17}H_{19}NO_3)_2.H_2SO_{44}.5H_2O$ — Lot No.___XYZ_____

MW 758.83

TEST	LIMIT Min. Max.	RESULTS
Assay	98.0% 102.0% (anhydrous basis)	100.5%
Identification	To Pass Test	Passes Test
Specific rotation	–107 º 109.5º	108.1°
Acidity	To Pass Test	Passes Test
Water	10.4% 13.4%	12.5%
Residue on ignition	nmt 0.1%	0.06%
Chloride	To Pass Test	Passes Test
Ammonium salts	To Pass Test	Passes Test
Limit of foreign alkaloids	To Pass Test	Passes Test
Physical Appearance: White, feathery, silky crystals, cubical masses of crystals, or white, crystalline powder.	To Pass Test	Passes Test

Manufacturer Name
Manufacturer Address
Manufacturer Telephone

Signature of Certificate of Analysis Coordinator _____

Figure 11.5 Typical certificate of analysis for morphine sulfate.

Example

How much adjustment should be made, if using lidocaine hydrochloride monohydrate in place of lidocaine hydrochloride anhydrous for a compounded prescription?

Lidocaine HCl monohydrate $C_{14}H_{22}N_2O.HCl.H_2O$ MW 288.81

Lidocaine HCl anhydrous $C_{14}H_{22}N_2O.HCl$ MW 270.80

A comparison of the molecular weights reveals a factor of 1.066 can be used for the adjustment:

(288.81)/(270.80) = 1.066

Example

If a prescription for lidocaine hydrochloride 2% gel (100 g) is to be made, then 2 g of anhydrous lidocaine HCl could be used, OR:

2 g × 1.066 = 2.132 g of lidocaine HCl monohydrate.

Also, a direct comparison of the molecular weights and the physical quantity required can be used, as follows:

$$\frac{\text{MW Hydrate}}{\text{MW Anhydrous}} = \frac{\text{Weight of Hydrated form}}{\text{Weight of Anhydrous form}}$$

$$\frac{288.81}{270.80} = \frac{X}{2g}$$

$$X = 2.133g$$

Further, the USP monograph for Lidocaine Hydrochloride Jelly USP, states "It contains not less than 95.0% and not more than 105.09% of the labeled amount of lidocaine hydrochloride ($C_{14}H_{22}N_2O.HCl$)." Note that this is the anhydrous form.

It is important to also check the Certificate of Analysis (C of A) for the lidocaine hydrochloride used to determine the water content. Fortunately, most pure powders (anhydrous) only contain 0.2 to 0.5% moisture, which can be insignificant, but needs to be checked, nevertheless.

Solvates and hydrates must be packaged in "tight" containers to prevent the loss or gain of moisture. In fact, it is best to have all chemicals used in compounding in "tight" containers, kept thoroughly closed at all times, except for the short time when a weighing step is involved. Storage at the indicated temperatures is also important to minimize any exposure to very high humidity levels.

- Hygroscopic powders are those that tend to absorb moisture from the air.
- Deliquescent powders are those that absorb moisture from the air and even liquefy.
- Efflorescent powders are those that may give up their water of crystallization and may even become damp and pasty.

When working with these powders, extra care must be taken. The USP description of a powder will state whether it has hygroscopic, deliquescent, or efflorescent properties. For these types of powders, storage in "tight containers" will decrease property changes in the chemicals.

One other factor is that if a hygroscopic or deliquescent powder is weighed on a balance and the compounder leaves for a short time and then returns, the powder may have absorbed moisture from the air and weigh heavier than it should. Therefore, weigh quickly after opening the bulk chemical containers, and then reseal them.

Compounding with inorganic salts[159]

Inorganic salts may not always be 100% of their composition. Topics involving inorganic salts include the effects of physical and chemical properties, and incompatibilities and solubilities of inorganic salts.

Physical and chemical properties include particle size, tendencies to absorb/give off water, pH properties, and others. Eutectic formation is another phenomenon that results when certain materials are mixed together and become pasty or even liquefy. Eutectic mixtures can be advantageous or deleterious, depending on how they are used. There are numerous methods (keeping problematic ingredients separate, addition of drying powders, etc.) to overcome these occurrences that can be utilized by the pharmacist.

Incompatibilities are defined as the inability of a substance to maintain its identity or to exercise its inherent properties when brought into contact with or into the sphere of influence of another substance or a physical force. From the pharmacist's position, incompatibilities fall into two classes: the desirable and the undesirable. Effervescent salts added to water represent the desirable, whereas a pH change resulting in hydrolysis and drug degradation represents the undesirable.

There are three classes of incompatibilities: physical, chemical, and physiologic. Only the first two are of interest here. Physical incompatibilities include insolubility, immiscibility, heat, pressure, cold, light, and percussion (violent reactions). Chemical incompatibilities commonly include hydrolysis, condensation, oxidation, reduction, precipitation, gas evolution, heat liberation, and heat absorption.

Regarding solubility of inorganic salts, there are some general rules that may be of interest.

1. If both the cation and anion of an ionic compound are monovalent, the solute–solute attractive forces are easily overcome, and, therefore, these compounds are water soluble (e.g., NaCl, LiBr, KI, NH_4NO_3, $NaNO_2$).
2. If only one of the two ions in an ionic compound is monovalent, the solute–solute interactions are also easily overcome and the compounds are water soluble (e.g., $BaCl_2$, MgI_2, Na_2SO_4, Na_3PO_4).
3. If both the cation and anion are multivalent, the solute–solute interaction may be too great to be

overcome by the solute–solvent interaction, and the compound may have poor water solubility (e.g., $CaSO_4$, $BaSO_4$, $BiPO_4$; exceptions: $ZnSO_4$, $FeSO_4$).

4. Common salts of alkali metals (e.g., Na, K, Li, Cs, Rb) are water soluble (exception: Li_2CO_3).
5. Ammonium and quaternary ammonium salts are water soluble.
6. Nitrates, nitrites, acetates, chlorates, and lactates are water soluble (exceptions: silver and mercurous acetate).
7. Sulfates, sulfites, and thiosulfates are water soluble (exceptions: calcium and barium salts).
8. Chlorides, bromides, and iodides are water soluble (exceptions: salts of silver and mercurous ions).
9. Acid salts corresponding to an insoluble salt will be more water soluble than the original salt.
10. Hydroxides and oxides of compounds, other than alkali metal cations and the ammonium ion, are water insoluble.
11. Sulfides are water insoluble, except for their alkali metal salts.
12. Phosphates, carbonates, silicates, borates, and hypochlorites are water insoluble, except for their alkali metal salts and ammonium salts.

Compounding with organic salts[160]

Many drugs are "salts," and the dose may be based on the "total salt" form or just the "base" form of the drug. The purity and form of all ingredients used in compounding, especially of APIs, must be known and considered during formulation. If a number of factors are not considered, the final compounded preparation may not fall within the strength requirements (e.g., 90 to 110% for compounded preparations or the USP monographs).

Sources of information that can be used to determine the "form" of the drug (i.e., base, salt, or ester), if it is commercially manufactured, would be the commercial products; also, the USP/NF can be used. For example, Albuterol Sulfate Tablets USP, are based on the "albuterol" content (present as the sulfate form). The USP states "Albuterol Tablets USP contain an amount of albuterol sulfate equivalent to not less than 90.0% and not more than 110.0% of the labeled amount of albuterol ($C_{13}H_{21}NO_3$)." In other words, sufficient albuterol sulfate is present to provide the labeled amount of the albuterol base.

Example

A prescription calls for 10 mL of fentanyl 1 mcg/0.1 mL (as the citrate) topical gel. How much fentanyl citrate will be required?

1. 50 mcg/0.1 mL = X mcg/10 mL
   X = 5 mg
2. Fentanyl MW = 336.47
3. Fentanyl citrate MW = 528.59
4. 336.47/5 mg = 528.59
   Y = 7.85 mg
5. Each mg of fentanyl equals 528.59/336.47 = 1.57 mg fentanyl citrate

In another scenario, Diphenhydramine Hydrochloride Capsules USP, are based on the total molecule (i.e., diphenhydramine hydrochloride). The USP states "Diphenhydramine Hydrochloride Capsules USP contain not less than 90.0% and not more than 110.0% of the labeled amount of diphenhydramine hydrochloride ($C_{17}H_{21}NO.HCl$)." As one can see, the weight of the "HCl" is considered in the dose of the drug.

Example

A prescription calls for 30 capsules of diphenhydramine hydrochloride 35 mg each. How much diphenhydramine hydrochloride will be required?

Since the total salt molecule is part of the dose, 30 × 35 mg = 1.05 g of diphenhydramine hydrochloride is required.

Because many drugs are either weak acids or weak bases and have limited water solubility, they are often used as their "salts" to increase their aqueous solubility. When salts are placed in an aqueous environment, they dissolve to some extent, based on their solubility in the aqueous media and the pH of the media. There will be a portion of the drug that is dissolved, and some may remain undissolved. Of the dissolved portion, there will be a part that is "ionized," and the

remainder will be "unionized," depending on the pH of the media. It is the "unionized" portion of the drug in solution that will be absorbed for systemic effect. This is described by the "dissociation constant" or "pK_a" of the drug.

As is evident from this discussion, the purpose of the "salt" form is to enhance the solubility of the drug, but it may also enhance the stability and change other attributes of the drug that make it easier to handle and manipulate for producing dosage forms.

Why do we have some drugs that are dosed on the "base" form of the drug (whether they be weak acids or weak bases) and some drugs that are dosed on the total weight of the "salt" form of the drug?

In reviewing older US Pharmacopeia revisions, it appears this has been an issue for many years with no apparent basis for which way the salts are dosed. However, both the official monographs and the FDA approved drug products appear inconsistent in how they determine how a drug is dosed. Pharmacists involved in compounding must be aware of the correct use of the verbiage, as follows:

It is the responsibility of the formulator (compounding pharmacist) to determine whether or not the base/acid of salt form of the drug is to be used in the calculations for the amount of API to actually be used. It should be routine procedure, when receiving a prescription, to correctly determine whether or not the salt or base/acid form of the drug is to be used as the basis for the dose. Resources include the USP, product package insert, and a call to the manufacturer or physician, as appropriate.

Compounding with esters[161]

Many drugs are available as the base form or as an "ester," and the dose may be calculated on the total ester form or just the base form of the drug. Some drugs are esters by virtue of their internal chemical structure (atropine, cocaine, many local anesthetics, etc.), and others are esters by the addition of a moiety that will form an ester for certain purposes. Only the latter are discussed here; those that are esters, due to their basic molecular structure, are not included.

An ester is a compound of the general formula R–C–O–R1, where R and R1 may be the same or different and may be either aliphatic or aromatic. The term "aliphatic" refers to acyclic or cyclic, saturated or unsaturated carbon compounds excluding aromatic compounds; the term "aromatic" was originally used to describe compounds that "smelled" but were later found to contain either benzene or fused benzene rings in the structure. The term has been generalized to include aromatic heterocyclic structures.

The dehydration of a molecule of an alcohol and a molecule of an organic acid can form an ester. For example, ethanol reacts with acetic acid to form ethyl acetate, an ester:

$$C_2H_5OH + CH_3COOH \rightarrow CH_3CH_2{-}O{-}CO{-}CH_3$$

Following salts, esters are the most important acid derivatives used in pharmacy. Esters can be prepared for a number of reasons, including solubility, stability, resistance to degradation after administration, and use as prodrugs.

Some drugs are very soluble but tend to degrade rapidly when in solution. One approach to increase their stability, and shelf-life, is to prepare esters that are poorly soluble. This results in a "suspension" dosage form in place of a "solution" dosage form. A drug in a suspension dosage form degrades at a much slower rate than one in solution. After oral administration, the ester is cleaved, and the active drug moiety released for absorption.

Some drugs may cause pain at the site of injection, especially if they precipitate and damage the surrounding tissue. This can be overcome by preparing a drug with increased solubility. Chloramphenicol has low water solubility, but the succinate ester is formed to increase the water solubility of the drug and facilitate parenteral administration. This succinate ester is inactive but is hydrolyzed to release the active chloramphenicol moiety.

Esters are an important means of preparing prodrugs, due to the number of esterases present in various parts of the body that will cleave the ester linkage, releasing the active moiety. Carboxylic acid esters are common in pharmacy and are neutral liquids or solids that can be hydrolyzed slowly by water and rapidly by acids or alkalais into their components.

Some of the simple esters are soluble in water, but those with more than four carbon atoms are practically insoluble in water.

One cannot simply look at the title and determine whether or not the drug is a salt or an ester. For example, "acetate salts" include calcium acetate,

chlorhexidine acetate, desmopressin acetate, flecainide acetate, gonadorelin acetate, guanabenz acetate, leuprolide acetate, lysine acetate, mafenide acetate, and zinc acetate, and "acetate esters" include cortisone acetate, desoxycorticosterone acetate, dexamethasone acetate, fludrocortisones acetate, fluorometholone acetate, hydrocortisone acetate, isoflupredone acetate, medroxyprogesterone acetate, megestrol acetate, melengestrol acetate, methylprednisolone acetate, norethindrone acetate, paramethasone acetate, prednisolone acetate, trenbolone acetate, and betamethasone acetate.

Further, "succinate salts" include sumatriptan succinate, doxylamine succinate, loxapine succinate and metoprolol succinate and "succinate esters" include chloramphenicol sodium succinate, hydrocortisone sodium succinate, hypromellose acetate succinate, methylprednisolone sodium succinate, and prednisolone sodium succinate.

Cefuroxime axetil is an example of an ester dosed on the base form.

1. Cefuroxime axetil is $C_{20}H_{22}N_4O_{10}S$, with a molecular weight of 510.47. Cefuroxime axetil is described as a mixture of the diastereoisomers of cefuroxime axetil and contains the equivalent of not less than 745 mcg and not more than 875 mcg of cefuroxime ($C_{16}H_{16}N_4O_8S$) per mg, calculated on the anhydrous basis.
2. Cefuroxime Axetil Tablets, USP, contain the equivalent of not less than 90.0% and not more than 110.0% of the labeled amount of cefuroxime ($C_{16}H_{16}N_4O_8S$).
3. Ceftin Tablets (cefuroxime axetil tablets) provide the equivalent of 250 or 500 mg of cefuroxime as cefuroxime axetil.
4. Ceftin for Oral Suspension (cefuroxime axetil powder for oral suspension), provides the equivalent of 125 mg or 250 mg of cefuroxime as cefuroxime axetil per 5 mL of suspension.
5. After oral administration, cefuroxime axetil is absorbed from the gastrointestingal tract and rapidly hydrolyzed by nonspecific esterases in the intestinal mucosa and blood to cefuroxime; the axetil moiety is metabolized to acetaldehyde and acetic acid.
6. The molecular weight of cefuroxime axetil is 510.47. The molecular weight of cefuroxime is 424.39. Therefore, 1 mg of cefuroxime is contained in 510.47/424.39 = 1.2 mg of cefuroxime axetil. A 250 mg cefuroxime tablet will contain 250 × 1.2 = 300 mg of cefuroxime axetil.
7. Therefore, if using a commercial product to prepare a dosage form, no conversion should be required. However, if using a bulk active ingredient, then the required amount of cefuroxime axetil that is equivalent to the desired dosage of cefuroxime must be calculated.

Dexamethasone labeled strengths pose an interesting challenge, as they are not consistent in naming either the base or the ester form, for example:

- "Dexamethasone" dosage form monographs are based on the labeled amount of "dexamethasone."
- "Dexamethasone Acetate" dosage form monograph is based on the labeled amount of "dexamethasone."
- "Dexamethasone Sodium Phosphate" dosage form monographs are based upon the labeled amount of "dexamethasone phosphate", not "dexamethasone."

There are a number of important sources of information that can be used to determine the "form" of the drug (i.e., base or ester). If it is commercially manufactured, the package insert terminology will provide the information. If it is a USP/NF monographed dosage form, then the USP/NF can be used.

Since some drugs may occur as salt forms, ester forms, and/or salt–ester forms, it is important to document what form is used and whether it is a salt, ester, or combination. An example of a drug that occurs as both salt and ester forms is the drug erythromycin: erythromycin estolate is a salt; erythromycin ethylsuccinate is an ester; erythromycin gluceptate is a salt; erythromycin lactobionate is a salt; and erythromycin stearate is a salt.

Compounding with aliquots, dilutions, and concentrates[162]

Substances are available as aliquots, dilutions, and concentrates for a number of reasons. First, the quantities required for dosing or compounding are so small they cannot be accurately weighed, so dilutions are prepared, assayed, and utilized. Second, some items

(e.g., nitroglycerin) are explosive and must be diluted in order to be safely handled. Third, many substances, such as acids and bases, are commercially available in percentage strengths that vary from one acid to another and depend on the solubility and stability of the solute in water and on the manufacturing process. The diluted acids are aqueous solutions 10% w/v, but diluted acetic acid is 6% w/v. The concentrations of the official undiluted acids are expressed as percentages weight in weight (w/w), but the strengths of official diluted acids are expressed as percentages weight in volume (w/v). Therefore, it is necessary to consider the specific gravities of the concentrated acids, when calculating the volume required to make a given quantity of diluted acid.

Compounding with potency-designated ingredients[163]

In the case of "potency-designated" drugs, the bulk substance, or API, is not 100% active drug in all cases. It is important to know the assayed-potency designation of the ingredient, so appropriate allowances can be made to obtain the correct amount.

Some APIs, including some antibiotics, endocrine products, biotechnology-derived products, and biologics, have potencies that are based on "activity" and are expressed in terms of "units of activity," "micrograms per milligram," or other standard terms of measurements. These are described for each API in the USP (see Table 11.9).

Regarding biologicals, the following is found in the General Notices of the USP:

> 5.50.10 Units of Potxency (Biological)
>
> For substances that cannot be completely characterized by chemical and physical means, it may be necessary to express quantities of activity in biological units of potency, each defined by an authoritative, designated reference standard.
>
> Units of biological potency defined by the World Health Organization (WHO) for International Biological Standards and International Biological Reference Preparations are termed International Units (IU). Monographs refer to the units defined by USP Reference Standards as 'USP Units.' For biological products, units of potency are defined by the corresponding US Standard established by FDA, whether or not International Units or 'USP Units' have been defined.

There is no relationship between the units of potency of one drug with that of another different drug. In the case of potency-designated drugs, there must be a "reference standard" for comparison. In actual usage, the potency specifications often include a range or "not less than __" and "not more than ___." In some cases, only a lower range is given, and, in a few cases, there is no upper limit.

The determinations of potency are done on the "dried or anhydrous basis." In the case of hygroscopic APIs, one must exercise precautions to maintain the substance in a dried state in tight containers. In some cases, there is a designation of specified solvent-free conditions.

In the case of dihydrostreptomycin, there are different potencies, depending on the use of the API. The potency may be not less than 450 mcg, 650 mcg, or 725 mcg, depending on its form or usage (route of administration).

In some cases, as in erythromycin ethylsuccinate and erythromycin stearate, the potency is based on the sum of the percentages of three different erythromycins that make up the API. The potency-designation is determined on the "base" of the drug, but, in a few instances, the salt or ester form is used.

The potency of antibiotics is commonly expressed as "mcg of activity per mg of substance." Obviously, there will be different equivalents for the base versus the salt forms of the drug. For example, tobramycin has not less than 900 mcg of tobramycin per mg, and tobramycin sulfate has a potency of not less than 634 mcg of tobramycin per mg, all on the anhydrous basis. As another example, ampicillin contains not less than 900 mcg and not more than 1050 mcg of ampicillin per mg, and ampicillin sodium contains not less than 845 mcg and not more than 988 mcg of ampicillin per mg, both calculated on the anhydrous basis. So, one can tell that it is extremely important to check the labels accompanying each batch of each API for the necessary values used in calculations.

In some drugs, the actual dose may be expressed in units, instead of mg. Examples of this include heparin and insulin. Other examples include enzymes (pancreatin, pancrelipase, papain), and antibiotics.

Each container must be labeled with the actual potency, and this information is to be used in calculations involving dosing prior to compounding activities. These calculations must be performed and checked and documented, as different lots of the same API may have different potencies. An example of a calculation follows:

Example

A formula calls for 500 mg of neomycin sulfate. The label on the API shows 650 mcg of neomycin activity per mg of powder. How much of this powder is required to provide the 500 mg of neomycin sulfate?

650 mcg/1000 mcg = 500 mg/X mg

X = 769 mg of the powder is required to provide 500 mg of actual neomycin sulfate.

Compounding with complex organic molecules[164]

Most complex molecules and biotechnology products are proteins; however, some may be smaller peptide-like molecules. Proteins are inherently unstable molecules and require special handling; also, their degradation profiles can be quite complex. Pharmacists involved in compounding with biologically active proteins must be knowledgeable of their stabilization, formulation, and delivery to the site of action.

In compounding with complex molecules, one must be cognizant of both the active drug constituent and the total drug formulation in which it is contained. Protein drugs are very potent and are used in quite low concentrations. The bulk of many manufactured products and compounded preparations may be the excipients, including the vehicle, buffers, stabilizers, and others that are often incorporated in these products. A number of different stabilizers can be used from different chemical classes and include buffers, surfactants, amino acids, polyhydric alcohols, fatty acids, proteins, antioxidants, reducing agents, and metal ions.

Factors

pH is one of the key important factors in formulating a stable preparation. The optimal pH range can be achieved through the selection of appropriate physiologic buffers, in buffer concentration ranges of 0.01 to 0.1 M. An increase in the buffer concentration means an increase in pain on injection, so it is kept as low as reasonable.

Chelating agents are incorporated to bind trace metals, such as copper, iron, calcium, and manganese, and minimize rates of degradation. Ethylenediaminetetraacetic acid (EDTA) is commonly used at a concentration of about 0.01 to 0.05%.

Since oxidation is one of the major factors in protein degradation, antioxidants are often incorporated. Examples include ascorbic acid, sodium disulfide, monothioglycerol, and α-tocopherol, which are frequently used at a concentration of about 0.05 to 0.1%.

Especially if multiple dose vials are prepared, preservatives are necessary, if the active ingredient is compatible. Example preservatives can include phenol (0.3 to 0.5%), chlorobutanol (0.3 to 0.5%), and benzyl alcohol (1.0 to 3.0%).

Other excipients may include the polyols, which are good stabilizers and are commonly used in concentrations from 1% to 10% and tonicity-adjusting agents, which include sodium chloride and dextrose in concentrations necessary to achieve isotonicity of approximately 290 mOsm/L.

Preparation

Complex molecule formulations and procedures should be kept as simple as possible. Sterility must be achieved and maintained in many preparations, and, since most do not contain a preservative, it is recommended that only one dose be prepared from each vial or container to minimize contamination. Sometimes, this may not be practical, and specific manipulations are needed to meet patient needs. Also, there are two special considerations in working with biotechnologically derived preparations – the use of filters and the sorption of these drugs to containers.

The use of filters in manipulating biotechnology products can result in "sorption" or the loss of some of the drug available to the patient. Sorption is "sticking" either by "absorption" into the filter or by "adsorption" onto the surface of the filter. Special filters have been prepared to minimize this problem. For example, muromonab-CD3 (Orthoclone OKT3) injection should be filtered with a low protein-binding filter of 0.2 to 0.22 µm. Many biotechnology products should not be filtered at all. If a filtration device is

part of the intravenous (IV) administration apparatus, large molecule drugs should be administered distal to the site of the filter. Filters shown to minimize protein adsorption are those made from polyvinylidene difluoride, polycarbonate, polysulfone, and regenerated cellulose. As a precaution, low protein-binding filters should be used.

Sorption of proteins to containers (glass or plastic) can result in drug loss. This loss can be minimized either by the use of albumin or by siliconization. Adding about 0.1% albumin to the preparation can decrease the sorption of proteins to containers. If glass or plastic containers are used, the albumin solution should be added and manipulated to coat the interior surface before adding the drug. If siliconization is used, one can prepare a silicon solution or emulsion and soak or rinse the glass vials in it. The drained vials should then be placed in an oven at about 250°C for 5 to 6 hours. This procedure will minimize protein adsorption to glass; it can be used for both the preparation equipment and the packaging containers.

Physicochemical considerations

Several factors must be considered to ensure retention of a large molecule drug's activity up to the time of administration to the patient and include selecting an appropriate vehicle for drug delivery, individualizing dosages, administering drugs through novel drug-delivery systems, preparing drugs for delivery through these systems, monitoring their efficacy, and counseling patients on their use. Specific issues relevant to large molecule drugs include the:

- Effect of agitation and/or frothing on a preparation's stability
- High molecular weight and potential for aggregation (i.e., a small change in structure can result in a change in activity)
- Assignment of potency to the reference standards, (when traditional pharmaceuticals are about 98% pure, these materials may be only 0.1 to 1% active, with their activity assigned by potentially variable assays)
- Use of micropipets, which can require frequent calibration
- Stability may be less than lyophilized preparations
- Interaction of the product with the inner wall of the glass vial or bag and with the elastomeric closure
- Effectiveness of the preservative if a multiple dose product is mixed with other products
- Immunogenic potential, because some are produced by a fermentation-type process and proteins can co-purify with proteins.

Also, physicochemical factors considered in compounding with protein drug products include the structure of the protein drug, isoelectric point, molecular weight, solubility and factors affecting solubility (e.g., surfactants, salts, metal ions, pH), stability and factors affecting stability (e.g., pH, temperature, light, oxygen, metal ions, freeze–thaw cycles, mechanical stress), polymorphism, stereoisomers, filtration media compatibility, shear, and surface denaturation.

Solubility can vary with changes in chemical structure, pH, and temperature. Proteins are more soluble in their native environment or medium or in a matrix that is similar to their native environment, which may include sodium chloride, trace elements, lipids, and other proteins in an aqueous medium. One must consider the ingredients' effects on the solubility of the active drug, especially since most of the products are currently administered parenterally. This is critical, because the actual drug is present in a small quantity and can go unnoticed if it precipitates.

The pH of the compound should be maintained close to the pH of the original approved, manufactured product. Changes in pH can affect proteins in numerous ways and result in altered activity. Chemical degradation rate constants are pH related, and hydrogen ion concentration can affect the actual structure of proteins (i.e., quaternary structure). Buffer systems may be needed in compounding; they should be prepared at the minimum buffer strength required to produce the most stable drug preparation, as previously mentioned.

Chemical and physical instability must be considered and addressed appropriately. Chemical instability of proteins is the modification of protein structures by bond formation or cleavage to yield a new compound. Physical instability involves changes in structure, conformation, or behavior in a particular environment. Stability, both chemical and physical, depends on pH, temperature, and agitation, as well

as the overall environment in which the drug is contained.

Sorption is a problem with colony-stimulating factors and with aldesleukin (Proleukin) at low concentrations. To minimize "sticking" of the protein to the glass or plastic, the addition of about 0.1% albumin to the product to occupy the potential binding sites in the container is often helpful. Pharmacists must consider this problem before making any changes in packaging.

Agitation resulting in frothing can create difficulties in two ways. First, frothing can cause difficulties in using a syringe to withdraw the required amount of drug from a vial. To avoid this problem, the formulator should mix the product by rolling the vial in the hands or gently swirling it. Second, excessive agitation can cause changes in a protein's quaternary structure that often reduce or eliminate a drug's therapeutic activity. Some products, such as filgrastim (Neupogen) and sargramostim (Leukine), are reconstituted by directing a soft stream of diluent against the inside of the container wall. Others, such as recombinant tissue plasminogen activator (tPA; alteplase), are reconstituted by directing a stream of diluent directly into the product at the bottom of the vial.

Packaging

The container used for packaging and storage after compounding must be chosen carefully. For example, the manufacturer's directions for interleukin-2 (aldesleukin) suggest the use of a plastic bag, because that type of dilution container enhances consistent drug delivery. Unless otherwise specified, USP type I glass should be used for packaging, when storage for extended time periods is indicated. The pharmacist should be aware of the potential for sorption of the drug to the glass walls. Closures and stoppers should be selected that are compatible and flexible, have low levels of particulates, and have few problems with adsorption, absorption, and permeation.

Storage/labeling

The recommended storage temperature depends on the specific preparation and may include room temperature (15° to 25°C), refrigerator temperature (2° to 8°C), frozen (−20°C), or ultrafrozen temperature (down to −80°C). Freezing does affect the activity of certain products; for instance, the activity of filgrastim decreases if frozen. Some products can retain potency at room temperature after reconstitution. Sargramostim retains potency for up to 30 days at 25°C. However, most manufacturers recommend refrigeration at 2 to 8°C, regardless of the product's potency at room temperature.

The short shelf-life of these products after reconstitution can be due to chemical, physical, or microbiological instability. The manufacturer's recommendations or those validated by the published literature should be followed for products after they are reconstituted and manipulated into preparations. One example is tPA (alteplase), which has been used in treating intraocular fibrin formation after a vitrectomy and in managing subconjunctival hemorrhage after glaucoma filtration surgery. The prepared solution is stable in a pH range of 5 to 7.5 and is incompatible with bacteriostatic agents. To prepare a compounded preparation, the commercial product is reconstituted according to the manufacturer's directions, using sterile water for injection without preservatives to yield a concentration of 1 mg/mL. This solution is further diluted with 0.9% sodium chloride injection to yield a concentration of 25 mcg/100 mcL. Aliquots of 0.3 mL are withdrawn into 1 mL tuberculin syringes and capped. The syringes are stored in an ultrafreezer at −70°C. This product has been shown, by both bioassay and clinical use, to retain its activity for at least 1 year. This type of specific preparation information is not included in the manufacturer's label information and is obtained from the literature or by asking the manufacturer directly.

Stability

Physical stability can involve degradation by aggregation, denaturation, and precipitation. Aggregation can be the result of covalent or non-covalent processes and can be either physical or chemical in nature. Aggregate formation can actually begin when primary particles are formed from protein molecules as a result of Brownian movement.

Denaturation can result from heat, cold, extreme pH values, organic solvents, hydrophilic surfaces, shear, agitation, mixing, filtering, shaking, freeze–thaw cycles, ionic strength, and other factors.

Denaturation can be quite complex and can be either reversible or irreversible.

Precipitation can result from shaking, heating, filtration, pH, and chemical interactions. The first step in a precipitation process is aggregation. When the aggregates gain a sufficient size, they precipitate out of solution and are clearly evident. Precipitation can occur on membrane filters, in equipment, in tubing, and in contact with other equipment and supplies.

Issues related to compounding with commercial products

Pharmacists have a choice for the source of ingredients used in compounding prescriptions for humans: bulk drug substances (APIs) or commercial products. Veterinary compounding may require the use of commercial products.

Is compounding using commercial products wise? Can one be assured of a quality preparation, if compounded marketed products are used? Can one meet the USP standards of USP Chapters <795> and <797> by using commercial products as the source of drugs? The answer to these questions is, "sometimes, but not always." Pharmacists are placed in an interesting situation, when required to use commercial products in compounding veterinary preparations, because this sometimes results in preparations outside USP standards and specifications.

In compounding for human patients, pharmacists have the choice to use bulk chemicals (APIs) or commercial products. When using commercial products as the source of active drugs, one does not really know if the final compounded preparation meets USP standards. As an example, one may prepare a relatively simple intravenous admixture containing 80 mg gentamicin injection in 50 mL of 5% dextrose solution. To prepare this, 2 mL of gentamicin injection (40 mg/mL) is added to 48 mL of 5% dextrose in water in a piggyback bag to make a final volume of 50 mL. In compounding, one is allowed a variance of 90.0 to 110.0% of the labeled potency of the finished compounded preparation. The USP specification for gentamicin injection is not less than 90.0% and not more than 125.0% of the labeled amount of gentamicin. If the specific batch analyzed at the manufacturer was at 120%, it met the USP specifications and entered the marketplace distribution system. A pharmacist adds 2 mL of that gentamicin injection to 48 mL of 5% dextrose in water and has just compounded a drug preparation that does not meet the USP compounding specifications of 90.0 to 110.0% of the labeled quantity. In other words, 2 mL of 40 mg/mL at 120% of labeled quantity equals 96 mg of gentamicin present. The acceptable range would only be 72 to 88 mg of gentamicin present. Since there is 96 mg of drug present and it exceeds the maximum 88 mg, this preparation does not meet the USP standard for compounding. If this solution was selected to be analyzed by a regulatory agency, it would be reported as "out of specification" and "superpotent." This is the system currently in effect that must be followed until such time that most compounding can be done using compendial standard (USP/NF) or other high quality bulk drug substances.

Different dosage forms have historically been used as the source of active drugs and the different dosage forms that they have been used to prepare. Oral tablets and capsules are commonly used to prepare oral liquids (solutions and suspensions) for pediatric use, and injectable drugs to prepare intravenous admixtures. Another fact to consider is that FDA-approved commercial products are used, but the final compounded preparation is not FDA-approved. There are many considerations and variables of which to be aware in using commercial dosage forms. Some commercial dosage forms are inappropriate for use in some situations in compounding.

Considerations when working with commercial products include the following:

1. The use of commercial products as a source of active drugs will result in a higher prescription cost to the patient, as compared to bulk drug substances (APIs). This is especially true if injectables are used as the drug source.
2. Uncertainties in compounding using commercial products involve the presence of excipients and actual assay potency.
3. When using commercial solutions as a source of drugs, one must be aware of the pH of the solution and the pH of the compounded preparation. If the pH range is significantly different (i.e., about 2 to 3 pH units different), this may result in changes in the solubility and stability of the drug and formulation. Regarding solubility, instead of a solution being prepared, it may result in a suspension if

the pH of the final compounded preparation is insufficient to keep the drug in solution.

4. The presence of buffers in the commercial drug product may influence and dictate the pH of the final compounded preparation.
5. If compounding large batches, it may be advisable to assay the commercial product used for potency. This is especially true if the allowable range in the USP for the commercial product is outside the 90.0 to 110.0% acceptable range in compounding. Some USP monographs for commercial products go much higher, but this is unusual. However, it is important to know the variables one is working with. Most commercial drugs are in the 95 to 105% and 90 to 110% range, with some in the 80 to 120% range; however, in some cases, it is even more. Compounded preparations are limited to a 90.0 to 110.0% standard. In summary, it may be that the pharmacist did everything exactly correct, but, if the final preparation was assayed, it would be out of specifications (OOS), due to the use of the commercial product where a wide variability was allowed.
6. Dosage Forms Not to be Used in Compounding: Modified-release dosage forms, including extended-release, delayed-release, repeat-action, and targeted-release, should not be used in compounding, unless it has been indicated or documented that they can be used.
7. Documentation: When using commercial products in compounding, it is important to list the manufacturer, lot number, and expiration date of the product used. This is especially important in the case of multi-source generic drugs, in which different excipients may be used by different manufacturers and in the event of a recall.
8. A limiting factor is the quantity of commercial drug product that must be used to provide the required amount of active drug. Often, the dosage quantity of the commercial product makes them impractical to use in compounding.

As previously mentioned, one concern in using commercial dosage forms is the excipients that are present. When compounding using these dosage forms, all the excipients must be considered as to their effect on the efficacy, safety, and stability of the final compounded preparation.

Summary

Pharmacy compounding is providing pharmacists with a unique opportunity to meet the needs of physicians and their patients by individualizing medications. It will become an even more important part of pharmacy practice in the future in all practice areas for humans and animals. Pharmaceutical compounding is a practice in which the clinical expertise of pharmacists can be merged with the scientific expertise of pharmacists to make pharmaceutical care a reality.

Pharmacists should not hesitate to become involved in pharmacy compounding but should be aware of the requirements and uniqueness of formulating a specific drug product for a specific patient. This is an important component in providing pharmaceutical care. After all, without the pharmaceutical product or preparation, there is no pharmaceutical care.

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12

Social, behavioral, economic and administrative sciences

Laws governing pharmacy

Pharmacists, whether community practitioners employed by an institution, or working for a pharmaceutical manufacturer, must be aware of the legal requirements that apply to their daily professional activities. The laws pertaining to the practice of pharmacy arise from a variety of sources, including statutory laws, such as the Food, Drug and Cosmetic Act (FDCA), the Controlled Substances Act (CSA), the Poison Prevention Packaging Act (PPPA) at the federal level, and Pharmacy Practice Acts or Codes at the state level. In addition, several regulatory agencies in the federal government, including the Food and Drug Administration (FDA), the Consumer Product Safety Commission (CPSC), and the Drug Enforcement Administration (DEA), have the authority to promulgate regulations that have the force of law. State agencies, such as a Board of Pharmacy, also adopt rules or regulations that have the force of law. Another source of law comes from court decisions that either interpret statutory and regulatory laws or make new laws based on judicial decisions; the latter type of rulings are often called "judge made" or "common" laws derived from the English court system.

Besides the various sources of laws, there are a multitude of types of law. Civil law governs the relationship between individuals within society, whereas criminal law governs the relationship of the individual to society as a whole. Two important subdivisions of civil law are the law of contracts and tort law. The former concerns relationships that the individuals enter into voluntarily, whereas the latter embodies relationships that exist automatically by virtue of law. Each type and source of law is applicable to pharmacists and pharmacy practice.

Laws governing the practice of pharmacy

Relationship between state and federal laws

Differentiating between state and federal laws governing the practice of pharmacy can be a daunting task, because some areas of the law are reserved exclusively to state governments, whereas other topics are governed exclusively by federal authorities. Complicating the subject even more, there are numerous issues that both the state and federal laws address. In the latter case, when both federal and state laws speak to the same issue, the governing bodies are said to have "concurrent jurisdiction." Determining which of the two sets of laws to apply to any given situation is sometimes difficult, especially in cases in which the two laws differ in their obligations or prohibitions. As a general rule, when there is a "conflict of laws," it is safer to apply and follow the more strict law. An example will help illustrate the point: DEA regulations require pharmacies to keep controlled substances records, including prescriptions, for at least 2 years. Several states have laws that all prescriptions be stored in a pharmacy for a longer period. In Michigan, for example, pharmacies must retain prescriptions a minimum of 5 years from the date of last refill. Because record retention is a subject of "concurrent jurisdiction" between state and federal governments, a pharmacist would follow the "stricter" law and, at least in Michigan, keep all prescriptions, including those for controlled substances, for a minimum of 5 years from the date of the last refill. Another area of "concurrent jurisdiction" that has sparked over a decade of controversy involves the compounding of drugs by pharmacists. Historically, compounding was thought to be exclusively in the realm of state jurisdiction. In the early 1990s, the FDA began an aggressive approach to regulate pharmacies engaging in large scale compounding more akin to manufacturing. Viewed another way, the FDA was attempting to regulate pharmacies that were manufacturing, and, therefore, subject to federal laws, under the guise of state regulated compounding practices. The furor over the subject led to an amendment to the FDCA that gave the FDA some regulatory authority over compounding, while leaving other aspects of compounding subject to state law. This, in turn, led the National Association of Boards of Pharmacy (NABP) to adopt model guidelines for states to enact. Animosities between the FDA and compounding pharmacies finally cumulated in a US Supreme Court decision in April, 2002 that should have settled the issue in favor of state authority to regulate compounding. Undaunted by the Supreme Court decision, within days, the FDA reissued guidelines to its field officers to distinguish between acceptable compounding activities and unlawful manufacturing by pharmacies without a federally issued manufacturing license.

The authority for states to regulate pharmacy originates in the 10th Amendment to the US Constitution, which reserves most "police powers" to the states. The terminology could be misleading, if "police power" were thought to refer to law enforcement officers only. In fact, as the term is used in the law, the "police power" reserved exclusively to the states means the states have the authority to pass laws designed to protect the health, safety, and welfare of its citizens. Note that the Constitution reserves most "police powers" to the states. As might be expected, there are exceptions that permit the federal government to "pre-empt" inconsistent state laws, if the federal government determines it will "occupy the field" of a particular subject matter. Another example is offered to clarify the point. Every state has laws regarding the labeling and packaging of drugs dispensed pursuant to a prescription. Some states even have laws regarding the type of container used to contain prescription drugs. The CPSC, a federal agency, acting under the auspices of the federal PPPA has "pre-empted" inconsistent state laws dealing with the packaging of "household substances," which include prescription drugs. Under the applicable regulations, nearly every drug dispensed by prescription must be in a child resistant container, unless the patient or prescriber requests otherwise. Due to the pre-emption, any state law not consistent with the demands of the CPSC regulations would have no force of law, and pharmacists are required to follow the federal mandates.

Perhaps it is too simplistic to put it this way, but another general rule to use in determining which jurisdictional body controls a subject matter is to think of state laws as regulating the *practice of pharmacy* and the federal government as regulating *pharmaceuticals*, including their marketing, production, and distribution. As with all laws, there are exceptions

to this general rule. Nonetheless, it should help readers better comprehend the scope of the jurisdictional authority of the different governmental bodies.

Pharmacoeconomics

Practitioners and managers face a multitude of economic challenges as the discovery of new therapies seems boundless, whereas payers' and patients' resources to purchase these cures are limited. How does a person decide which are the best medicines to use within restricted budgets? The continuing impact of cost containment is causing administrators and policy makers in all health fields to closely examine the costs and benefits of both proposed and existing programs. It is increasingly evident that private employers and public agencies demand that health programs be evaluated in terms of clinical and social outcomes related to costs incurred. Cost–benefit analysis and other pharmacoeconomic tools are ways to analyze the value of interventions and services to patients. These methods supplement the traditional marketplace value as measured by the prices the patient or patron is willing to pay. As public and private insurance agencies continue to pay for a higher percentage of prescriptions dispensed, pharmacists are very cognizant that pharmacy services and therapeutic interventions require substantial cost justification to survive and thrive in the future.[1–7]

Pharmacy entrepreneurs have established numerous innovative roles for pharmacists, such as home intravenous therapy, drug-level monitoring, parenteral nutrition management, hospice care, and self-care counseling, among others. The use of valid economic evaluation methods (e.g., cost–benefit and cost-effectiveness analysis) to measure the value and impact of new services, such as medication therapy management (MTM), can increase acceptance and benefit of such programs by the medical profession, third-party payers, and consumers.[8–10]

There is increasing competition among health professionals for the limited dollars and resources available. Within institutions and communities, pharmacists have to increasingly compete with nursing, medical, and other groups for adequate reimbursement and payment.[11,12] Therefore, pharmacy must document the cost-benefits of distinct pharmacy services and must develop priorities for those interventions to successfully compete in the ever-changing healthcare landscapes.

As a general background, it is important to appreciate the types of evaluations involved when examining costs and consequences in health interventions. To facilitate an understanding of terminology used in this section, the reader is referred to the glossary of terms in Table 12.1. In addition, Table 12.2 provides a concise framework which differentiates the key pharmacoeconomic methods. Drummond *et al.*[13] emphasize that full economic evaluations involve the comparison of at least two interventions and an examination of all costs and consequences.

Community pharmacy economics and management

The economic effect of the healthcare industry on our society is difficult to evaluate. However, recognizing that healthcare currently represents more than 17% of national gross domestic product (GDP) should give some indication of its effect.[14] It is accepted that advances made by the industry during the past few decades have reduced morbidity and mortality rates that, in turn, have increased productivity and added to the gross domestic product. At the same time, the cost of healthcare is rising at a faster rate than the consumer price index (CPI) for all items, and this cost continues to represent an increasing share of the GDP.

Economics of pharmaceuticals

The magnitude of healthcare expenditures in the United States and the growing governmental involvement as a third-party payer of healthcare costs are evidence of society's commitment to providing the best care possible for all citizens. Those involved in the delivery of healthcare share society's commitment and, therefore, must be concerned with the economics of the delivery system.

In 2011, recent market trends in prescription drug sales continued together with important new developments in the treatment of several diseases. Spending grew slowly, in line with the trend of annual growth of 5% or less since 2007. Total healthcare spending reached $320 billion, up by about $50 billion since

Table 12.1 Glossary of terms	
Contingent valuation	A method for evaluation of benefit or value to individuals of therapy that uses survey methods to establish willingness-to-pay.
Cost–benefit analysis (CBA)	A type of analysis that measures costs and benefits in pecuniary units and computes a net monetary gain/loss or a cost–benefit ratio.
Cost-effectiveness analysis (CEA)	A type of analysis that compares interventions or programs having a common health outcome (e.g., reduction of blood pressure, life-years saved) in a situation in which, for a given level of resources, the decision maker wishes to maximize the health benefits conferred to the population of concern. This type of analysis can be used to assess cost-effectiveness efficiency.
Cost-minimization analysis (CMA)	A comparison in which inputs are measured in monetary values and outputs are assumed to be identical.
Cost-utility analysis (CUA)	A type of analysis that measures benefits in utility-weighted life-years (QALYs) and that computes a cost per utility-measure ratio for comparison between programs.
Decision analysis	An explicit quantitative approach for prescribing decisions under conditions of uncertainty.
Decision tree	A framework for representing alternatives for use in decision analysis.
Direct costs	Those costs that are wholly attributable to the service in question, for example, the services of professional and paraprofessional personnel, equipment, and materials.
Discount rate	Rate of discount used to convert future costs and benefits into equivalent present values; typically 2–6% per annum.
Equity	Fairness in the allocation of resources or treatments among different individuals or groups
Indirect costs	(1) Societal, economic, and productivity losses due to morbidity and early mortality; also (2) sometimes used to refer to overhead costs based on costs that are shared by many services concurrently, for example, maintenance, electricity, and administration.
Net benefit	Total benefit (in monetary units) minus total cost (in monetary units); a basic decision criterion in cost–benefit analysis.
Opportunity cost	The opportunity cost of a commodity is the value of the best alternative use to which those resources could have been put; the value of the productive opportunities foregone by the decision to use them in producing that commodity.
Pharmacoeconomics	The study of how individuals and societies choose to allocate scarce pharmaceutical and health resources among competing alternative uses and to distribute the products and services among members of the society.
Preference-based measures	Also referred to a utility measures or quality-adjusted life year measures. Patients are asked to imagine possible health states and provide score to reflect their preferences for various scenarios, on a scale of 1.0 (perfect health) to 0 (worst possible health state or death).
Quality of life (QOL)	Physical, social, and emotional aspects of a patient's well-being that are relevant and important to the individual.

(continued overleaf)

Table 12.1 *(continued)*

Quality-adjusted life year (QALY)	A common measure of health improvement used in cost-utility analysis; combines mortality and quality of life gains (outcome of a treatment measured as the number of years of life saved, adjusted for quality).
Sensitivity analysis	A process through which the robustness of an economic model is assessed by examining the changes in results of the analysis when key variables are varied over a specified range.
Utility	A measure of value of an outcome that reflects attitudes toward risk. Utility scores are often obtained from patients with questionnaires (EQ-5D) or instruments, such Visual Analog Scales (VAS), Standard Gamble (SG), or Time Trade Off (TTO).
Willingness-to-pay	The maximum amount of money an individual is prepared to give up to ensure that a proposed healthcare intervention is undertaken.

For a more comprehensive glossary see Berger ML *et al. Health Care Cost, Quality, and Outcomes. ISPOR Book of Terms*. Lawrenceville, NJ: International Society for Pharmacoeconomics and Outcomes Research, 2003.[1]

Table 12.2 Types of pharmacoeconomic evaluations

		Are both costs and consequences of the alternatives examined ?		
		NO		YES
		Examines only consequences	Examines only costs	Examines both
Is there comparison of two or more alternatives?	**NO**	Outcome description	Cost description	Cost-outcome description
YES	Efficacy description	Cost analysis	Full economic evalution (CBA, CEA, CUA, etc.)	

Adapted from Drummond MF *et al. Methods for the Economic Evaluation of Health Care Programs*. Oxford: Oxford University Press, 2005.[13]

2006 and $125 billion since 2002, representing an increase in nominal spending of 3.7%, but when calculated on a real *per capita* basis an increase of only 0.5%.[15,16]

The share of prescription drug spending by third-party payers has increased significantly over the past 15 years.[17,18] Although some look on third-party payment as a mechanism for solving the high cost of healthcare, including the drug-cost segment, it should be understood that third-party payment does not reduce the cost. It simply spreads it over a larger population. Actually, third-party payment may increase the total cost of healthcare as additional administrative costs and increased use of products and services are inherent in these programs. It follows that third-party payers, whether governmental or private, have an obligation to their beneficiaries to ensure access and the delivery of quality services at reasonable prices. In this regard, health professionals, including community pharmacists, find their products and services under scrutiny by a sophisticated group of agencies representing a large portion of the general public.

Today, approximately 85 to 90% of prescriptions filled in a community pharmacy are partially or completely paid by a third-party payer.[17,18] Private insurance funds about 42% of the nation's prescription costs, the government funds 37%, and the consumer funds 21% through out-of-pocket expenses.[17] The implementation of Medicare Part D in 2006 has increased the public funding of prescription drugs. Those who provide pharmacy services must consider economic and professional factors as they make

decisions about participation in these programs. Pharmacy owners and managers face the challenge of maintaining the economic practicality of their pharmacies when contracting with pharmacy benefit managers and other payers. Participation in such contracts often increases administrative expenses for the pharmacy, while providing reimbursement that may not be adequate to cover the costs of providing quality pharmacy services.

Previously, the cost of healthcare was given little attention by the providers of health services. It was assumed that the primary obligation of the provider was to ensure the physical well-being of the patient, without regard to cost. It is now apparent that it does little good to develop a level of healthcare unsurpassed in the world, if a sizable segment of the population cannot afford to pay for it. The obligation of health professionals to consider the economic dimensions of healthcare is now recognized.

In 2010, the average generic prescription, both for short-term and 90 day medications, cost $72, compared with $198 for the average brand-name drug. Average co-payments for that year were $6 for generics, but brand-name drugs given preferred status by an insurer were four times as expensive, and non-preferred brands almost six times as costly.[19]

Pharmacy practice laws in all states have been amended to allow pharmacists to practice generic substitution. These amendments allow the pharmacist, under specified conditions, to choose drug products with due regard for both the physical and the economic well-being of the patient. The generic substitution amendments are tangible evidence of societal concern with the cost of healthcare. Additionally, pharmacy and therapeutic committees who develop formularies and recommend prescription benefit designs consider cost in their decision-making. The concern of health professionals with the cost of healthcare now reinforces the efforts of consumer groups, government, and others involved in financing healthcare, to the end of providing the best care for all, regardless of economic status.

The Institute of Medicine (IOM) is an independent organization that conducts studies and issues reports to provide unbiased and authoritative advice to policy makers and the public.[20] The IOM has issued several reports related to medication safety problems in the United States. With the publication of these reports and the implementation of Medicare Part D, there is increased focus on the appropriate and safe use of pharmaceuticals. A 2009 study found that the cost of drug-related morbidity in the United States is nearly $289 billion annually, representing 13% of total healthcare expenditures.[21] Poor medication adherence leads to emergency room visits and hospitalizations, and ultimately poor patient outcomes.[22] The Medicare Prescription Drug, Improvement, and Modernization Act included medication therapy management (MTM) in the regulation to improve medication use and reduce unnecessary costs. MTM is defined as "a distinct service or group of services that optimize therapeutic outcomes for individual patients."[23] MTM includes conducting medication reviews, developing personal medication records and medication action plans, and intervening to prevent or resolve medication-related problems. Studies, such as the Asheville Project, have shown that MTM services provided by community pharmacists can reduce direct medical costs and improve patient outcomes.[24] Community pharmacists have an important role in ensuring appropriate use of medications and reducing unnecessary healthcare costs.

Product recalls and withdrawals, and disposal of unused medicines

Occasionally, pharmaceutical manufacturers must recall or withdraw products from wholesalers, pharmacies, and/or patients. In the preceding two decades we have seen the number of drug recalls range from approximately 300 per year, to over 400 per year. (In the year 2009 the number of recalls jumped to over 1700. Approximately 1000 of them were due to one repackaging firm that is no longer a going concern. That year is an anomaly, and as such will not be addressed further.) The reasons for recalls and withdrawals range from life-threatening situations (e.g., a product that is supposed to be sterile but is instead contaminated with bacteria) to situations where there is no health hazard or risk, but simply, the product does not measure up to the quality control standards that the pharmaceutical community wishes to present to the public (e.g., a label that appears upside-down on its container).

It is impossible to anticipate every situation, and it is unwise to have a "cookie cutter" solution for every

recall or withdrawal.[25] It is hoped that pharmacists will take these guidelines and then enhance or modify them to fit their particular practice.

It is helpful to employ a simple aid that the ancients used in analyzing rhetorical thoughts and questions.[26] Today a vast number of people seem to be familiar with them as a journalistic tool for gathering facts and circumstances: The "W"s; Who What When Where Why How.

Marketing pharmacy care services

"Marketing is a discipline that promotes the resolution of problems by identifying and meeting the needs of customers. In pharmacy practice, the customers served by marketing may be patients, physicians, nurses, or anyone else who interacts with pharmacists."[27]

"Marketing can be used to solve almost any problem in pharmacy. It can be used in personal career management, in influencing change in practice settings, and in enhancing job effectiveness. Marketing can help persuade patients to adhere to medication plans, physicians to prescribe medicines appropriately, and management to support pharmacy practice initiatives. It can be used to recruit good employees, attract and keep patients, provide innovative services, and compete with other health professions for a portion of the health care pie."[28]

Marketing is a proven approach that can be used by pharmacists to better serve their patients. As pharmacists work to expand their role in providing pharmacy care services, the process of marketing can be used to influence demand for these services. In recent years practitioners have worked to re-engineer their practices to incorporate a philosophy of pharmacy care into their practices. This re-engineering has resulted in pharmacies presenting a *new look* to their patients by incorporating patient consultation areas, workflow improvements, and the increased use of pharmacy technicians within the practice. Along with the new look, pharmacists are performing *new activities* in their practices as new services are offered to their patients. To reach their full potential, pharmacists must effectively market their services.

An understanding of patients' needs and wants is essential for developing and implementing a successful plan for marketing pharmacy services. The need for most patients is to have good health. If their health deteriorates, a need exists to return to a healthy state. Patients have many alternative products, services, and providers to help them achieve this healthy state, including pharmacists and pharmacy care services. Patients choose healthcare options that they believe will best fit their needs and desires at an acceptable price. To compete with the various options available to patients, pharmacists should incorporate the marketing process into the planning, design, and management of their operations.

To successfully implement pharmacy care services, pharmacists need to effectively market these services. The steps of the marketing process provide a basic framework that can be applied to any practice. Each step of the marketing process may be individualized to a particular practice site, demographic area, patient base, competitive environment, and recognized financial constraints. Regardless of the pharmacy involved, however, the key to success lies in knowing the customer through market research and systematic planning of strategies to reach and serve targeted individuals.

A thorough analysis of one's environment is essential to identify key targets and stakeholders, recognize opportunities and threats to the practice's success, and ensure that marketing resources are used in the most cost-effective manner.

When implementing the marketing plan in an individual pharmacy, pharmacists should use goals, objectives, and individual tasks to give direction to the marketing process. Including all employees in this process, from clerks to pharmacists, helps to ensure consistency and commitment from all involved. During the implementation phase of the marketing plan, regularly scheduled meetings should be held to keep employees updated and informed on the marketing efforts. By carefully considering the concepts described in this section and by involving all employees of the pharmacy in the process, pharmacists can achieve the optimal results from their marketing plan.

Clinical pharmacy services

The addition of clinical pharmacy services to healthcare teams has demonstrated significant improvement in therapy outcomes, as well as patient and provider

satisfaction, and promotes cost savings for the healthcare system.[29,30] Pharmacy services designed to improve patients' access to care, provide disease management, and that are focused on quality-related outcomes contribute to optimizing drug costs within the total costs of patient care. Despite efforts by national pharmacy organizations, lack of recognition by Medicare of pharmacists as providers under Part B limits pharmacists' ability to obtain reimbursement for such services and remains a major barrier for continued expansion or justification of new clinical pharmacy services in the ambulatory environment. Exploration of mechanisms for reimbursement for clinical services is needed to further advance the provision of cognitive services in this arena.

The Medicare Modernization Act of 2003 created a prescription drug benefit (Part D) for Medicare recipients, and, for the first time, Congress included an MTM benefit that named pharmacists as the key providers.[31] The legislation requires payers to reimburse providers of MTM services for specific high-risk patient groups. This is a precedent for reimbursing pharmacists for patient care services that are not associated with product.[31] However, due to the lack of recognition of provider status for pharmacists under Medicare Part B, many state Medicaid plans, and many private payers, it is necessary for pharmacists to pursue alternative reimbursement mechanisms to create viable ambulatory practice models. Pharmacists practicing in all settings should become familiar with opportunities allowing for reimbursement for services not associated with dispensed drug product (i.e., cognitive pharmacy services).[32] Pharmacists practicing in a variety of settings, including ambulatory clinics, outpatient pharmacies, and potentially inpatient pharmacy settings are eligible to obtain reimbursement for specific services.

Current billing methods for pharmacists

Medication Therapy Management (MTM)

MTM is a term used to describe a broad range of healthcare services provided by pharmacists. In a document developed by the American Pharmacists Association, the MTM service model is described as including the following core elements:[33]

1. medication therapy review (MTR),
2. personal medication record (PMR),
3. medication-related action plan (MAP),
4. intervention and/or referral, and
5. documentation and follow-up.

MTM services can be provided by pharmacists at any point along the continuum of healthcare. Patients with potential to benefit from MTM provision by a pharmacist can be identified by physicians, pharmacists, or self, and who are at higher risk for medication-related problems. Those patients taking multiple medications for disease states associated with high morbidity, mortality, or low quality of life may benefit most from pharmacists' provision of MTM. Other opportunities to improve care by provision of MTM by a pharmacist include patients transitioned from the inpatient setting to the ambulatory environment, patients discharged from skilled nursing care and re-integrated into the primary care setting, and immediately subsequent to emergency department visits.

MTM programs are demonstrating positive clinical, economic, and humanistic outcomes across diverse patient populations in various patient care settings. Examples of successful MTM programs provided by pharmacists are emerging in the public and private sector. In the public sector, examples of state Medicaid reimbursement and Medicare Part D reimbursement programs exist, whereas, in the private sector, MTM programs are offered to traditionally insured groups, managed care populations, and self-insured employers.[33]

Codes specific to MTM services have been assigned by the American Medical Association Current Procedural Terminology (CPT) Editorial Panel. Briefly the codes are as follows:

- 99605 – MTM service(s) provided by a pharmacist to an individual patient during a face-to-face encounter that involve an assessment and intervention if provided; used to code the initial 15 minutes of an initial encounter with a new MTM patient
- 99606 – Initial 15 minutes with an established patient
- 99607 – Each additional 15 minutes of an initial or subsequent MTM encounter; list separately in addition to code for primary service and in conjunction with 99605 or 99606

"Facility billing"

For those pharmacists practicing in a hospital-associated clinic setting, facility billing has proven a viable billing method to sustain existing clinical services, as well as justify expansion of such services in the outpatient arena. Facility billing refers to the use of the hospital's technical charge for services provided in an outpatient department of a hospital and represents "hospital resources utilized." Pharmacists can bill for services in hospital-based clinics using CPT Evaluation and Management (E&M) Codes 99211–99215 for facility billing. The terms "technical fees" and "facility fees" are often used interchangeably and represent "incident-to" billing in a hospital-based outpatient clinic. A hospital-based clinic is a clinic financially tied to the hospital and appears on the hospital's cost report.[34]

"Incident to"

"Incident-to" means the pharmacist is billing under a recognized CMS provider, including a physician, clinical psychologist, licensed clinical social worker, physician assistant, nurse practitioner, clinical nurse specialist, or certified nurse midwife. The criteria for billing "incident to" in a hospital-based clinic include services that are:

1. furnished by or under arrangements made by the participating hospital;
2. an integral, although incidental, part of a physician's or non-physician practitioner's services;
3. furnished in the hospital or in a department of the hospital; and
4. furnished under direct supervision of a physician or non-physician practitioner.[35]

Incident-to billing may also be used in a physician office setting for those services provided by a non-physician, if the physician determines such services medically necessary. Reimbursement under this method of billing tends to be substantially less than other types of billing methods, and, therefore, other justification methods (i.e., cost-reduction, cost-avoidance, patient/provider satisfaction) are typically employed to substantiate pharmacy services within a physician office setting.

"First-party" payment

First-party payment refers to direct out-of-pocket payment for clinical pharmacy services. Pharmacists practicing within their scope, as outlined by state pharmacy practice laws under collaborative practice agreements, can directly bill patients for services rendered. This is an often overlooked, yet important, method of billing for services, the importance of which should not be minimized.

"Third-party contracting"

Contracting directly with third-party payers for reimbursement for cognitive services is becoming more prevalnt. However, a discrepancy still exists among payers; many third-party organizations do not recognize pharmacists as providers of MTM, and claims are often denied. Pharmacists should be diligent in their pursuit of identifying insurers that recognize the benefits realized by pharmacists' intervention and the profession's ability to improve clinical outcomes and decrease inappropriate healthcare resource utilization and overall healthcare-related costs.

Diabetes Self-Management Training (DSMT)

Pharmacists involved in diabetes education programs can receive reimbursement. Diabetes self-management training (DSMT) is defined as a collaborative process through which people with or at risk for diabetes gain the knowledge and skills needed to modify behavior and successfully self-manage the disease and its related conditions. Pharmacists who provide diabetes care and those interested in initiating services should be aware of the national standards for diabetes education. The most recent revision was completed in the summer of 2007, and the standards are available online at http://www.diabetes.org/uedocuments/erp-national-standards-revised-0707.pdf. The education program must meet all national standards for diabetes education.[36] Minimum program staff is defined as one or more instructors. The instructors should be of one of three disciplines: a registered nurse RN, registered dietician RD, or a pharmacist. The 2007 standards provide additional opportunities for more pharmacists to offer ongoing diabetes education

programs that are financially sustainable. Medicare will only reimburse for the diabetes education codes if the program is recognized by one of two accrediting agencies: the American Diabetes Association (ADA) or the American Association of Diabetes Educators (AADE). Recently, the Indian Health Service (IHS) was removed as an accrediting agency, and IHS programs will continue their credentialing with either ADA or AADE. More detailed information regarding the application process can be found at http://professional.diabetes.org/Recognition.aspx?typ=15andcid=84040 and http://www.diabeteseducator.org/ProfessionalResources/accred/.[37,38] DSMT must be ordered by the provider (physician or non-physician) managing the patient's diabetes. DSMT is a standalone provision. This means the "incident-to" requirements do not apply to DSMT services. There are 10 hours of initial training, billed as G0108 (individual) or G0109 (group), in 30 minute increments each. Two additional hours per year are available thereafter. Diabetes programs exist in multiple settings. DSMT can be billed from a hospital, hospital-based clinic, free-standing clinic, or community pharmacy. Kentucky recently approved licensing of diabetes educators. This licensing allows educators to bill for DSMT directly to all payers. Similar efforts have been proposed on the national level. If certified diabetes educators (CDEs) were considered approved Medicare providers, pharmacist CDEs would have another direct route to Medicare reimbursement, other than as a mass immunizer.[36–39]

Laboratory testing

Pharmacists providing point-of-care laboratory testing can bill for labs by obtaining a Clinical Laboratories Improvement Amendments (CLIA)-waived laboratory license. Particularly in chronic disease, point-of-care testing allows for more rapid decision making. Most often, results are available in less than 5 minutes, and running the test is minimally complex. All laboratory tests have a specific CPT code, and all laboratory tests must have a matching International Classification of Disease (ICD-9) code. For example, HbA1c for diabetes assessment is billed 83036 and is coded 250.00. A complete guide to establishing a CLIA waived lab license in outpatient settings is available.[40]

Documentation: The SOAP System

Many advancements in clinical documentation can be traced to the work of Dr. Lawrence Weed, a physician and pioneer in creating systematic approaches to organizing the collection, storage, and use of clinical information.[41] Weed's intuitive problem-oriented medical record (POMR) represented a significant advance from the fragmented source-oriented record that had preceded it, in which notes were filed according to the source from which they had come, such as physician orders, nursing notes, or laboratory reports.

As described by Weed, the POMR consisted of four essential components:

1. defined database,
2. complete problem list,
3. initial plan, and
4. progress notes.

Weed recommended that progress notes be further organized to reflect the four types of information commonly found in clinical documentation. This has come to be known as the SOAP approach to clinical documentation SOAP as an acronym for Subjective, Objective, Assessment, and Plan.

Subjective information includes a description of the problem and the associated symptoms in the patient's own words. These notes often contain verbatim quotes from the patient ("I feel hot and achy, and I have a splitting headache") and/or those close to the patient, such as a relative or friend ("She has been complaining of fever and headache for a couple of days").

Objective information includes observations made and data collected and/or considered by the caregiver that is relevant to the problem, including physical exam or assessment or laboratory data (e.g., Patient presents to the pharmacy in acute distress, complaining of flu-like symptoms for the past 2 days. Complexion is pale, skin is warm and dry to the touch, and temperature is 101°F orally).

The assessment component of the note allows the caregiver to express his or her net conclusion or opinion about the problem based on the subjective and objective information available (e.g., Patient's symptoms are consistent with flu). The assessment note may be seen as a diagnosis, clinical impression,

or a change in the condition of the patient for better or worse.

The plan component of the progress note describes the recommended course of action based on the new information considered by the caregiver. This may include revising a previous plan or establishing a new plan and may contain recommended treatment, patient education/instruction, and/or the need for additional information (e.g., recommended acetaminophen 650 mg every 4–6 hours, push fluids, and bed rest. If symptoms worsen, or if not improved in 48 hours, patient is instructed to see physician).

Many permutations of the SOAP approach to clinical documentation have appeared over the years. However, even under different acronyms, most are essentially minor derivations of Weed's simple, yet effective approach. By organizing clinical documentation in a logical and consistent format, SOAP maintains significant advantages over unstructured approaches for ensuring greater accuracy and completeness of a patient care encounter. Additionally, since the SOAP approach is widely used in the clinical training of many different health disciplines, it is likely more familiar and, therefore, more acceptable to health professionals and claims administrators working for third-party payers.[42]

Pharmacists should maintain and adequately document a comprehensive pharmaceutical care plan, preferably as a component of a multidisciplinary, collaborative drug therapy agreement. The care plan, if separate, must be accessible to prescribers, pharmacists, and other healthcare providers involved in patient care. The pharmacist is responsible for communicating the plan to the patient and other healthcare providers. The care plan should document the following:

1. patient's medical and medication history;
2. medication therapy assessment;
3. medication therapy regimen, including drug name, strength, route of administration, and indication for therapy;
4. goal(s) of therapy;
5. monitoring parameters; and
6. proposed length of therapy.

Ongoing assessment and evaluation of the patient's response to therapy and achievement of therapeutic goals should be documented in the patient's care plan. Ideally, an electronic medical record (EMR) would be utilized, as this is accessible to all professionals involved in patient care. Meticulous documentation of patient care activities performed by pharmacists must be maintained to substantiate the level of service billed by the pharmacist. Standardized formatting for documentation of MTM services exists; pharmacists engaging in the provision of MTM should familiarize themselves with documentation requirements for reimbursement. Multiple resources and websites available to pharmacists describe documentation specifically for MTM programs.[42–44]

Pharmacist credentialing

Pharmacists participating in direct patient care activities should demonstrate competency in the areas of care provided. Board and/or continuing education certification programs should be completed by all pharmacists and documented in a retrievable format. Examples of minimum requirements may include demonstration of proficient communication skills, basic physical assessment skills, laboratory interpretation, and disease- and age-specific competencies. Minimum requirements for level of education, experience, and/or post-graduate training may be established for specific responsibilities or positions. A model for ongoing evaluation should be developed to ensure pharmacists remain competent.

The Board of Pharmaceutical Specialties (BPS) has recognized six specialty areas of pharmacy practice, including ambulatory care, nuclear pharmacy, nutrition support, oncology, pharmacotherapy, and psychiatry. The newest certification offered by the BPS is the Board Certified Ambulatory Care Pharmacist (BCACP) designation. This exam was offered for the first time in October, 2011.

From patient to provider, the value of the BPS-certified practitioner registers throughout the healthcare continuum. For pharmacy professionals, documentation of specialized experience and skills yields the additional benefits of personal satisfaction, financial rewards, and career advancement.[45]

Other disease-specific certification may be obtained as a means to increase competency of

pharmacists participating in MTM activities. The certified diabetes educator (CDE) credential is available to pharmacists, physicians, and other allied health professionals. This credential recognizes a healthcare professional is competent to provide diabetes education. For pharmacists involved in diabetes management under collaborative practice agreements, the Board Certification-Advanced Diabetes Management (BC-ADM) credential signifies a pharmacist is competent in pharmacologic management of diabetes. The American Association of Diabetes Educators oversees this exam. To sit for the BC-ADM examination, candidates must hold a current, active RN, RD, or RPh license and hold a graduate degree from an accredited program, and, within 48 months prior to applying, the applicant must complete a minimum of 500 clinical practice hours in advanced diabetes management. The BC-ADM exam is offered in June and December of each year. Additionally, pharmacists involved in anticoagulation management can apply to the National Certification Board of Anticoagulation Providers to obtain the Certified Anticoagulation Care Provider (CACP) credential. Eligible disciplines include RN, Nurse Practitioner (NP), registered or licensed pharmacist (BS pharmacy or PharmD), licensed physician (MD or DO), or physician assistant (PA). The applicant must provide documentation of a minimum of 750 hours of active anticoagulation patient management in the 18 months immediately preceding the application deadline.

National provider identifier

The Health Insurance Portability and Accountability Act (HIPAA) was passed by Congress in 1996 to set a national standard for electronic transfer of all health data, even medical claims. To meet HIPAA compliance, all health professionals, regardless of discipline, are required to obtain a national provider identifier. This number is unique to each provider and healthcare entity. Every pharmacist and pharmacy should have an National Provider Identifier (NPI) number. Pharmacists can obtain an NPI by applying online at https://nppes.cms.hhs.gov/NPPES/Welcome.do. The application process takes approximately 15 minutes, and the NPI number is received electronically within 1 week.[46]

Medical claims and basic billing terminology

One significant limitation to written documentation is the difficulty in translating it into quantifiable data consistent with claims administration systems. Submitting claims for services requires that key data related to the care of the patient be converted by standardized coding systems into recognizable codes. Standardized coding systems exist that allow a claim to reflect what happened in a healthcare encounter.

Billing using the CMS-1500

The CMS-1500 claim form is the most widely recognized and accepted format for billing third-party payers for healthcare services. It is required by Medicare and many other third-party payers for payment of healthcare services. The form consists of 33 boxes or fields of required information. Fields 1–13 contain information about the patient and the insured beneficiary. The remaining 20 fields, 14–33, contain information about the provider or supplier of the service. Two fields on the form are particularly important for ensuring prompt and correct payment: field 21 and field 24D.

The first rule of third-party payment for healthcare services is there must be a demonstrated medical need for the service performed. On the CMS-1500, need is established by the patient's diagnosis and related background facts about the condition being treated.

International classification of diseases coding

Field 21 on the CMS-1500 form is labeled 'Diagnosis or Nature of Illness or Injury.' This field contains four slots, numbered 1–4, for entering patient diagnostic information using the ICD-9-CM (International Classification of Diseases, 9th Revision, Clinical Modification) coding system, commonly referred to simply as 'ICD-9.' This reference is available through a variety of medical publishers.

At least one diagnosis code must be reported on each claim. Up to four codes may be reported, if needed to accurately represent the reason for the service that was provided. When more than one is reported, the code that represents the disease, condition, or problem primarily responsible for the service

provided should be listed first. Any additional or supplementary codes are listed after, in order of their proximal relationship to the primary code.

The ICD-9 coding system contains 19 categories of codes. Categories 1 to 15 (codes 001–779) identify diseases and related medical conditions. Category 16 (codes 780–799) designates symptoms, signs, and ill-defined conditions. Category 19 (codes 800–999) relates to injury and poisoning. Each of these categories contains numerical codes of three to five digits, depending on the level of specificity and precision. For example, undifferentiated asthma is coded as 493 in the ICD-9 system. For asthma with an allergic cause, 493.9 would be the appropriate selection. An additional fifth digit is also available if the patient does or does not have a history of status asthmaticus (i.e., 493.91 or 493.90, respectively). This system of five-digit codes means the level of diagnostic precision increases with each successive digit. With few exceptions, payers require the submission of diagnoses coded to at least the fourth digit. Failure to do so often results in payment delay or rejection. In addition, other common coding problems include:

- the patient's chronic diagnosis, which is not the reason for the encounter, is incorrectly billed as the primary diagnosis;
- the ICD-9 code selected is inaccurate or insufficiently precise (i.e., not coded to the fourth or fifth digit when appropriate); and
- a supplementary code is used inappropriately as the primary reason for the encounter.

In addition to the previous 19 categories of numerical codes, the ICD-9 system provides two categories of supplementary codes. The first of these is the Supplementary Classification of Factors Influencing Health Status and Contact with Health Services (V01–V82), more commonly known as the "V codes." Of particular interest to pharmacists within the V codes are V58.67 – Encounter for long term use of insulin and V58.61 – Long-term (current) use of anticoagulants. Adding a V-code to the claim is similar to adding adjectives to further describe nouns.

Because there is no place for narrative description of the patient's condition on the CMS-1500, it is particularly important that code selection is as accurate and specific as possible.

CPT Coding

Field 24D on the CMS-1500 form is labeled "Procedures, Services, or Supplies." Payers who require the CMS-1500 require the use of Physician's Current Procedural Terms (CPT) codes or the Centers for Medicare and Medicaid Services (CMS) Common Procedure Coding System. Although CMS recently changed its name from the former Health Care Financing Administration (HCFA), these codes are still commonly referred to as HCPCS (pronounced hick-picks) codes. As with diagnosis, it is essential that pharmacists thoroughly understand the codes used in this field to describe the service that was performed.

The CPT codes were created by the American Medical Association in 1966 to be a listing of descriptive terms and identifying codes for reporting medical services and procedures performed by physicians. In 1983, HCFA developed HCPCS as a uniform method for healthcare providers and medical suppliers to code professional services, procedures, and supplies to meet the operational needs of the Medicare and Medicaid programs.

The HCPCS classification is organized into three numbered levels of codes, each of which represents a unique coding system. Most pharmacists who wish to bill for their patient care activities will find the CPT codes the most useful, especially that section known as the Evaluation and Management, or E&M codes. Each five-digit numerical E&M code begins with a "99" prefix (i.e., 99201–99499). The codes are divided into several categories, including office visits, hospital visits, and consultations. These categories are further subdivided into two or more subcategories. For example, separate codes are available for an outpatient office visit with a provider, depending whether the patient is established or new to the practice.

E&M code selection is based on three key components, with additional considerations becoming relevant only under special circumstances. Once the appropriate category is selected (e.g., outpatient office visit with an established patient), the proper code is determined on the basis of:

1. the level of history taken on the patient (the four levels of history include problem focused, expanded problem focused, detailed, and comprehensive;

2. the extent of the examination that was performed (the four levels of examination include problem focused, expanded problem focused, detailed, and comprehensive); and
3. the level of medical decision making that was required to perform the service (the four levels of medical decision making include straightforward, low complexity, moderate complexity and high complexity).

Selection of the level of medical decision making required is itself determined on the basis of three additional considerations:

1. the number of diagnosis or management options,
2. the amount and/or complexity of data reviewed, and
3. the risk of complications and/or morbidity or mortality.

Five different codes are available to describe an office visit with a new patient (99201–99205). Likewise, five codes are available to describe an office visit with an established patient (99211–99215). Many pharmacists in the community practice setting find that these ten codes fit most of their needs related to completing a CMS-1500 claim form.

Table 12.3 illustrates how a provider would use the three key components of history, examination, and medical decision making to select the code that best represents the nature of a patient care encounter. For example, 99213 would be the most appropriate code to describe an office visit with an established patient that required expanded problem-focused history and examination, and a relatively low level of medical decision making.

Under special circumstances, other considerations become operative in code selection. For example, when counseling or coordination of care activities

Table 12.3 Definitions of selected evaluation and management (E&M) codes

Codes for a new patient office visit					
E & M codes	**History**	**Examination**	**Medical decision making**	**Time**	**RVUs**
99201	Problem focused	Problem focused	Straightforward	10 min	.82
99202	Exp. problem focused	Exp. problem focused	Straightforward	20 min	1.32
99203	Detailed	Detailed	Low complexity	30 min	1.80
99204	Comprehensive	Comprehensive	Mod. complexity	45 min	2.66
99205	Comprehensive	Comprehensive	High complexity	60 min	3.33
Codes for an established patient office visit					
E & M codes	**History**	**Examination**	**Medical decision making**	**Time**	**RVUs**
99211	Minimal problems			5 min	.40
99212	Problem focused	Problem focused	Low complexity	10 min	.71
99213	Exp. problem focused	Exp. problem focused	Low complexity	15 min	1.00
99214	Detailed	Detailed	Mod. complexity	25 min	1.55
99215	Comprehensive	Comprehensive	High complexity	40 min	2.53

account for more than 50% of a patient encounter, selection of the proper E&M code among a sequence involving different levels of care is based exclusively on the amount of time the provider spent with the patient. For example, 99204 would be the most appropriate code to describe an office visit with an established patient dominated by counseling and requiring about 45 minutes to complete.

Table 12.3 illustrates the relative value unit scores (RVUs) that CMS has assigned to each of the codes using the resource-based relative value scale (RBRVS). The resulting RVU score is then regionally adjusted and multiplied by a monetary conversion factor to determine the dollar amount a provider will be paid for a particular service or procedure under Medicare.

As previously discussed, CPT codes specific to the provision of MTM are available and should be used by the pharmacist when submitting charges for services rendered to third-party organizations with whom contracts exist and who recognize pharmacists as providers of MTM services.

Additional information about CPT/HCPCS coding is available through the American Medical Association, CMS, and various commercial publishers of medical coding materials.[47]

Fee setting and the resource-based relative value scale (RBRVS)

At present, there exists no widely accepted standard for assigning professional fees to pharmacist services. For private pay patients, professional service fees are set by pharmacists in much the same way that other products and services are priced. Where these services are covered by insurance or third-party benefit plans, the pharmacist's professional fees are determined in negotiation with payers.

Many pharmacists who routinely bill major medical carriers for their services know that, under the Medicare program, physicians' fees are set by a resource-based relative value scale (RBRVS). Resource based relative value units (RBRVUs) are assigned to each CPT code and, as such, are a measure of physician productivity in some settings. Because some pharmacists using an "incident to model" positively impact the physician's RVUs by generating the 99211 CPT code, it is useful to describe the RBRVS system within the context of general medical billing.

By the early 1980s, government third-party payers had concluded that the UCR (usual, customary, and reasonable) method of compensating physicians and other medical care providers was financially unsound and encouraged abuse. This opinion was particularly prevalent in the Medicare program, in which it was decided that a standard fee schedule was needed for physician services. The result was the creation of an ongoing research project at Harvard University, known as the RBRVS project.

The RBRVS project was an attempt to create a method of reimbursing physician services based on the estimated resource input costs required to perform the services. The RBRVS used by Medicare to determine physicians' fees defines the resource input costs as consisting of four components:

1. the time required by the physician before, during, and after the service;
2. the intensity with which the time was spent;
3. the practice costs necessary to supply the service; and
4. the opportunity costs of additional training or specialization the physician may have been required to complete to provide the service.

The RBRVS combines these resource inputs into a model intended to reflect the relative costs efficient physicians would incur providing a given service, if a perfectly competitive market existed. Since it was not considered feasible to gather data on all 7000 Medicare procedure codes, researchers surveyed 3000 physicians in 18 specialties to determine the work necessary to perform over 400 medical services. They then grouped the procedures into broad classes of services assumed to be relatively similar in terms of resource inputs and extrapolated the results to procedures that were not surveyed.

The general approach used in the RBRVS has received widespread support from policymakers, as well as some physician organizations. As a result, it has been suggested that a similar approach may eventually be applied to determine the professional fees of other providers, including pharmacists.[42,48,49]

Claims for pharmacist services

As discussed previously, most pharmacists successfully billing third-party payers for their professional

services are doing so through the major medical carrier using the CMS-1500 universal claim form. Routine payment for professional pharmacy services has simply not made its way into prescription benefit plans in any meaningful way, since most prescription benefit managers (PBMs) continue to consider these services beyond the scope of the prescription benefit plans they manage. Since the X12N 837 claim represents the electronic equivalent of the CMS-1500 form, the HIPAA ruling effectively eliminates National Council for Prescription Drug Programs (NCPDP) and its code sets from relevance in the future electronic billing for professional pharmacy services, except where the service is traceable to a particular prescription drug claim, and is billed to a PBM. Clearly, there exists a split between prescription-related product billing (NCPDP) and the myriad other professional cognitive services pharmacists perform in their care of patients (CMS-1500, MTM).

Using the CMS-1500 to file pharmacist care claims

First issued in the early 1980s, the CMS-1500 (i.e., universal) claim form is the most widely recognized and accepted format for billing third-party payers for healthcare services. It is required by Medicare and many other third-party payers for payment of healthcare services. Still commonly referred to as the HCFA-1500 (pronounced hickfa), the most recent version was released in August, 2005 and is illustrated in Fig. 12.1.

In deciding whether to use the CMS-1500 to bill for pharmacist care services, the pharmacist should consider the nature of the service provided, as well as the payer to whom the claim will be submitted. Many pharmacist care services are discrete events that occur during the routine process of providing care, particularly prescription care, to patients. For some of these services, the value created is confined primarily to the prescription benefit plan. For example, when a pharmacist recommends a therapeutically equivalent, but less expensive product to a prescriber, the value created by the pharmacist is restricted to the differential in the ingredient costs of the two drug products.

In other cases, the value of the pharmacist's professional service goes beyond, or is less likely to be recognized as directly relevant to, the prescription drug benefit. An example would be the pharmacist's involvement in patient education, instruction, or disease state management activities. Since there are often no "hard dollar" savings to the prescription benefit plan from such services, the value created by the pharmacist is likely better recognized and appreciated by that component of the patient's medical insurance plan concerned with the total care of the patient, and the total cost of that care. This is what is commonly referred to as the "major medical" component of the patient's health insurance plan.

Pharmacists should consider filing the claim with the patient's major medical insurance carrier whenever they provide a service with which the primary value is likely realized through positive patient health outcomes or the prevention of negative health outcomes and their related economic sequelae. Although each carrier has its own policies and procedures for filing major medical claims, most require a CMS-1500 be submitted.[42]

Future directions

Patient centered medical home (PCMH)

The PCMH model is based on the premise that the best healthcare is not episodic and illness-oriented. Rather, high quality care is patient-centered, physician-guided, on-going, and cost-efficient.[49] A PCMH is an interdisciplinary practice that promotes a partnership between a patient and his or her healthcare team. The physician, with the assistance of his/her practice team, helps the patient navigate the complex and confusing healthcare system by coordinating and facilitating services with other qualified medical professionals.[49]

In 2011, the National Committee for Quality Assurance (NCQA) updated the current standards for recognizing a primary care practice as a PCMH. The PCMH 2011 program's six standards align with the core components of primary care:

- PCMH 1: Enhance Access and Continuity,
- PCMH 2: Identify and Manage Patient Populations,
- PCMH 3: Plan and Manage Care,
- PCMH 4: Provide Self-Care and Community Support,
- PCMH 5: Track and Coordinate Care, and
- PCMH 6: Measure and Improve Performance.

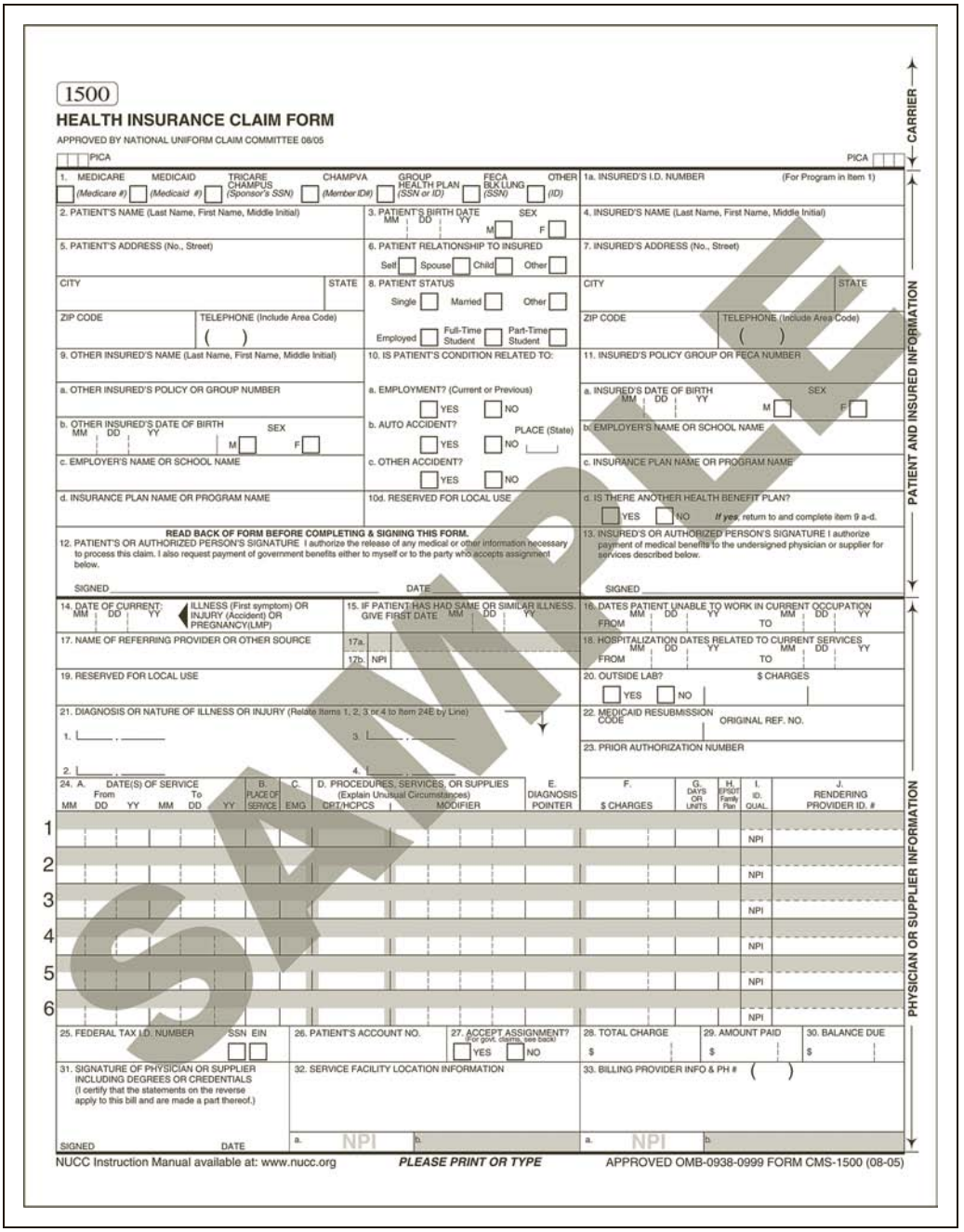

Figure 12.1 The most recent version of form "HCFA-1500."

These standards specify that physician-led practices implement evidence-based care plans, use non-physicians in care management, coordinate care transitions, support patient self-management, and track test results and patient referrals.[49] Pharmacists can play important roles in optimizing therapeutic outcomes and promoting safe, cost-effective medication use for patients in medical homes.

Budnitz *et al*. reported that up to 32% of adverse events leading to hospitalization were due to medications; furthermore, only 33 to 50% of patients with chronic conditions are adherent to their prescribed

medications.[50] Pharmacists can greatly impact medication-related patient outcomes by contributing to interdisciplinary care as the medication experts. Pharmacists can evaluate, through comprehensive medication review, the presence of therapeutic duplication, response to therapy, adverse drug reactions, suboptimal dosing, and adherence-related issues, and intervene to improve patient outcomes.

As the concept of PCMH continues to develop and expand at the core of healthcare reform, pharmacists can make substantial contributions to innovative, collaborative, interdisciplinary primary care models. Health-care professional teamwork is essential for care coordination and quality improvement initiatives to optimize chronic disease medication outcomes and promote medication safety.[51–53]

Conclusions

Like pharmacy practice itself, documentation is a learned skill. Increasingly, technology is assisting pharmacists to accurately and consistently document the care they provide. However, repetition and practice are required for pharmacists to develop good documentation skills. Until recently, pharmacy curricula provided relatively little opportunity for students to develop their written communication skills. The same can be said for the professional careers of most pharmacists. Due to the pharmaceutical care movement and the economic imperatives now facing the profession, these conditions are rapidly changing. Pharmacists who are participating currently or wish to participate in patient-centered care and who expect to be paid for their activities must master the art of clinical documentation and billing.

Pharmacists who wish to pursue compensation for their professional services must recognize that successful payment for pharmacist services is relatively new. Billing department personnel in most settings are largely unfamiliar with mechanisms for pharmacist reimbursement. Most government and private third-party payers still do not have well-defined policies for paying pharmacists for their professional services. This is not to say that payers have no interest in pharmaceutical care. Rather, for the most part, they simply do not understand what it is or how it will benefit them and their beneficiaries. Health reform will further define how care is delivered and reimbursed for healthcare professionals and healthcare entities in the years ahead.

The creation of pharmacy services terminology and related electronic claims transmissions standards will help speed the evolution of new payment systems. Likewise, the growing body of research in health outcomes assessment will allow the pharmacy profession to better communicate value to payers. Demonstrating the value of pharmacists' services to payers represents a priority for pharmacy practice-related research in the years ahead.

Pharmaceutical risk management

The new era of risk management

In the United States, drugs are approved only if they are determined to be safe to use for the conditions described in their label: This basic tenet of the Food, Drug, and Cosmetic Act (FDCA) has not changed. What has changed, though, in recent years is the interpretation of the term "safe." Modern concepts of pharmaceutical risk management are based on the premise that drug manufacturers, healthcare professionals, and patients have a responsibility to minimize the risks of using pharmaceutical products. It is not enough to make drugs minimally safe; they must be as safe as possible over the lifecycle of the product's use.[54–56] This approach represents a role shift for the FDA, pharmaceutical manufacturers, and health professionals to more proactive risk assessment and management by using special tools and programs to support a product's safe use.

Historically, the FDA interpreted the requirement that a drug must be "safe" to mean that the benefits of a drug outweigh its risks. The determination was made on a "categorical" basis, in which the totality of risks was weighted against the totality of benefits when considered for the indications outlined in the drug product's labeling. If a drug did not meet this criterion, it was not approved or its label was rewritten to narrow the indications for use. This logic was endemic in the FDA for most of the twentieth century. On average, two to four drugs over each five-year period were withdrawn from the marketplace after post-marketing surveillance data uncovered new risks.[57] Similarly, on occasion, the FDA would require some special "tool" or intervention to improve a product's safety profile.

For example, mandatory distribution of patient package inserts was instituted in 1976 to warn women about the risks related to birth control pill use,[58] and a special distribution system was instituted in 1990 to limit the dispensing of Clozaril (clozapine) to patients who underwent blood testing that demonstrated they were not having a serious adverse reaction.[59] However, beginning in the early 1990s, this philosophy started to change as the FDA began to take a more active role in post-marketing surveillance and began instituting a more aggressive "management" process to assure greater safety in the use of marketed drugs. No longer do the manufacturer and FDA provide passive oversight and labeling changes to control risks; now the manufacturer must actively monitor for suspected, but unquantified, risks and actively manage and minimize known risks.

On September 27, 2007 the President signed into law the Food and Drug Amendments Act (FDAAA, PL 110–85).[60] This Act granted the FDA new authority to require manufacturers to implement a Risk Evaluation and Mitigation Strategy (REMS (can be singular or plural)) when new drugs are approved or when new risks are discovered for already approved medicines. A REMS is a series of interventions that companies may implement to presumably lessen the risks of their therapies. There are three risk mitigation strategy levels outlined in the FDAAA:

1. Distribution of a Medication Guide or similar patient information booklet with the medicine,
2. A communications plan directed to health professionals, for example letters to healthcare providers/pharmacists, professional societies messaging, professional education, etc., and
3. "Elements to assure safe use," abbreviated as ETASU, or a plan to control and limit the distribution of medicines to only qualified prescribers, distribution centers, or patients who meet predefined criteria.

The ETASUs may include

- Training/certification of prescribers
- Training/certification of pharmacists/pharmacies
- Restrictions on where and how the drug is dispensed
- Evidence of patient safe use conditions
- Patient monitoring
- Patient enrollment in a registry.

ETASUs are not to be "unduly burdensome on patient access" to the drug, according to the law. Considerations are to be given to patients with serious or life-threatening diseases, and those in rural or medically underserved areas who may have difficulty accessing services. ETASUs are also not to be overly burdensome on the healthcare delivery system and should be compatible with established systems supply chain distribution and dispensing systems. REMS also may have an implementation system to monitor, evaluate, and improve elements to assure safe use.

For generic drugs, REMS components are limited to MedGuides, patient package inserts, and ETASUs. However, if an innovator drug required a communication plan, then the FDA must require any generic drugs that are approved later to do the same. Generic drugs use a shared ETASU system with the innovator product as well, although a waiver can be granted.

REMS programs are legally enforceable, with monetary implications. All REMS include evaluating the implemented risk mitigation interventions at 18 months, 3 years, and 7 years after they are implemented. REMS programs may allow some products that might otherwise be withdrawn to remain on the market because there are tools in place to manage the product's risk. Everyone involved in drug manufacture, handling, prescribing, dispensing, or dosing is responsible for ensuring compliance with REMS programs.

The FDA must consider a number of factors in determining if a REMS is necessary according to FDAAA, including

- The number of people estimated to use the drug
- The seriousness of the disease or condition the drug will treat
- The expected benefit of the drug
- The expected or actual duration of drug treatment
- The seriousness of the drug's known or potential adverse events and the incidence of such events in the population likely to use the drug
- Whether the drug is a new molecular entity.

If the Agency determines a REMS is necessary, the drug product's manufacturer has 120 days from

Table 12.4 Number of REMS programs approved by the FDA

	July 8, 2011	December 29, 2011
REMS element	**Total**	**Total**
Total REMS currently approved	149	105
MedGuide only	77	31
More than a MedGuide	64	57
Of those with more than a MedGuide:		
Those with communication plan	46	36
Those with elements to assure safe use	30	31
Those with implementation system	26	26
Communication plan only	8	17
Products releases from REMS requirement	44	94

Source: FDA Web site: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111350.htm

notification to develop and submit it for FDA review. Manufacturers can file disputes for resolution with the FDA Drug Safety Oversight Board, although none has been filed. A drug cannot be sold if it is in violation of a REMS requirement, and the FDA can find it misbranded under the FDCA with accordant civil penalties.

The FDA's Drug Safety and Risk Management Advisory Committee evaluates elements of each REMS program annually and must seek input from physicians, pharmacists, other healthcare professionals, and patients about program elements. This may lead to modifications in a REMS program.

As of December 2011, 199 REMS plans have been approved and implemented, with 94 products released from REMS requirements, most of those occurring in mid–late 2011 because the FDA issued new Guidance on "Medication Guides-Distribution Requirements and Inclusion in Risk Evaluation and Mitigation Strategies (REMS)".[61] Of all the REMS plans, the vast majority have included a Medication Guide requirement (88 in December 2011, down from 141 in July). Currently, 53 REMS include a communications plan requirement, and 31 include the elements to assure safe use (controlled distribution) requirement.[62] Table 12.4 summarizes REMS requirements at mid- and year-end 2011. It is becoming increasingly common for some form of risk management intervention to be required for new chemical entities approved for distribution in the United States.

Pharmacoepidemiology and pharmacovigilance

Pharmacoepidemiology, or drug epidemiology, is the study of the effects of drugs in populations of people. The discipline is an amalgam of clinical pharmacology, clinical epidemiology, medical informatics, and biostatistics. There are a number of reasons pharmacoepidemiology has recently emerged as a discipline. Traditional clinical pharmacology directs much of its attention to the pharmacokinetics and pharmacodynamics of drugs. These studies involve small numbers of subjects (6 to 25) who are studied intensively to obtain an understanding of drug absorption, distribution, metabolism, or excretion. Studies of these parameters determine the dose and frequency of administration of new drugs in the treatment of

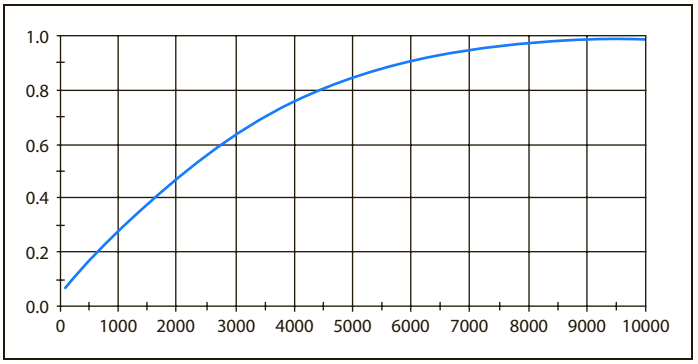

Figure 12.2 Power as a function of sample size in two treatment groups. The study was designed to detect an event that occurs in four out of 1000 patients in one group and one patient in 1000 in the other group.

patients, and are required before drugs are marketed. However, such studies tell us little about certain experiences of drugs after they are marketed. It is in this post-marketing phase that the tools of clinical epidemiology come into play, especially in determining the frequency of adverse drug effects. Pharmacovigilance is a subset of pharmacoepidemiology, involving surveillance or drug monitoring to detect and assess adverse drug events.

Though new drug products undergo the careful scrutiny of Phase I through III testing, some drug products are recalled soon after they are marketed. There are a litany of experiences, including phocomelia from thalidomide, Guillain Barré syndrome from influenza vaccine, endometrial cancer from diethylstilbestrol, cardiac valve disorders from the combination use of fenfluramine and phentermine (Fen-Fen), anaphylaxis from zomepirac, hepatic failure from bromfenac, and cardiac arrest from interactions from drugs like mibefradil or terfenadine when administered with drugs that inhibit P-450 CYP 3A4, such as ketoconazole and erythromycin. More recently, the safety of rosiglitazone, pioglitazone, and a variety of NSAIDs has been called into question by pharmacoepidemiologists. A major reason for these drug product recalls is that premarketing studies treat too few patients (typically 3000 to 4000) to detect uncommon drug effects. An adverse effect that occurs in only 1 in 25,000 persons would go unnoticed in only 4000 treated patients in the pre-marketing phase. Yet once the drugs are marketed, they often reach millions of patients and rare events can manifest. Hence, premarketing studies have insufficient statistical power to detect rare adverse effects.

Figure 12.2 shows the effect of sample size on the statistical power of a study. In general terms, the "power" of a test is the ability of a statistical test used in a study to detect a relationship between an exposure (drug) and an event or outcome. The highest value the power can have is unity, and the lowest is zero. Figure 12.2 shows the power curve for a clinical trial in which the outcome of interest occurs in four of every 1000 patients in one treatment group and in one in every 1000 patients in another treatment group. For clinical trials, it is desirable to keep the power of a study above 0.80. From Fig. 12.2, it can be seen that fewer than 4000 patients in each group would yield insufficient power to detect a difference between groups, when alpha is 0.05 and a two-tailed test is performed. Another way to interpret the curve is to consider that an adverse effect occurred in 0.4% of patients receiving a drug, and the same adverse effect occurred in 0.1% of patients receiving placebo; more than 8000 patients would need to be recruited into the study to detect such an effect. The cost of such a study would be prohibitive.

Another important reason adverse events are not identified in the pre-marketing drug experience is that, although subjects in pre-marketing studies have the disease or disorder the drug is targeted to treat, they are otherwise healthy people. Typically, premarketing studies exclude patients who have complicating factors, such as renal or hepatic insufficiency, diabetes mellitus, or heart failure. Pre-marketing studies are conducted to determine the efficacy of a specific drug often compared to a placebo. Such studies are helpful to ascertain whether a drug works for a specific disease or condition (i.e., "Does it work?"), but once

the drugs are marketed, they often reach patients with a multitude of comorbidities and complicating conditions. In this real world setting of care, treated patients are sicker, and adverse drug reactions are more common. Post-marketing studies are conducted to determine the effectiveness of a drug or an assessment of the drug's effect in the typical setting of patient care (i.e., "Does it work in real world care?"). This scenario has been a driving impetus behind the interest in comparative effectiveness research (CER), which calls for the conduct of studies of commonly used drugs in the types of patients likely to receive those drugs in typical clinical settings. CER tells us which drug works best among available, marketed alternatives and for what types of patients receiving usual care. However, it is an especially broad concept. An Institute of Medicine panel defined CER as "the generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat, and monitor a clinical condition or to improve the delivery of care. The purpose of CER is to assist consumers, clinicians, purchasers, and policy makers to make informed decisions that will improve healthcare at both the individual and population levels."[63] The relevance of CER to pharmacoepidemiology is particularly relevant in terms of determining beneficial and harmful drug effects at the population level. Several programs have evolved out of the need for more rapid and valid data pertaining to adverse drug effects for new and previously marketed drugs within the realm of pharmacovigilance.

Because adverse effects of drug products are more commonly observed after marketing, the FDA created the MedWatch Medical Products Reporting Program, the largest drug and device surveillance program in the United States (http://www.fda.gov). A similar program is operated by the World Health Organization (WHO) for 86 countries, including the United States. Such spontaneous report drug surveillance programs are important for drug regulatory agencies to keep their fingers on the pulse of the adverse drug experiences of countries. These programs analyze reports provided by the pharmaceutical industry, practicing pharmacists, and physicians, and, although extremely important for finding adverse drug events, they are passive surveillance programs.

Complementing spontaneous reporting systems are several exciting, recently established, active surveillance programs, including the FDA Sentinel Initiative,[64] the Observation Medical Outcomes Partnership (OMOP; http://www.omop.fnih.org),[65] and the European Union Adverse Drug Reporting Program (EU-ADR; http://www.alert-project.org).[66] Pharmacoepidemiologists involved in these programs pool large claims and electronic health databases, containing up to 300 million people, to determine the presence and magnitude of drug–event associations and detect signals that could represent important new problems with marketed drugs. These programs have spawned a variety of new methods in pharmacovigilance.

Now that the interface between pharmacoepidemiology and clinical pharmacology and clinical epidemiology is clearer, the question remains as to how medical informatics and biostatistics enter into the mix. Health systems, such as managed care organizations, hospitals, clinics, and medical centers, generate a large volume of data on patients. Increasingly, such data are captured and stored in huge databases. Data found in these warehouses often come from many sources, including the pharmacy, laboratory, radiology, and patient care clinics and wards. To conduct studies of outcomes of patients who have been prescribed drugs requires merging these large files from disparate sources. Such integrated databases are becoming larger and richer. When datasets contain millions of people with many clinical observations per person, super computers or cloud computing must be used to analyze the data. When such data are available through time and are linked using a unique patient identifier, a variety of longitudinal studies of the effects of drugs in large populations of patients (i.e., pharmacoepidemiologic studies) are possible.[67] The analysis of such large temporal data sets requires the tools of biostatistics. The types of statistical procedures used in the analysis of data for pharmacoepidemiologic studies can range from simple counts of events to sophisticated mathematical models.

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13

Patient care

Pharmacists and disease state management

Introduction

Disease state management (DSM) is a systematic population-based approach to medical care that is being used with increased frequency in a variety of healthcare systems as an effort to standardize and improve provider adherence to treatment guidelines. DSM programs tailor population-based outcomes to individualized patient care. Success in using the DSM format for patient management is demonstrated by improved quality of care and outcomes that outweigh the resources used.

DSM utilizes a multi-disciplinary model that employs evidence-based medicine to set therapeutic targets and emphasizes patient education to encourage self-management. Typically, DSM programs focus on chronic disease states, such as diabetes mellitus, chronic heart failure, and asthma. Only about 55% of Americans with chronic medical conditions receive care consistent with consensus guidelines, as reported in one study.[1] The goal of DSM is to improve treatment outcomes such as reduction of symptom severity, morbidity, and hospitalization rate, while controlling healthcare costs.

Both the aging US population and legislative mandate are promoting DSM growth. Four out of five Americans live with at least one chronic disease.[2] The federal Patient Protection and Affordable Care Act (PPACA), passed in 2010, calls for reimbursement structures that promote the development of DSM programs that improve the quality of care.[3]

DSM has been defined by Zitter as "a comprehensive integrated approach to care and reimbursement based fundamentally on the natural course of a disease with treatment designed to address the illness with maximum effectiveness and efficiency."[4] Therefore, in this management system, each patient may be proactively triaged at different stages in his or her disease process, using a defined care plan established from evidence-based protocols or guidelines, rather than a series of fragmented encounters with various parts of the healthcare system. This integrated approach is developed with a quantifiable economic structure and a defined quality improvement process. The Care Continuum Alliance (formerly the Disease Management Association of America, DMAA) is a non-profit membership organization founded in 1999 to represent the disease management community. It defines those components needed for a quality disease management program, as shown in Table 13.1.[5]

Pharmacists can play an integral role in various aspects of disease management care delivery and have demonstrated success in doing so.[6,7] As part of a prescription drug management program, DSM can be used as one of the methods to control medication utilization and pharmacy expenditures. Other methods include utilization management (e.g., quantity limitations and prior authorizations), open or closed formulary management, retail and mail-order delivery systems, and benefit design and consumer cost sharing (e.g., copayments and coinsurance).

Table 13.1 Disease Management Association of America (DMAA) definition of what components need to be included for full service disease management programs

Components of a disease management program

- Population identification processes
- Evidence-based practice guidelines
- Collaborative practice models to include physician and support-service providers
- Patient self-management education (may include primary prevention, behavior modification programs, and compliance/surveillance)
- Process and outcomes measurement, evaluation, and management
- Routine reporting/feedback loop (may include communication with patient, physician, health plan and ancillary providers, and practice profiling)

Full service disease management programs must include all six components. Programs consisting of fewer components are disease management support services.

Historical background

Until the 1970s, the primary mode of healthcare reimbursement was through fee-for-service, whereby the insured enjoyed unrestricted access to all forms of healthcare. In this model, healthcare costs skyrocketed, physicians relied largely on accumulated individual practice experience for disease treatment, and patient care interventions, rational or not, were reimbursed. New technologies added to the cost of healthcare, and in a fee-for-service environment their values were rarely assessed.

Managed care was "born" as the diagnosis-related groups (DRG) system was instituted in the early 1980s by the federal government as a means to rein in healthcare costs, with beneficial results observed by the early 1990s (Fig. 13.1).[8] Private payers, while watching their bottom line, also demanded that costs be curtailed. Neither the public nor private sectors, however, were willing to forego quality. Therefore, managed care is ever evolving to adapt to the seemingly diametric opposition of cost and quality.

DSM is both an example of and a microcosm for this evolution. Managed care first targeted hospital and physician costs, using once-novel approaches such as disease payment capitation and performance incentives because these were and are the most costly components of healthcare. After hospital and physician cost containment, managed care organizations (MCOs) addressed prescription drug costs, which are the third most costly healthcare budget item. By the mid-1980s most large MCOs had prescription drug management programs, either internally developed or contracted, with cost containment as their primary focus.[9] The skyrocketing cost of pharmaceuticals continues to be a driving force behind cost containment measures employed by MCOs.

Although quality and cost containment have always been mutual goals of managed care, skyrocketing costs, coupled with a "silo" approach to hospital, physician, and pharmaceutical cost containment, had a neutral – and sometimes negative – effect on quality care delivery. Consumers of healthcare began to perceive a sacrifice in the quality of care to maintain

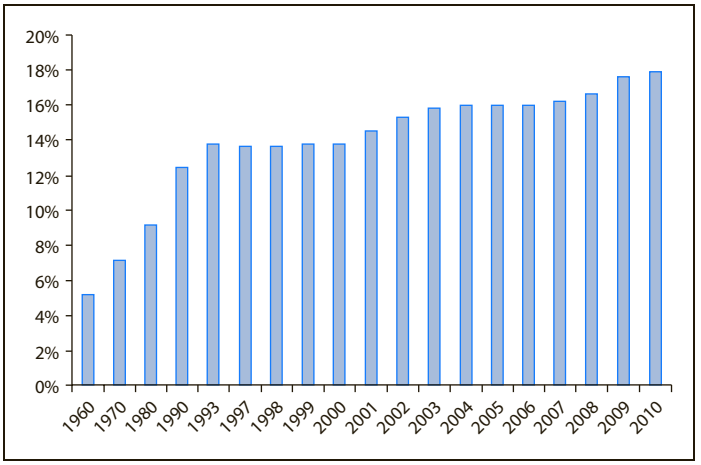

Figure 13.1 National healthcare expenditure as a precentage of gross domestic product 1960–2010.

the bottom line. The healthcare industry responded with the development of DSM programs that would, if effective, integrate healthcare services across the patient care continuum, positively influence quality care, and maximize efficiencies that would lead to cost containment.

Initially, DSM programs were focused on single disease states as out-sourced products developed by stand-alone vendors or by pharmaceutical manufacturers. The next phase was characterized by the consolidation of multiple disease state management programs under one roof.[10] Some industry examples include Diabetex, with its focus on diabetes mellitus management, which underwent a name change to XLHealth as it expanded to become a full-service DSM company. Another is Healthways, an internationally-present full service DSM company that began as The Diabetes Treatment Centers of America. Most recently, the industry has seen a consolidation of vendors, and increasingly, DSM programs are developed and/or operated through healthcare systems (e.g., accountable care organizations, or ACOs) that work to identify proven processes for population health management and apply these to the care of patients enrolled in their system.

As healthcare costs are again on the rise as a function of gross domestic product (Fig. 13.1), state and federal government interest is again keen on exploring DSM to make inroads on improved cost and quality. The federal Patient Protection and Affordable Care Act of 2010 promotes chronic DSM programs as a "minimum essential health benefit" to improve health outcomes and reduce costs.[2] However, the theoretical benefits of DSM – improved care quality and cost containment – remain to be thoroughly vetted through controlled studies. Interim results of the Medicare Health Support pilot program, launched by congressional mandate in 2003 to test the viability of DSM programs for improving cost and quality for Medicare fee-for-service enrolees, has so far not demonstrated benefit.[11]

Initial start-up costs for DSM are resource-intensive. It can be argued that health outcomes follow-up in studies to date have not been of sufficient duration to flesh out cost benefit. It may also become apparent that some diseases are more amenable to the beneficial effects of DSM than others. The recent healthcare reform legislation promoting DSM should provide the DSM industry some breathing room to sort out the answers to these questions.

Certain diseases or treatments lend themselves to DSM (Table 13.2). They include those in which the disease course is well-defined and/or propel healthcare costs. Chronicity, prevalence, available benchmarks or definable, measurable outcomes, variability in treatment methodology, expensive therapies, and high incidence of non-adherence or preventable therapeutic misadventure are common characteristics. "Rare" diseases may qualify because DSM programs can centrally manage a large number of cases drawn from a broad geographic area. Table 13.3 is an adaptation of the list of most costly medical conditions

Table 13.2 Appropriate medical conditions or characteristics to be targeted for a disease state management program characteristics

- Well-defined disease course
- High cost
- Chronic diseases or conditions
- High frequency
- Available outcomes benchmarks
- Measurable outcomes
- Treatment methods variable
- High incidence of non-adherence
- Preventable therapeutic misadventure is common or catastrophic
- Rare occurrence

Table 13.3 Total Expenses for Selected Conditions by Type of Service: United States, 2010

Condition	Ranking	Expense ($ million)
Heart conditions	1	107,186.40
Mental disorders	4	73,060.24
COPD, asthma	5	63,782.99
Diabetes mellitus	7	51,310.57
Hypertension	8	42,943.38

treated in the United States in 2010 to show DSM-appropriate conditions.[12–25]

Pharmacists and disease state management

It is well documented that pharmacotherapy-related outcomes can be improved with implementation of protocol-driven disease management programs by pharmacists in collaboration with other healthcare providers. Noteworthy examples include an increased percentage of patients achieving National Cholesterol Education Program LDL cholesterol targets following lipid-optimization;[21,22,26] a reduction in the length of hospitalization in patients taking warfarin guided by a pharmacist;[14] significant improvement in $A1_C$, triglyceride, and LDL cholesterol levels in patients with poorly controlled diabetes, who were previously unresponsive to usual care;[27] and a reduction in all-cause mortality in patients with heart failure receiving medication evaluation by pharmacy.[16] Additionally, models exist showing that pharmacist-directed care can also serve to improve patient medication adherence, ensure appropriate drug use, decrease expenditures, and improve access to necessary drug therapy.[28,29] There is increasing evidence that the participation and intervention of pharmacists in the direct care of the patient has a positive influence on patient outcomes.[30]

Schools and colleges of pharmacy voted in 1992 to adopt the six-year Doctor of Pharmacy degree as the only professional degree in pharmacy. Around the same time, the profession of pharmacy began moving toward a patient-centered, outcome-oriented practice (the pharmaceutical care model as first outlined by Hepler and Strand) and away from product-orientation as a primary focus.[15] This patient-centered practice resulted from advances in information technology, the implementation and increasing role of pharmacy technicians, and the evolution of pharmacy automation. These changes place pharmacists in a unique position to broaden their scope of practice and to increase services, where appropriate, as collaborative care providers with a goal toward maximizing health-related outcomes and minimizing potential drug therapy problems, while assuring cost-effective care. Healthcare administrators, physicians, ancillary care providers, and the public are increasingly recognizing the unique training and knowledge that pharmacists have in support of these activities.

Requirements for pharmacists who are involved in DSM vary from state to state and among healthcare organizations. For pharmacists desiring to expand their scope of practice into a specialty area, training beyond the pharmacy degree and subsequent licensure is becoming increasingly necessary to achieve that goal. Typically, pharmacists involved in DSM have advanced training either through a residency, or fellowship, or by acquiring additional skills from years of experience. Various credentialing and certification programs exist that provide some of the foundations needed for effective DSM participation.

The Council on Credentialing in Pharmacy (CCP), founded in 1999, is a coalition of 12 national organizations and serves as a coordinating body for credentialing programs. CCP serves as a good resource for currently available credentialing and certification programs, with further information available at http://pharmacycredentialing.org/ccp/index.htm.

The Board of Pharmaceutical Specialties (BPS), and the Commission for Certification in Geriatric Pharmacy (CCGP) are among agencies that offer certification to pharmacists in specialty areas. The BPS, established by the American Pharmaceutical Association (APhA) in 1976, certifies pharmacists in six practice concentrations: ambulatory care, nuclear pharmacy, nutrition support, oncology, pharmacotherapy, and psychiatric pharmacy. Added qualifications in either infectious diseases or cardiovascular pharmacy are also available for pharmacists certified in pharmacotherapy. The CCGP, established by the American Society of Consultant Pharmacists (ASCP) in 1997, supervises the certification program in geriatric pharmacy. Additional information for each of these agencies is available at http://bpsweb.org/specialties/qualification.cfm and http://www.ccgp.org/ respectively.

A pharmacist's role

Three strategies have been described[9] that, if followed, should help pharmacists develop practices that embody pharmaceutical care and DSM. First, careful planning of provided services should be carried out with buy-in from collaborative partners (e.g., third party payers, physicians, and ancillary staff) and patients. Second, close communication should be maintained with the primary care physician regarding each patient's care. Finally, clear documentation of processes and outcomes should be maintained, and these outcomes measured against a reasonable benchmark.

Pharmacists are positioned well to take a significant role in DSM because effective drug therapy is integral to managing most conditions targeted in these programs. Many examples exist that support the role of the DSM pharmacist in the community pharmacy, hospital, managed care, and other non-traditional practice settings.[31] The DSM services that pharmacists may provide vary and can include glucose and cholesterol screening (requiring a Clinical Laboratory Improvement Amendments waiver), vaccine provision, blood pressure monitoring, and education on smoking cessation or asthma management. In this role, pharmacists apply "pharmaceutical care" principles to manage patients with chronic medical problems. They may make recommendations to a primary care or specialty physician or may prescribe drug therapy under protocol.

State law determines the level to which a pharmacist can be involved in DSM or similar services, such as when prescribing or changing drug therapy under protocol, and laws vary between states. In California, upon a physician's patient-specific authorization or under protocol, pharmacists are authorized to initiate or adjust a drug regimen and order or perform routine drug therapy-related patient assessments, such as vital signs, order drug therapy-related laboratory tests, and administer drugs and biologicals by injection, including immunizations. Prior to performing any of these activities, the pharmacist shall have successfully completed clinical residency training or demonstrated clinical experience in direct patient care delivery.[32] While some states require advanced educational training, others are more stringent and require board approval, notification, or registration for collaborative practice agreements. It is paramount that pharmacists know the precise rules and regulations within their home state in order to take advantage of DSM opportunities.[33]

Pharmacists' extensive training in pharmacology, pharmacokinetics, pharmacodynamics, and pharmacotherapeutics makes them uniquely qualified to evaluate drug literature. Drug information activities performed by managed care pharmacists are used to support drug utilization review or medication use evaluation, as well as formulary management. All are important components for devising cost containment and utilization management strategies. These activities are also used to support an evidenced-based approach to DSM for developing population-based treatment plans and protocols. Further, pharmacists conduct physician and allied health professional education to offer a balanced assessment of supporting literature and facilitate the team's buy-in of the treatment plans.

Pharmacists may serve as care managers in a DSM program. This is particularly advantageous when the

drug therapy regimen used to treat the disease is susceptible to drug–drug, drug–food, or drug–disease complications. As detailed in the literature referenced in Table 13.4, DSM programs that incorporate pharmacists as care managers have been successfully deployed to patients with various conditons and concerns, including treating diabetes mellitus, depression, smoking cessation, cardiovascular risk reduction, anticoagulation, and hypertension.

Careers in health informatics, pharmacoeconomics and outcomes research provide other expanded opportunities for pharmacists in DSM. Pharmacists in these roles use their enhanced analytical and research skills to determine the value of medications for the treatment and prevention of disease, and the research may involve either a drug-specific focus or population-based healthcare delivery. Most pharmacy schools provide a solid background in science, therapeutics, and economics necessary for this enhanced role. Postgraduate training (e.g., graduate study and fellowships) enhances these skills and prepares pharmacists for independent research.

Components of a successful DSM program

There are certain characteristics that successful DSM programs share. A reliable and extensive medical informatics infrastructure allows for easy access to patients and their medical records. This includes telecommunications, computer networking, and data storage. Care managers working within a DSM program may monitor patients' progress using telephone surveillance and/or web-based telephone data collection devices. Integrated data collection and storage across the continuum of care, though not required, best serves the practitioners of DSM for patient follow-up and for reporting cost and quality outcomes. Complete data that are accurate and timely are essential to the success of a DSM program. Data collected should be analyzed and compared to benchmarked data points when available [as, for

Table 13.4 Published reports of pharmacist involved in disease state management (DSM) programs

Disease State	Findings	Reference
Asthma	Significant reduction in ER visits, hospital admissions, total asthma-related costs, disease severity classification, FEV_1	Bunting and Cranor[13]
Anticoagulation	Significant reduction in length of hospitalization	Dager *et al.*[14]
	Significant reduction in total hospital costs	Mamdani *et al.*[15]
Heart failure	Significantly lower all-cause mortality	Gattis *et al.*[16]
	Significant decrease in hospital readmissions	Riegel *et al.*[17]
ICU patients	Decreased bleeding, mortality and ICU LOS	MacLaren and Bond.[18]
	Significant reduction in preventable ADEs	Leape *et al.*[19]
H. pylori	Cost-avoidance of $95 per patient	Segarra-Newnham and Siebert[20]
Hyperlipidemia	Improved attainment of $LDL\text{-}_C$ goal	Palmieri *et al.*[21], Ito *et al.*[22]
Diabetes mellitus	Reduction in mean HbA_{1c}, total healthcare costs, increase in patient self-care	Garrett and Bluml[23]
Hypertension	Significant improvement in systolic and diastolic BP	Santschi *et al.*[24]
General DSM	Decrease total monthly medical costs	Munroe *et al.*[25]

example, from the National Committee for Quality Assurance's (NCQA) Health Plan Employer Data and Information Set (HEDIS)] to demonstrate quality outcomes. Medical claims, clinical, and humanistic (satisfaction) data are all useful data points to benchmark.

As mentioned previously, one of the basic principles of DSM is identifying and offering a patient the best care for their disease. Successful DSM programs base goals on evidence-based outcomes. They incorporate treatment guidelines to reduce the amount of variability in practice that can lead to cost and quality inefficiencies. Development of treatment guidelines should be a cooperative consensus of all disciplines involved, as well as expert opinion and evidence from the scientific literature (e.g., using published evidence grading).

Care in a DSM program should be physician-directed, yet take advantage of the expertise of a multidisciplinary healthcare team (mid-level providers and pharmacists) to improve care and cost efficiency. Proper use of ancillary care for patient monitoring and management can improve quality, reduce care costs, and have a positive effect on physicians workload, making room for patient visits requiring diagnosis-related activities.

Acceptance of the program by the primary care physician and/or health plan is of paramount importance to the success of a DSM program. Authorization from one or both entities is required for patients to have access to the DSM program. A key to acceptance may include shared risk, which also includes shared cost savings. Changing prescribing patterns and adherence to treatment guidelines might be enhanced by reasonable financial incentive. In addition, the practitioners affected by DSM programs need to be included early in development of the program to gain their support.

DSM programs should be financially viable. As such, demonstrable outcomes are only part of the story. They must be couched within a reimbursement system that acknowledges benefit of integrated care delivery. For example, payers should recognize that the costs for pharmaceuticals (e.g., beta-blockers and angiotensin converting enzyme inhibitors) may increase in a DSM program targeting chronic heart failure, but that other, offsetting costs (e.g., hospitalizations, surgical procedures, lost productive time and patient discomfort) should be reduced. In contrast, a DSM program that increases total healthcare costs with improvement in outcomes may be at odds with the goal of the healthcare system.

Patient and physician education helps ensure that a DSM program is successful. Patients are empowered through learning about their disease. Signs of proper therapeutic management, as well as therapeutic misadventure, enable the patient to stay out of trouble if they are taught how to identify these. Likewise, physicians are more apt to incorporate proven therapeutic modalities into patient care if they are informed of evidence-based best practices.[34]

Finally, continuous quality improvement (CQI) processes should be incorporated into the practice model to monitor and enhance care practices. Compliance with guidelines and assessment outcomes (humanistic, clinical, and economic) should be evaluated periodically and new evidenced-based information needs to be incorporated into the treatment guidelines as well.

Development of a DSM protocol

The Protocol

One of the first tasks for the pharmacist planning to provide DSM is a detailed and specific protocol. Generally, this would be specific to a particular disease condition or area. The protocol should spell out in detail the responsibility of the pharmacist and specific endpoints for drug therapy.

The pharmacist wishing to develop such a protocol need not start from "ground zero." Numerous examples of DSM services and protocols have been published or are readily available from national organizations (see Table 13.4).

The protocol should clearly define pharmacist responsibility, including prescriptive privileges, authority to order and monitor selected laboratory indices, and consultation privileges. In addition, patient follow-up intervals and outcomes expected of pharmaceutical care should be included. Quality improvement measures may also be included as part of the protocol and are highly recommended, as discussed above.

Documentation of the DSM activities in the patient care record is also a key element. Without proper documentation the pharmacist will be unable

to manage accurately and safely the patient's disease condition. In addition, without adequate documentation the pharmacist will be unable to obtain compensation for services as well as determine the economics of the program. Finally, programs with poor or absent documentation of patient care activities may run afoul of various regulatory bodies such as the Centers for Medicare and Medicaid Services (CMS, formerly the Healthcare Financing Administration, or HCFA), the Department of Health and Human Services (DHHS), and the Joint Commission on Accreditation of Healthcare Organizations (JCAHO). Documentation of the complexity of the interventions should be included, such as details about the amount of time spent with a patient and the extent of the examination.

Objectives within DSM protocols should be realistic. Unrealistic objectives that have a low likelihood of being attained will serve to frustrate the pharmacist and disappoint the patient. Of equal importance, failure to meet one's objectives while increasing the utilization of resources will be a conflict for one's healthcare system.

As mentioned in the previous section, when developing DSM protocols and determining objectives for such services, pharmacists should consult clinical practice guidelines established by government agencies, professional organizations, or international bodies. Historically, such guidelines are evidence-based and comprise a consensus of experts in a disease area or diagnosis group. A comprehensive database of evidence-based clinical practice guidelines and related documents is available online through the National Guideline Clearinghouse at http://www.guidelines.gov, supported by the Agency for Healthcare Research and Quality.

The protocol should make some effort to define the organizational structure of the DSM program or clinic. The schedule of the clinic (days meeting, hours of clinic), how patients are checked in or out and screened, and the time periods allotted for appointments should be included. Consideration must be given for the amount of time necessary to consult new patients versus returning patients. Policies for handling patients who do not keep appointments, for the rescheduling of patients, and for the number of times a patient can be rescheduled prior to being dropped from the service need to be established.

Periodic review and update of the protocol is also essential. The ultimate goal is a DSM protocol that is dynamic, current with evidence-based medical care, and designed to be easily applied to the care of patients.

Collaborative Agreement with Health Providers

Pharmacists who desire to establish DSM programs must be willing to invest time and energy to establish strong, professional working relationships with other healthcare providers and staff members. DSM programs may also include additional service provisions (e.g., behavioral health, nutrition screening, or other patient monitoring services) to fulfil more patient specific needs, so collaboration with those having expertise in select specialties is also key.[35] Typically one individual caregiver does not have complete patient information. Coordinating services with other providers helps assure the DSM program is comprehensive and the care of the patient is seamless.

Several keys to building working relationships are being responsive, doing more than what is expected of the pharmacist, and being willing to spend time with patients. Most often, examples of pharmacists providing DSM involve the pharmacist having identified a physician "champion" or advocate for his or her activity. Often this individual is a general practitioner in primary practice or a specialist in a particular disease area (e.g., cardiologist or endocrinologist). In addition, support from physicians higher up the administrative hierarchy can be invaluable in allowing the pharmacist to establish and manage disease-specific clinic activities and/or clinics. Physician support is now trending towards collaborative practice. Data presented by the American College of Physicians – American Society of Internal Medicine shows that physicians support pharmaceutical care services and pharmacists' involvement in collaborative care.[35]

If pharmacist services are contracted, a collaborative practice agreement with a provider should be established as part of the DSM protocol. When establishing collaborative practice agreements, pharmacists and physicians must evaluate their needs to determine the types of services the pharmacist will provide. The majority of states have passed legislation that allows

pharmacists to practice collaborative drug therapy management with physicians. However, even without legislation most medicine and pharmacy practice acts are broadly worded to allow collaborative practice arrangements (including drug therapy management) to exist between pharmacists and physicians. As previously discussed, some states may require pharmacists credentialing in DSM to practice under a collaborative agreement with a physician. The pharmacist will need to evaluate his or her own individual state requirements.

Promoting/Influencing Stakeholders

Once the DSM protocol has been developed, the pharmacist must consider promoting their services and influencing stakeholders (e.g., patients, physicians, and the MCO). This may require tremendous educational efforts in some cases. As mentioned in the previous section, a physician "champion" will be essential to develop a favorable partnership with the stakeholders. The pharmacist must be prepared and flexible enough to meet the concerns of all stakeholders. The collection of member and provider satisfaction data will help to ensure the longevity of the program.

Requisite Equipment and Set-Up

The minimum equipment and space required to practice DSM is a private area to interview and examine the patient. An examination room in a clinic or physician's office may be available for this purpose. In the case of a clinic that is telephone surveillance-based, a private desk area that includes a telephone and personal computer is necessary. If not already available in the examination area, a small desk, several chairs, and electrical power access will be required. This additional space would be required for equipment, such as computers, and to allow for processing of paperwork. In addition, a combination television/DVD player is a very helpful option in case instructional videos need to be viewed by the patient. The ideal situation would be a separate interview/counselling room that would also double as the pharmacist's office.

Documentation and Forms

Documentation is a key element of DSM. Before initiating the service forms should be available that document accurately and adequately all activities of the pharmacist. There are numerous Windows-based software programs available to support pharmacist DSM documentation efforts in the acute, subacute, and ambulatory care areas. There is little reason, in this era, to utilize paper forms for processing this information. Every effort should be made to computerize all documentation and interventions of the pharmacist. Online documentation submission and systems integration is also becoming easier with the continued progression of many institutions and physician clinics towards "electronic" medical record-keeping. The Veterans Affairs Medical Centers, for example, have been utilizing electronic medical notes and medical record for several years.

If paper documentation is necessary, the pharmacists should be certain to develop forms or use a documentation style which reflects the complexity of the intervention. Use of a SOAP format (subjective, objective, assessment, plan) remains a common format for payer reimbursement consideration.[36] All documentation should be clear and concise, preserve patient confidentiality, and include standardized detail (e.g., the amount of time spent with a patient, the extent of an examination, or the medical decision making involved). This allows for good patient management and appropriate billing consideration.

Billing and Reimbursement

Pharmacists have faced challenges when attempting to seek reimbursement for DSM services, although recent improvements in this process are noted. Traditionally, pharmacists have been restricted in their ability to bill for DSM, and there have been discrepancies in compensation for their services.[37] Despite these problems, some pharmacists have been successful in submitting claims for reimbursement to insurance companies for DSM while others have found patients willing to pay directly for these services. Still others use DSM as a way to differentiate their pharmacy from the competition, increasing the loyalty of their patients and, in turn, their prescription and over-the-counter sales.

Pharmacists can use a variety of mechanisms to obtain reimbursement through the Centers for Medicare and Medicaid Services (CMS) that oversees Medicare and Medicaid financing. These include new Current Procedural Terminology (CPT) codes for pharmacists, "incident to" billing, under an outpatient technical component using ambulatory patient

classification (APC) codes, or for outpatient diabetes self-management training as part of a multidisciplinary team.

CPT codes for pharmacists were initially approved for the provision of medication therapy management (MTM) services through the Medicare Part D drug benefit. Initially established as a five-year pilot on January 1, 2006, this became permanent as of January 1, 2008.[38] These codes enable the billing of government healthcare programs, managed care organizations, and other payers for pharmacists' clinical services, including MTM and DSM. CPT codes are published by the American Medical Association with the intent to be used for the listing and coding of medical, surgical, and diagnostic services.[39]

These new CPT codes are to be used to bill only for services performed face-to-face between a pharmacist and a patient. Code 99605 is used for a first-encounter performed face-to-face with a patient, in time increments of up to 15 minutes, while Code 99606 is for services provided to the same patient for time up to 15 minutes for a subsequent or follow-up encounter. Code 99607 is an additional code used to bill for additional increments of 15 minutes of time following use of the other two codes. MTM services provided can include a review of the patient's medical history and medication profile, development of an action plan, interventions, recommendations for medication therapy optimization, referrals, and compliance assessment, as well as provider and other communications pertinent to the patient's care. The codes are not to be used for standard patient counselling during prescription dispensing.[39]

In institutions and physicians' offices, the pharmacist can continue use of the physician provider number ("incident to" billing) to seek payment for professional services. Pharmacists under collaborative practice agreements would bill under the CPT counselling code series 99211 to 99215 (levels I–IV) for the assessment and management of patients "incident to" the physician visit, most often using the CPT code 99211 (reflecting a 5 to 15 minute consultation). Specific requirements must be met in order to support a pharmacist's use of these billing codes, for example, only if the encounter occurred in a clinic with the physician present. The rules for billing vary from state to state and by regional Medicare payers. Billing at a higher CPT code for services such as 99212 to 99215 is controversial and may be determined by regional payers. Pharmacists in some states providing pharmacy DSM services are billing at the higher CPT codes and getting reimbursement from payers (e.g., Medicare).

Medicare initiated a prospective payment system for reimbursement of the technical component (i.e., facility fees) of outpatient visits in July 2000. Reimbursement for outpatient services is procedure-based, whereas inpatient is diagnosis-related reimbursement. Medicare-approved providers continue to bill professional services retrospectively. This new system sets consistent reimbursement rates for outpatient services and charts nonprofessional procedures performed to known patient-care level APC codes. APC stands for Medicare's Ambulatory Payment Classification. Since pharmacists cannot bill as a provider, their services become part of the overall facility reimbursement. The pharmacist's time to provide care increases the technical level, allowing reimbursement which is often several times higher than the lowest "incident to" physician fee. In January 2001 CMS (then HCFA) finalized rules on Medicare coverage of outpatient diabetes self-management training, which allows payment of the pharmacist for diabetes training as part of a multidisciplinary team.

Payment for professional services for community pharmacists is more challenging, but opportunities continue to improve. Pharmacists approved by CMS as immunization providers may bill for immunizations. The first step in billing for services is to obtain a Medicare provider number to allow for billing. Provider status can be obtained through local Medicare offices, which also process CMS claims for reimbursement (CMS-1500 claims) or electronically submitting through the CMS website at http://www.cms.hhs.gov. Pharmacists should review each third party plan's coverage and reimbursement policies for immunizations as a cost-effective preventative measure for patient care. Other options are to charge a professional fee. Some pharmacists, particularly in community pharmacy, have found success billing a professional fee directly to the patient.

Potential barriers

Potential barriers to DSM practices have been alluded to or discussed in some detail in previous sections.

The main barriers are acceptance by other providers of the services of the pharmacist and the reimbursement issues covered above.

Each discipline that participates in the DSM program will have different interests, goals, and views. It is not critical that there is total agreement on every issue. However, trust is one of the most important elements to be established and confirmed in order to overcome obstacles.

Pharmacists earn the acceptance of other providers by investing the time and energy to create strong professional relationships. The pharmacist must be engaged and willing to spend time providing direct patient care.

Successful reimbursement strategies must include thorough documentation of the care provided and adherence to proper and legal billing requirements. Specific reimbursement strategies may include "incident-to" billing to CMS and other third-party payers, direct third-party pharmacy contracting for services, MTM, and direct fee for service.

Business plans

It is common for pharmacists in managed care and at private healthcare facilities to create a business plan when considering the incorporation of DSM services into their current practice. The business plan may contain some background and description of the service, market analysis and strategy, operational structure and process, financial projections, milestones, schedule, action plan, risks, opportunities, conclusions, and any supporting documentation. The plan should emphasize total care (and costs of care) for the patient while de-emphasizing the traditional product-oriented "distribution" role of the pharmacist. Key to the plan is correctly identifying the viable patient market (disease state) that matches the needs of the providers and healthcare organizations in the area that may serve as a DSM provider. This niche should also be within the pharmacist's area of interest or at least not fall too far outside the "trainable" area of expertise.

A continuous evaluation of the impact on current practice is important. There should be a plan of action for continuously monitoring the program's impact on other aspects of the pharmacy business, including but not limited to impact on staffing, patient and provider satisfaction, program profitability, and goal attainment. Some DSM programs may increase drug utilization but lower total healthcare costs by reducing hospitalizations and emergency room visits. Thus, a means for measuring DSM program outcomes should be incorporated into the plan.

Quality assurance

Evaluation of Outcomes

Evaluation of health outcomes is the ultimate measure of success of DSM. Measures of health outcomes should be an essential part of the management protocol. Usually, the initial step is a baseline evaluation of current indicators of performance for disease control and outcome. Measured outcomes of the DSM program may include well-known indicators of disease control such as glycosylated hemoglobin, blood pressure, or lipid concentrations, as well as secondary complications, hospitalizations, quality of life (QOL), patient and physician satisfaction, mortality, or healthcare costs. As mentioned previously, these outcomes should be benchmarked to measures such as those from NCQA HEDIS or TJC.

In addition, measuring process-oriented outcomes, such as percentage of patients treated to established guidelines which are a component of the DSM protocol may be another useful measure of service quality. After implementation of the program, outcomes assessment leads to continuous modification of the program from feedback and constantly updated practice standards.

One of the dichotomies of pharmacists' activities in DSM is that, to improve overall patient health and outcomes, increasing the overall quality of care may require the need for increased prescription costs through increased utilization. Success is demonstrated when overall healthcare savings, recognized by maximizing medication efficacy, offset the overall costs.[23,24]

More difficult measures of quality of care associated with DSM include reduction of disease events and mortality. Because long-term outcomes require longer-term data collection and a concurrent control group (using historical controls have their own inherent problems), which are not always practical, intermediate outcomes (i.e., LDL cholesterol) are often substituted.

Final measures of quality of DSM services are humanistic (patient-specific) outcome measures such as patient satisfaction, QOL measures, and functional status. Patient satisfaction may assess numerous aspects of a DSM services, including satisfaction with clinic process and waiting times, pharmaceutical care, disease control and endpoint attainment, and provider communication.

Summary

Many diseases go untreated or are not managed optimally in the United States and other countries. DSM programs can be used as an effective strategy for enhancing patient outcomes and reducing management cost of diseases by ensuring consistent care using evidence-based treatment algorithms or protocols. Multidisciplinary care is a hallmark of DSM, and pharmacists are a valuable asset to the care team. The type and depth of training pharmacists receive during their formal pharmacy education and postgraduate training programs, as well as enhanced recognition through board certification, has opened up opportunities for collaborative care and other cognitive services within DSM programs. DSM programs are becoming more popular with healthcare systems, and MCO and many programs now showcase the unique expertise of the pharmacist toward making them effective. As such, pharmacist reimbursement for such services is becoming more common. Taking all of this into account, the opportunity is upon us for pharmacists to enhance their role in disease-oriented approaches to patient care.

Development of a pharmacy care plan and patient problem solving

Introduction to pharmaceutical care

The practice of pharmacy continues to undergo significant growth in response to its evolving role. Emphasis on the creation, preparation, and dispensing of pharmaceuticals has given way to pharmacotherapeutic decision making and measurable patient outcomes, with increasing focus on patient safety. As this emphasis has shifted, academic pharmacy has adopted new paradigms and approaches in its preparation of future practitioners. Examples include introductory pharmacy practice experiences, emphasis on medication therapy management, and training for immunization delivery. Students must identify their current roles, as well as anticipate future opportunities in the ever-changing healthcare system. Further, students' didactic experience should include elements that develop and nurture their knowledge, skills, attitudes, and values. One central concept that often forms the framework for this approach to learning is that of pharmaceutical care.

On the surface, pharmaceutical care appears to be a straightforward concept. It involves the pharmacist working in concert with his or her patients and other healthcare providers to identify, monitor, and achieve desirable health-related outcomes through the appropriate use of medications. While many consider the first reference to modern-day pharmaceutical care to be in 1989,[40] the theoretical construct was described several years before.[41] This expanded approach to care has been the subject of much discussion ever since, as well as recognized and supported in recent years by other healthcare providers.[42,43] And, while this advance appears to be logical and sensible, pharmaceutical care remains very difficult to define. At times pharmaceutical care is perceived to include only a specific set of practitioners or practice settings. Further, in spite of a variety of excellent models for the provision of this care, i.e., inpatient and outpatient, the delivery of pharmaceutical care is far from uniform within the profession.

In spite of our advancing knowledge and technology, drug-related problems and adverse drug events are a major source of morbidity and mortality in the United States. In one study the incidence of serious adverse events reported to the FDA increased 2.6-fold for the years studied.[44] In a recent study, 4.4 adverse drug events were found to have occurred per 100 patient days in an inpatient setting, with 58% deemed to be preventable.[45] These findings support other studies.[46,47] Further, medication-related errors have been identified as a significant cause of emergency room visits and subsequent hospitalizations.[48–52] Thus, new approaches to the safe and effective use of medicinal products should be considered. One way this may be accomplished is through the enhanced utilization of the pharmacist in the drug delivery and utilization process.

Comparison to Clinical Pharmacy

Recently, the American College of Clinical Pharmacy (ACCP) has defined clinical pharmacy as "a health science discipline that embodies the application and development, by pharmacists, of scientific principles of pharmacology, toxicology, therapeutics, clinical pharmacokinetics, pharmacoeconomics, and other life sciences for the care of patients."[53] The origin of the phrase appears to be related closely to the development of cognitive services in the inpatient setting[54] as well as to a focus on patients and their needs. As these services are intended to optimize the care provided to patients by pharmacists, there appears to be a significant amount of overlap with the provision of pharmaceutical care.[55] In fact, all providers of pharmaceutical care should be considered to be practicing as clinical pharmacists, regardless of practice setting. However, the explicit definition of pharmaceutical care requires the provider to assume a shared responsibility for therapeutic outcomes, as well as for the communication of their efforts with other healthcare professionals. This requires an expanded view of pharmaceutical care as a strategy rather than a discipline. Further, while clinical pharmacy is by definition provided by pharmacists, it has been proposed that pharmaceutical care may be provided by a variety of healthcare professionals.[40]

This section is intended to contribute toward the pharmacy student's and the practitioner's ability to provide pharmaceutical care. The care provided must be based upon a logical, effective, and patient-specific pharmaceutical care plan.

Who Provides Pharmaceutical Care?

Pharmaceutical care is an equally appropriate practice model for independent community practice, chain community practice, and institutional practice, among other settings. While the specific services provided may differ among these practice environments, the underpinning philosophy of pharmaceutical care remains the same, i.e., achieving definitive outcomes for patients. Some examples of the various care settings include outpatient clinics, emergency patient care centers, and specific inpatient units such as medical/surgical intensive care, infectious disease, transplant, pediatrics, trauma, internal medicine, and cardiac, among others.

A central feature of pharmaceutical care is to identify, prevent, and resolve drug-related problems (DRPs). Pharmaceutical care and pharmacist-managed drug-related problems may differ among practice settings and from patient to patient. Examples of pharmaceutical care services offered include generic and therapeutic interchange, pharmacokinetic and therapeutic consultation, patient interviewing, patient counseling, team rounding, drug information, laboratory monitoring, and monitoring drugs with high costs or narrow therapeutic windows or potential adverse effects if used indiscriminately, to list just a few.

Role of a Pharmacist

The profession and the roles of pharmacists are continuously evolving, but at the foundation of all pharmacist roles is the same provision to provide quality pharmaceutical care to patients. In fact, there is a consensus among all major pharmacy organizations since the 1990s that the mission of the profession is to provide pharmaceutical care and, as such, all students of pharmacy should be trained to provide it.[56] Pharmaceutical care is defined by Hepler and Strand[40] as the responsible provision for providing drug therapy for the purposes of achieving definite outcomes. Pharmaceutical care focuses on activities that are patient centered and lead to positive medication therapy outcomes. According to Penna,[57] to practice pharmaceutical care, a pharmacist must be a scientific problem solver, a good communicator, educator, and learner. Primary activities involved in the provision of pharmaceutical care include obtaining a thorough medication history; identifying real and potential drug-related problems; developing and implementing a pharmacy care plan, which includes monitoring parameters to prevent drug-related problems, periodically evaluating the plan for achievement of predefined clinical outcomes; and consulting with patients to ensure successful plan implementation. Encompassing all these components in a patient care plan is essential to achievement of positive patient outcomes but requires a pharmacist that is competent and knowledgeable in providing cognitive services or value-added services (e.g., patient drug or disease counseling).[58]

Cognitive services are closely linked with the concepts of clinical pharmacy and pharmaceutical

care. Key components of both include application of one's judgment, knowledge, and abilities to solve DRPs. To practice effectively, pharmaceutical care focus must be placed on patient satisfaction. It is important to conduct a one-on-one patient session to review past disease and medical histories, current drug, herbal, dietary supplement and non-drug therapies, related signs and symptoms, and desired outcomes. Collection of this information allows the pharmacist to identify patient drug-related problems and develop a pharmacy care plan to help resolve these problems.[59,60] Box 13.1 demonstrates the proposed nine steps to pharmaceutical care for pharmacists.

Box 13.1 Nine steps to pharmaceutical care

1. Develop a covenantal relationship between the pharmacist and the patient
2. Collect relevant drug, disease, and patient information
3. Interpret this information to identify all the patient's drug-related problems
4. Prioritize the patient's drug-related problems
5. Identify those drug-related problems for which the pharmacist will assume responsibility
6. Identify patient-specific outcomes for each drug-related problem for which the pharmacist has assumed responsibility.
7. Develop a therapeutic plan to attain the desired patient-specific outcomes for each drug-related problem
8. Develop a monitoring plan to assess whether predetermined outcomes have been attained
9. Implement and follow the pharmacy care plan, which consists of desired outcomes, therapeutic plan, and monitoring plan.

(Adapted from Winslade NE, Bajcar JM, *et al*. Pharmacist's management of drug-related problems: a tool for teaching and providing pharmaceutical care. *Pharmacotherapy* 1997; 17 (4): 805; with permission.)

In carrying out daily responsibilities, identifying DRPs, or developing a pharmacy care plan, pharmacists must also address societal needs. Societal needs may be identified by providing value-added services for patients and performing these activities with ethical and professional prerogatives in mind. On a daily basis, pharmacists may be confronted with professional dilemmas that are legally, ethically and/or morally challenging (e.g., patient confidentiality issues and pro-life issues). One must learn to balance these challenges while maintaining a level of personal comfort to practice successfully and deliver optimal care on behalf of the patient.[61]

Student Responsibilities

Education

According to the AACP Commission, the goal of pharmaceutical education is to "inculcate students with values necessary to serve society as caring, ethical, learning, professional, and enlightened citizens."[61] This is accomplished by providing a curriculum which enables students to learn and develop knowledge, skills, attitudes, and values necessary to meet the needs of patients and society both today and tomorrow. This knowledge and skill should be developed in three core areas according to the CAPE educational outcome of 2004: pharmaceutical care, systems management, and public health.[56] It is also imperative for students to acquire appropriate attitudes and good values in the areas of professionalism, self-directed learning, leadership and advocacy, interprofessional collaboration, and cultural competency.[62] Education that encompasses all these components lays the foundation for students to acquire the knowledge and abilities required to be successful pharmacists in the future. Students are responsible for becoming active participants in this process, incorporating knowledge and developing skills in their careers, and embracing life-long learning.[61]

Importance of Skills

Skills necessary for the delivery of pharmaceutical care include patient care skills, clinical skills, application of drug knowledge and drug information skills, and professional skills (e.g., interpersonal skills with a service orientation). Collecting, collating, and organizing patient information from medical charts and

computer databases is necessary. Equally important is the personal time a pharmacist invests in obtaining information directly from the patient. The concept of patient-centered practice or patient care skills becomes evident when the pharmacist attempts to build a relationship of trust with the patient. This interaction will help identify and determine patients' preferences for their healthcare outcomes. Patient encounters for students are planned to occur during internship and/or the experiential component (e.g., fourth professional year clerkship rotations) of their curriculum. Routinely, students on rotation provide clinical pharmacy services under the direct supervision of a clinical pharmacy preceptor. The goal of the preceptor is to bridge classroom learning and real-life clinical experiences, enhance the students' drug knowledge, and help develop the students' professional judgment and values. Clinical skills (e.g., being capable of interpreting blood levels and laboratory data, assess the patient's needs, and apply therapeutic data to drug-related problems) are key factors for an optimal drug regimen. Furthermore, drug knowledge and information skills, as well as the ability to rationalize therapeutic decisions, are equally important in achieving optimal patient care. Finally, professional skills remain essential for a successful, future practicing pharmacist. Professional responsibilities, whether learned through school courses or heightened during clerkship rotations, distinguish all healthcare professionals.[61] Examples of professional responsibilities for pharmacists may include holding high professional aspirations for the practice of pharmacy, upholding a commitment to serve the community and humanity, serving as mentors for future pharmacists, and maintaining personal standards of integrity, competency, reasoning, and life-long learning.

For one to be proficient in skills gained or acquired, one must demonstrate competency or mastery of skills learned. In pharmacy school competency may be ascertained through successful outcomes on examinations, quizzes, and simulated patient exercises, among others. To test student competency and skill sets in a clinical setting, the use of algorithms and flow charts may be used on clerkship rotations. Flow charts (Fig. 13.2) encourage a uniform approach to problem solving and assist students in identifying DRPs, learning to ask appropriate questions, and becoming capable of formulating recommendations for monitoring and follow-up planning.[63]

Experiential practice and the work environment also help students gain experience toward identifying and resolving DRPs, not all of which will be clear-cut textbook scenarios. Awareness of such ambiguities exists throughout pharmacy practice and in other healthcare arenas. Professional prerogatives, ethical dilemmas, and the balance of both may be quite challenging. The American Pharmacists Association (APhA) Code of Ethics states, "A pharmacist should hold the health and safety of patients to be of first consideration and should render to each patient the full measure of professional ability as an essential health practitioner."[61] In some instances, a pharmacist's moral and ethical beliefs may conflict with his or her professional duty. For this reason, as a future pharmacist it is important to be comfortable making decisions in the face of these uncertainties.[64]

Identifying Patients to Follow

To develop a pharmacy care plan and problem-solve, the student will need to identify patients with DRPs to follow. Numerous studies have indicated that elderly patients (e.g., over 65 years of age) are at an increased risk for DRPs because, typically, they have multiple medical problems, have multiple drug therapies, and suffer the physiological effects of aging, which warrants close monitoring on the disposition of drugs. Greater than three concomitant diseases, five or more medication regimens, twelve or more doses of drugs a day, and frequent medication regimen changes in the past year can lead to non-adherence and demand further investigation. Students may also learn, by monitoring patients with compromised renal or hepatic function, to identify abnormal clinical laboratory values, and to monitor for potential drug–drug and drug–disease state. Sometimes regulatory or reimbursement issues dictate or necessitate tracking the care of certain patients (e.g., high cost drugs and therapies). By this selective process, the student can concentrate his or her activity effectively on those patients who have the greatest potential for benefit from clinical services.[65]

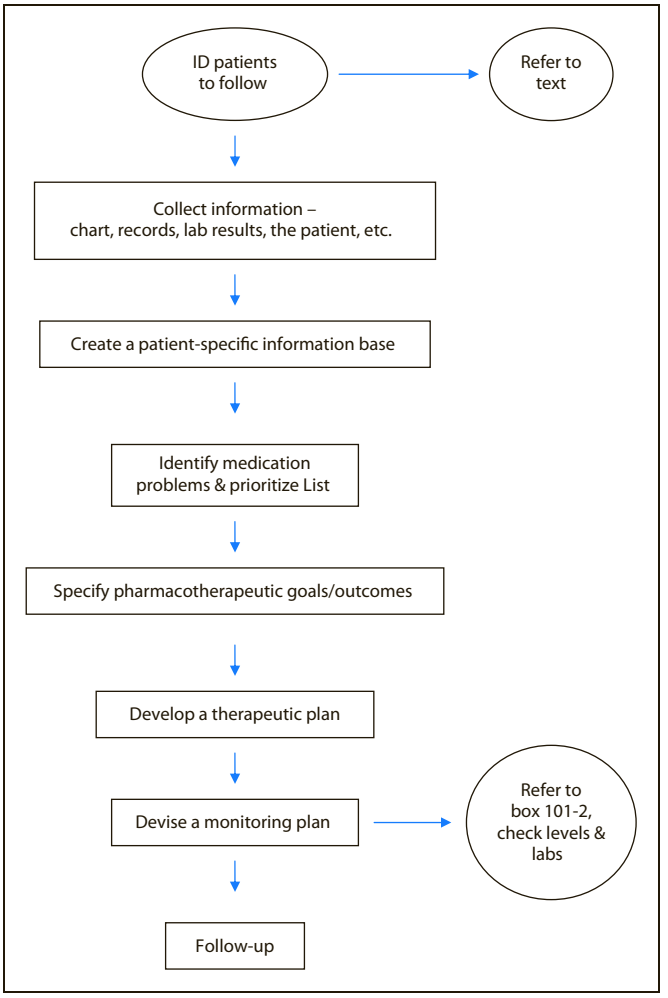

Figure 13.2 Example of a flow chart.

Specialization in pharmacy practice

Introduction

Compared with many other professions, only recently has the profession of pharmacy entered the arena of advanced level credentialing. The medical profession has formally recognized specialty practice for nearly 100 years. Several other health professions, e.g., nursing, optometry, and dentistry, also demonstrate a long history of advanced level credentialing of qualified members. In fact, specialization in the healing arts is probably as old as the first declaration by a priest or shaman that he possessed special knowledge, insight, and power to heal. Therefore, he differed from other members of the tribe and was so recognized.[66]

History of Specialization in Medicine

Specialization in medicine enjoys a long history. Medicine's evolution to its current highly credentialed state provides an interesting study in the professional, economic, and political forces that influence such a transformation. While there are major differences between medicine and many other health professions, medicine can serve as a model for other professions seeking to have credentialed specialists.

In medicine, the growth of specialization began in the 1920s and 1930s and is directly connected to the development of medical science and the resulting improvements made in medical care delivery. In the United States, the growth of medical specialization is largely due to the physician's need to master the special tools and skills needed to deliver quality healthcare and the intricacies of social, political, and economic forces.

Most specialty areas developed around organ systems, e.g., ophthalmology, otolaryngology, urology, neurosurgery, gastroenterology, and cardiology. However, physicians were the only assessors of their own qualifications to practice a given specialty. There was no formal system to assure the public that the heart specialist was different from the general practitioner or that a physician claiming to be a specialist was indeed qualified. Consequently, specialty societies and medical education institutions collaborated on developing boards to define specialty qualifications and to issue credentials that would assure the public of the specialist's qualifications. The American Board of Ophthalmology, established in 1917, was the first specialty board in the United States.[67] It established the guidelines for the education, training, and evaluation of candidates desiring certification to practice ophthalmology. The second specialty board, the American Board of Otolaryngology, was established in 1924. The third and fourth boards, the American Board of Obstetrics and Gynecology and the American Board of Dermatology and Syphilology, were established in 1930 and 1932, respectively. These were followed by several other specialties, such as the American Board of Internal Medicine in 1936 and the American Board of Surgery in 1937.

The objectives of each specialty board were to elevate the standards of a specialty area, to familiarize the public with its aims and ideals, to protect the public against irresponsible and unqualified practitioners, to receive applications for examinations in a specialty area, to conduct examinations of such applicants, and to issue certificates of qualification in a specialty area. Since 1934, official recognition of specialty boards in medicine has been achieved by the collaborative efforts of the American Board of Medical Specialties and the American Medical Association (AMA) Council on Medical Education. The American Board of Medical Specialties (ABMS) approves 24 medical specialties. This organization has become the standard by which the profession and the public recognize physician specialists in the United States.[68] In addition to the 24 ABMS member boards, approximately 180 non-ABMS boards issue specialty certification.

The establishment of board certification for physician specialists was based on the concept that a physician, who successfully met certain predetermined qualifications and attained the requisite level of knowledge, skill, and experience in a well-defined specialized area of medicine, would be a better practitioner than one who did not meet these qualifications. The implication was that a specialist would produce better healthcare outcomes, less morbidity, and/or greater efficiency in providing healthcare. However, while intuitively logical, this concept has not been validated by any studies.[69] One may argue that physicians with specialties provide state-of-the-art knowledge and that the patients ultimately benefit from specialist-dominated care. On the other hand, there may be instances where the sophisticated, expensive, specialist-dominated care may not produce any better health outcomes than did other, simpler, less-expensive healthcare delivery systems.

Value of Specialization in Medicine

Although board certification is not required for an individual physician to practice medicine, the value of specialty certification in medicine, at least in medically sophisticated societies, is quite clear. Most hospitals and managed care organizations require that at least a certain percentage of their staff be board certified. Specialty board certification status for a physician is often used as a standard of excellence. Most hospitals, managed care organizations, and health insurance plans require board certification for physicians for them to obtain clinical privileges and hospital appointments. Furthermore, The Joint Commission and the National Committee for Quality Assurance embrace medical specialty board certification by incorporating it into their accreditation standards.[70] Commonly, the public also views medical specialty board certification as a measure of a physician's clinical expertise.

History of specialization in pharmacy

The Basis of Specialization

For most of its history as a profession, pharmacy was relatively undifferentiated. Prior to the

mid-1900s, most pharmacists concentrated on providing drug products to patients in response to an order of a physician or other credentialed prescriber. The emergence of practice differentiation really began to be recognized in the late 1960s and early 1970s. In a 1968 editorial, Paul Parker described hospital pharmacists who had developed unique roles that were distinct from the traditional dispensing roles of the pharmacist.[71] These pioneering "clinical pharmacists" participated with physicians in therapeutic decision-making, and Parker suggested that their level of knowledge and practice skills required special educational and experiential preparation. Further, he encouraged hospital pharmacists to organize their departments to recognize and utilize these emerging "specialists" and proposed that the medical model of specialty organization might be applicable to pharmacy.[71] Shortly thereafter, the Study Commission on Pharmacy, known synonymously as the Millis Commission, was chartered by the American Association of Colleges of Pharmacy (AACP). Its report, published in 1975, acknowledged that differentiation in pharmacy practice was occurring and that this was, in general, expected and desirable. While not specifying specialty practice areas, the commission suggested that a structure be established to oversee all pharmacist credentialing.

In a series of editorials between 1974 and 1976, Donald Francke outlined his concept of a structure for the practice of pharmacy.[72] Specialization was addressed as part of the continuum of education, and he identified the pharmacotherapeutic specialist, the clinical radiopharmacist specialist, the drug information specialist, the pediatric clinical pharmacy specialist, and the pharmacy practice specialist, among others.[72]

Task Force on Specialization in Pharmacy – Role of APHA

Perceiving the evolving interest in differentiated practice within the pharmacy profession, the Board of Trustees of the American Pharmaceutical Association (APhA, now the American Pharmacists Association) appointed a Task Force on Specialties in Pharmacy in early 1973. This group was charged to (1) identify existing or potential areas of specialization (or, alternatively, to determine that there were no specialties and that the practice of pharmacy was not likely to become specialized), (2) propose a means by which specialties could be identified, and (3) develop the means by which individuals could become recognized as specialists, as well as make recommendations for recertification.

The Task Force published its report in 1974.[73] While not concluding whether specialties existed at that time, it did determine that one or more specialties would develop in the near future and that there was need for an independent agency to recognize these specialists. It made several recommendations concerning the recognition process and proposed the establishment of a Board of Pharmaceutical Specialties, now the Board of Pharmacy Specialties (BPS), to develop a mechanism to identify specialty practice areas and recognize individual specialists.

Development of the Board of Pharmacy Specialties (BPS)

The Board of Pharmacy Specialties was officially established on January 5, 1976, when APhA members approved the BPS bylaws within the APhA structure. The initial mission of BPS was based on responsibilities outlined in its bylaws. (1) BPS recognizes appropriate specialties in pharmacy practice, using specific criteria developed for this purpose. *These criteria are discussed below in the Petition Process*. (2) BPS sets standards for certification and recertification of pharmacists in designated areas of specialty practice. *This is achieved primarily by individual specialty councils, within the BPS structure, which make recommendations to the full Board*. (3) BPS administers the examination and evaluation of individuals who seek certification and recertification as specialists. (4) BPS serves as an information clearinghouse and coordinating agency for organizations and pharmacists with regard to the specialty practice of pharmacy.

The organizational relationship of the BPS to the APhA was intended to provide financial and administrative support for the young organization while ensuring that decisions regarding recognition of specialties and credentialing of specialists would be independent. Today BPS operates as an autonomous division of APhA. BPS Governing Policies adopted in July 2008 provide for an eleven-member Board, comprising eight pharmacists and three non-pharmacists (i.e., two other health professions members and one public/consumer member.) This Board is advised by Specialty Councils, representing each recognized

specialty. The Specialty Councils are composed of six pharmacists who hold BPS certification in a specialty practice area and three pharmacists representing the profession in general. The Specialty Council Chairs (i.e., currently numbering six and representing the specialties of Nuclear Pharmacy, Nutrition Support Pharmacy, Oncology Pharmacy, Pharmacotherapy, Psychiatric Pharmacy, and Ambulatory Care Pharmacy), as well as the Executive Director of BPS (an administrative staff position), serve as *ex-officio* members of the Board of Pharmacy Specialties.

BPS New Specialty Petition Process

A key role of the Board of Pharmacy Specialties is the recognition of new specialties within the profession. To their credit, the founders of BPS sought to make this a very formal and participative process for the pharmacy profession. Seven criteria for recognition of a new specialty were established and remain in effect today.[74] These criteria must be addressed in detail in the petition which is submitted to BPS by an organization or group seeking new specialty recognition in pharmacy. A more detailed description of the petition process is available from BPS and detailed on its web site, which provides additional guidelines for needed supporting information under each criterion. The BPS criteria, which must be met for any new specialty to be recognized, are as follows:

1. The profession of pharmacy **needs** specifically trained practitioners in the specialty practice area to fulfill the responsibilities of the profession in improving the health and welfare of the public. Licensed pharmacy generalists or other healthcare professionals cannot provide the level of services that pharmacist specialists can, and pharmacies' responsibilities may not be fulfilled effectively without their contributions.
2. A clear, significant demand for the specialty is made by the public and healthcare systems.
3. A reasonable number of pharmacist specialists practice in and *devote significant time* to provision of services in the specialty area.
4. Practice in a specialty area requires specialized knowledge of pharmaceutical sciences based upon the biological, physical, and behavioral sciences. The specialty may not be based solely on the practice environment or managerial, procedural, or technical services.
5. Pharmacists in the specialty practice area perform specialized functions, acquired through education and training beyond the basic level attained by licensed pharmacy generalists.
6. Pharmacy schools and other organizations offer education and training in the specialty practice area.
7. Transmission of knowledge in the specialty practice area occurs through books, journals, symposia, professional meetings, and other formal media or mechanisms.

Petition Review and Approval

The formal review process begins when the BPS receives a petition proposing a new specialty. The petition is released for comment by the profession and the public if an initial review by BPS staff and the Board of Directors indicate that the petition is complete and reasonably meets criteria. At least two open hearings are usually held at major pharmacy meetings to solicit input from the pharmacy profession, other health professions, third-party payers, and the public. Finally, the Board will consider the detailed information in the petition and any comments provided during the petition review period to determine whether the criteria for new specialty establishment are met. The Board's decision is appealable in accordance with established BPS appeals policy. Once a new specialty has been approved, the initial Specialty Council is appointed. The organization or group which submitted the petition appoints the six, non-certified specialist members to the Council, and BPS appoints the three non-specialist pharmacist members. After the first certification examination is administered, and the first group of specialists is certified, there will be three new appointees each year to replace the original Specialty Council. Two appointees will be Board Certified in that specialty, and one will be a pharmacy generalist appointee.

The major charge of the Specialty Council is to work with the BPS testing consultant to develop and maintain the examination process itself.

Establishment of a Specialty Certification Process

Across all professional fields, there are relatively consistent procedures that need to be followed for the development and implementation of an advanced

practice certification process. To be respected and successful, a certification examination must be psychometrically sound and legally defensible. This process begins when the BPS determines that legitimate criteria for the establishment of the specialty have been met. An early part of the specialty recognition process is to conduct a role delineation study, also known as a job analysis. This is a very comprehensive survey designed to identify what specific knowledge, skills, and tasks characterize the specialty and can be used to differentiate between practitioners who are, and are not, at the specialist level. This is administered to a large group of pharmacists, generally believed to be practicing at the specialist level.

When appropriately analyzed, the results of this study serve two purposes: (1) to determine if there is both the presence of specialized knowledge and functions within the proposed specialty and (2) if the petition is approved by BPS, the study forms the Content Outline or Examination Specifications for the specialty's certification examination. This determines the types of questions that should comprise the examination. Once a specialty has been approved by BPS, the Council is established and convenes groups of knowledgeable individuals to draft questions (also known as test items) which meet established test specifications. When appropriate, test items are based on evidence-based clinical practice guidelines and randomized clinical trial data, and each item is referenced for validation purposes. Following an extensive review, these questions are used to create the specialty examination itself. All BPS specialty certification examinations consist of 200 multiple-choice questions. Each has four possible answers, only one of which is correct. After the first examination has been drafted, the Council and other experts conduct a passing point study, which results in a psychometrically valid passing score. A passing point study involves determining what fraction of competent specialists would likely select the correct answer for each item. BPS and most similar advanced practice certifications utilize a criterion referenced scoring system, rather than the more familiar norm referenced system more common in academic institutions. Detailed discussion of these systems in included on the BPS website (http://www.bpsweb.org) and educational testing references. Recertification in all six BPS specialties is required every 7 years, with recertification examinations consisting of 100 multiple choice questions in the same format as the original certification examination. When available, a BPS-approved professional development program may be substituted for the written recertification examination.

Evolution of Specialties

In the pre-BPS discussions across the pharmacy profession, several potential specialties were identified. It was not surprising that Nuclear Pharmacy emerged as the first petition to be submitted to the BPS. A section on Nuclear Pharmacy had been established within the APhA structure in 1975, and there was little debate that specialized knowledge and skill was required to practice nuclear pharmacy safely and competently. The community of nuclear pharmacy practitioners was relatively small and close-knit, and the APhA was in an excellent position to assist BPS to develop the specialty.[75] It was nearly 12 years, however, before any other specialties were proposed. Since that time, five additional specialties have been recognized. Those petitions were submitted by three other major professional organizations, marking the profession's recognition that the BPS could ideally serve the entire pharmacy profession as its specialty certification body. Although other certifications have emerged in recent years under other auspices, BPS remains the largest organization and most rigorous in offering specialty level certification.

The bar graph (Fig. 13.3) illustrates the development and growth of specialties in pharmacy since 2002. Note that numbers represent individuals currently certified by BPS as of the year indicated. Individuals who failed to recertify when required are removed from these totals. It should also be noted that the number of BPS certified pharmacists has doubled between 2005 and 2010.

Current specialties in pharmacy

Nuclear Pharmacy

1. **Supporting Organization(s)**: American Pharmacists Association
2. **Year of Specialty Recognition**: 1978
3. **Description of the Specialty**:
   Nuclear Pharmacy seeks to improve and promote the public health through the safe and effective use

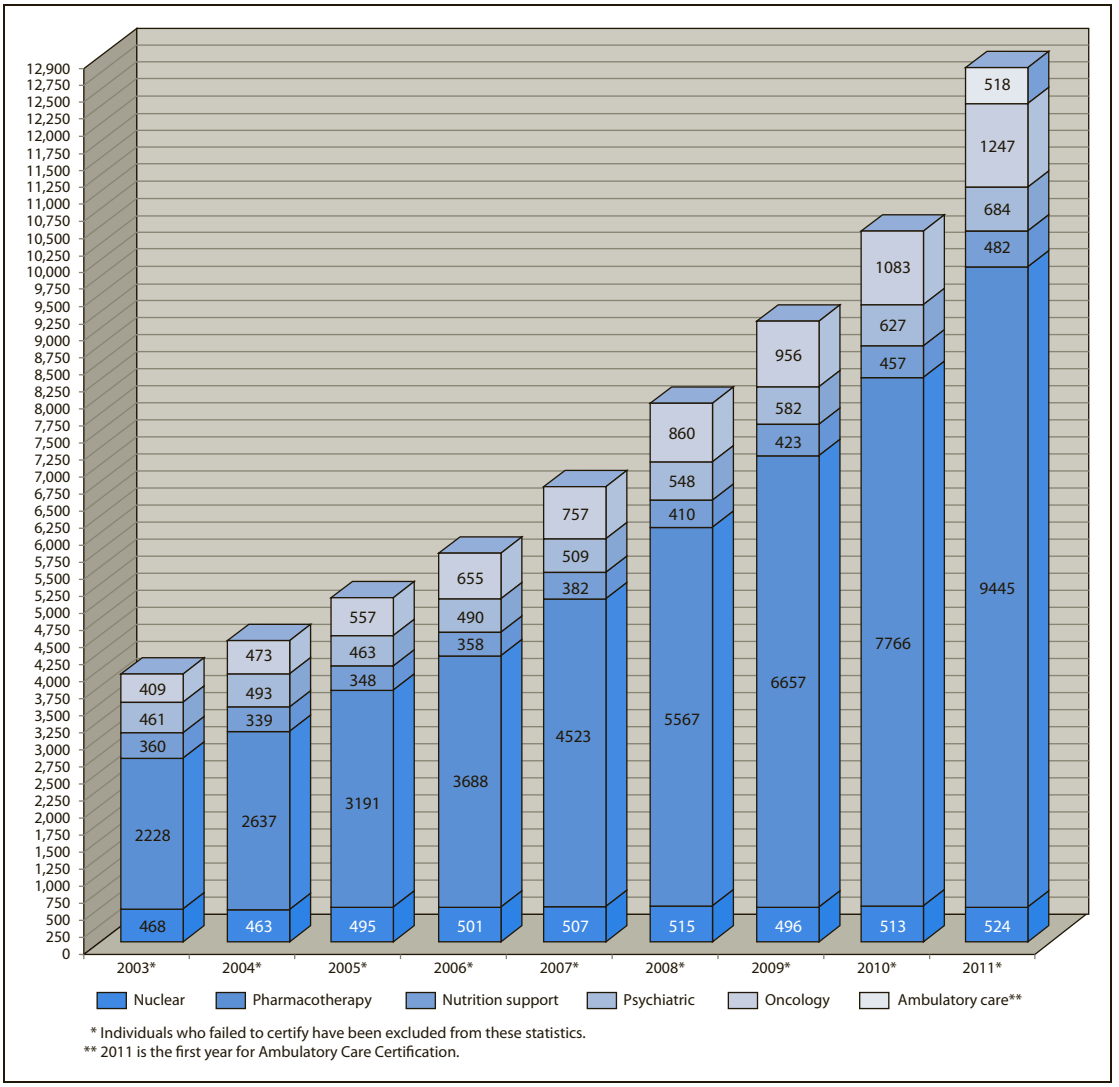

Figure 13.3 Pharmacists certified by the Board of Pharmacy Specialties.

of radioactive drugs for diagnosis and therapy. A nuclear pharmacist, as a member of the nuclear medicine team, specializes in the procurement, compounding, quality control testing, dispensing, distribution, and monitoring of radiopharmaceuticals. In addition, the nuclear pharmacist provides consultation regarding health and safety issues, as well as the use of non-radioactive drugs and patient care. Those who are granted certification in this specialty may use the designation, Board Certified Nuclear Pharmacist and the initials BCNP, as long as their certification is valid.

4. **Eligibility Requirements**
   The minimum requirements for certification in nuclear pharmacy are
   - Graduation from a pharmacy program accredited by the Accreditation Council for Pharmacy Education (ACPE) or program outside the US that qualifies the individual to practice in the jurisdiction. Foreign trained pharmacists must pass the Foreign Pharmacy Graduate Examination Committee (FPGEC) examination.
   - Current, active license to practice pharmacy in the US or another jurisdiction

- 4000 hours of training/experience in nuclear pharmacy practice
- Achieving a passing score on the Nuclear Pharmacy Specialty Certification Examination.

The required 4000 hours of experience may be earned in a variety of settings.

Academic – up to 2000 hours:

- Undergraduate courses in nuclear pharmacy: up to 100 hours experience for every quarter credit hour or 150 hours experience for every semester credit hour, to a maximum of 1500 hours
- Postgraduate courses in nuclear pharmacy: up to 100 hours experience for every quarter credit hour or 150 hours experience for every semester credit hour, to a maximum of 1500 hours
- MS or PhD degree in nuclear pharmacy: 2000 hours
- Successful completion of the Nuclear Pharmacy Certificate Program offered by Purdue University (217 hours) or The Ohio State University (214 hours), or the Nuclear Education Online (NEO) Program offered by the Universities of New Mexico and Arkansas (250 hours). Credit for other courses will be assessed on a case-by-case basis.

Training/practice – up to 4000 hours:

- Residency in nuclear pharmacy: hour-for-hour credit to a maximum of 2000 hours
- Internship to satisfy requirements of state boards of pharmacy: hour-for-hour credit in a licensed nuclear pharmacy or facility authorized to handle radioactive materials, to a maximum of 2000 hours
- Nuclear pharmacy practice: hour-for-hour credit in a licensed nuclear pharmacy or healthcare facility approved by state or federal agencies to handle radioactive materials, to a maximum of 4000 hours.

5. Examination Content

Domain 1: Drug Order Provision (66% of the examination)

- Subdomain A: Procurement (8% of the examination)
- Subdomain B: Compounding (26% of the examination)
- Subdomain C: Quality Assurance (9% of the examination)
- Subdomain D: Dispensing (23% of the examination)

Domain 2: Health and Safety (24% of the examination)

Domain 3: Drug Information Provision (10% of the examination).

6. Recertification

Recertification for Board Certified Nuclear Pharmacists (BCNP) is a three-step process:

- Self-evaluation: Review of the nuclear pharmacy practice activities/functions that have changed since initial certification or last recertification.
- Peer review: Documentation of nuclear pharmacy practice over the seven year certification period.
- Formal Assessment: This assessment of a practitioner's knowledge and skills will be accomplished through one of two methods:
  - *Option One: Examination*
    Achieve a passing score on the 100-item, multiple choice objective recertification examination based on the content outline. (Refer to the Nuclear Pharmacy Content Outline for details.)
  - *Option Two: Continuing Education*
    The continuing education option for recertification was implemented in 1976 with BPS designation of the University of New Mexico College of Pharmacy's Correspondence Continuing Education Courses for Nuclear Pharmacists, beginning with Volume V, as an acceptable professional development program.

A BCNP recertifying is required to earn 70 hours over the 7 year certification period. At least 30 of these hours MUST be earned within the last 3 years of the certification period. There are no other restrictions as to which lessons in which years may be used to obtain the required number of hours, other than the lesson must have been issued in 1996 or thereafter (Volume V or later volumes).

A current, active license to practice pharmacy is required for recertification. As part of the recertification process, every BCNP is asked to complete an annual practice report form provided by BPS. The information is compiled by BPS at the beginning of the recertification process and sent to the BCNP for verification and updating. At the time of recertification, the BCNP is also required to certify that he or she is not currently under suspension by either the US Nuclear Regulatory Commission or a state Radiation Control Organization.

Nutrition Support Pharmacy

1. **Supporting Organization(s):** American Society of Health-System Pharmacists and American Society for Parenteral and Enteral Nutrition
2. **Year of Recognition:** 1988
3. **Description of the Specialty**
   Nutrition Support Pharmacy addresses the care of patients who receive specialized nutrition support, including parenteral and enteral nutrition. The nutrition support pharmacist has responsibility for promoting maintenance and/or restoration of optimal nutritional status and designing and modifying treatment according to patient needs. The nutrition support pharmacist has responsibility for direct patient care and often functions as a member of a multidisciplinary nutrition support team. Those who are granted certification in this specialty may use the designation Board Certified Nutrition Support Pharmacist and the initials BCNSP, as long as their certification is valid.
4. **Eligibility Requirements**
   The minimum requirements for this specialty certification are
   - Graduation from a pharmacy program accredited by the Accreditation Council for Pharmacy Education (ACPE) or program outside the US that qualifies the individual to practice in the jurisdiction.
   - Current, active license to practice pharmacy in the US or another jurisdiction.
   - Completion of 3 years practice experience with at least 50% of time spent in nutrition support pharmacy activities (as defined by the BPS Nutrition Support Content Outline)
     OR
   - Completion of a (PGY2) residency* in nutrition support pharmacy.
   - **Effective January 1, 2013, only residencies accredited by the American Health-System Pharmacists or other recognized bodies are creditable for this purpose.*
   - Achieving a passing score on the Nutrition Support Pharmacy Specialty Certification Examination.
5. **Examination Content**
   Domain 1: Clinical Practice/Provision of Individualized Nutrition Support to Patients (68% of the examination)
   - Subdomain A: Assessment (21% of the examination)
   - Subdomain B: Develop and Implement a Therapeutic Plan of Care (21% of the examination)
   - Subdomain C: Monitoring and Clinical Management (26% of the examination)

   Domain 2: Management of Nutrition Support Operations (20% of the examination)
   - Subdomain A: Patient Care Management (12% of the examination)
   - Subdomain B: Compounding Operations (8% of the examination)

   Domain 3: Advancement of Nutrition Support Practice (12% of the examination).
6. **Recertification**
   Recertification for Board Certified Nutrition Support Pharmacists (BCNSP) is based on the following activities:
   - Earning a minimum of 30 hours of continuing education in nutrition support with no less than 10 hours earned every two years. These hours must be from providers approved by the Accreditation Council for Pharmacy Education (ACPE).
   - Achieving a passing score on the 100-item, multiple-choice recertification examination, which is based on the content outline of the certification examination
   - A current, active license to practice pharmacy is required for recertification.

Pharmacotherapy

1. **Supporting Organization(s):** American College of Clinical Pharmacy

2. **Year of Recognition**: 1988
3. **Description of the Specialty**
   Pharmacotherapy is that area of pharmacy practice that is responsible for ensuring the safe, appropriate, and economical use of drugs in patient care. The pharmacotherapy specialist has responsibility for direct patient care, often functions as a member of a multidisciplinary team, and is frequently the primary source of drug information for other healthcare professionals. Those who are granted certification in this specialty may use the designation Board Certified Pharmacotherapy Specialist and the initials BCPS, as long as their certification is valid.
4. **Eligibility Requirements**
   The minimum requirements for this specialty certification are
   - Graduation from a pharmacy program accredited by the Accreditation Council for Pharmacy Education (ACPE) or a program outside the US that qualifies the individual to practice in the jurisdiction.
   - Current, active license to practice pharmacy in the US or another jurisdiction.
   - Completion of 3 years of practice experience with at least 50% of time spent in pharmacotherapy activities (as defined by the BPS Pharmacotherapy Content Outline)
     OR
   - Completion of a PGY1 residency.
     **Effective January 1, 2013, only residencies accredited by the American Society of Health-System Pharmacists or other recognized bodies are creditable for this purpose.*
   - Achieving a passing score on the Pharmacotherapy Specialty Certification Examination.
5. **Examination Content**.
   Domain 1: Patient-specific Pharmacotherapy (60% of the examination)
   Domain 2: Retrieval, generation, interpretation, and dissemination of knowledge in pharmacotherapy (25% of the examination)
   Domain 3: Systems and Population-based Pharmacotherapy (15% of the examination)
6. **Recertification**
   Recertification for Board Certified Pharmacotherapy Specialists (BCPS) is an assessment of a practitioner's knowledge and skills through one of two methods:
   - Achieving a passing score on the 100-item, multiple-choice objective recertification examination, based on the content outline of the certification examination
     OR
   - Earning 120 hours of continuing education credit provided by a professional development program approved by BPS. The approved professional development program provider for the pharmacotherapy specialty is the American College of Clinical Pharmacy.
   - A current, active license to practice pharmacy is required for recertification.

Psychiatric Pharmacy

1. **Supporting Organization(s)**: American Society of Health-System Pharmacists
2. **Year of Recognition**: 1994
3. **Description of the Specialty**
   Psychiatric Pharmacy addresses the pharmaceutical care of patients with psychiatric-related illnesses. As a member of a multidisciplinary treatment team, the psychiatric pharmacy specialist is often responsible for optimizing drug treatment and patient care by conducting such activities as monitoring patient response, patient assessment, recognizing drug-induced problems, and recommending appropriate treatment plans. Those who are granted certification in this specialty may use the designation Board Certified Psychiatric Pharmacist and the initials BCPP, as long as their certification is valid.
4. **Eligibility Requirements**
   The minimum requirements for this specialty certification are:
   - Graduation from a pharmacy program accredited by the Accreditation Council for Pharmacy Education (ACPE) or a program outside the US that qualifies the individual to practice in the jurisdiction.
   - Current, active license to practice pharmacy in the US or another jurisdiction.
   - Completion of 4 years of practice with at least 50% of time spent in psychiatric pharmacy activities (as defined by the BPS Psychiatric Pharmacy Content Outline)

OR

Completion of a specialty (PGY2) residency* in psychiatric pharmacy plus one (1) additional year of practice with at least 50% of time spent in psychiatric pharmacy activities (as defined by the BPS Psychiatric Pharmacy Content Outline)

**Effective January 1, 2013, only residencies accredited by the American Society of Health-System Pharmacists or other recognized bodies are creditable for this purpose.*

- Achieving a passing score on the Psychiatric Pharmacy Specialty Certification Examination.

5. **Examination Content**

Domain 1: Clinical Skills and Therapeutic Management (65% of the examination)
Domain 2: Education and Dissemination of Information (25% of the examination)
Domain 3: Clinical Administration (10% of the examination).
Check the BPS website at http://www.bpsweb.org for updates.

6. **Recertification**

Recertification of Board Certified Psychiatric Pharmacists (BCPP) requires an assessment of a practitioner's knowledge and skills through one of two methods:

- Achieving a passing score on the 100-item multiple choice recertification examination, based on the content outline of the certification examination

  OR
- Earning 100 hours of continuing education credit provided by a professional development program approved by BPS. The approved professional development program provider for psychiatric pharmacy is the College of Psychiatric and Neurologic Pharmacists.
- A current, active license to practice pharmacy is required for recertification.

Oncology Pharmacy

1. **Supporting Organization(s)**: American Society of Health-System Pharmacists
2. **Year of Recognition**: 1996
3. **Description of the Specialty**

Oncology Pharmacy specialists recommend, design, implement, monitor and modify pharmacotherapeutic plans to optimize outcomes in patients with malignant diseases. Those who are granted certification in this specialty may use the designation Board Certified Oncology Pharmacist and the initials BCOP, as long as their certification is valid.

4. **Eligibility Requirements**

The minimum requirements for this specialty certification are

- Graduation from a pharmacy program accredited by the Accreditation Council for Pharmacy Education (ACPE) or a program outside the US that qualifies the individual to practice in the jurisdiction.
- Current, active license to practice pharmacy in the US or another jurisdiction.
- Completion of 4 years of practice experience with at least 50% of time spent in oncology pharmacy activities (as defined by the BPS Oncology Pharmacy Content Outline)

  OR

  Completion of a specialty (PGY2) residency* in oncology pharmacy plus one (1) additional year of practice with at least 50% of time spent in oncology pharmacy activities (as defined by the BPS Oncology Pharmacy Content Outline)

  **Effective January 1, 2013, only residencies accredited by the American Society of Health-System Pharmacists or other recognized bodies are creditable for this purpose.*
- Achieving a passing score on the Oncology Pharmacy Specialty Certification Examination.

5. **Examination Content**

Domain 1: Clinical Skills and Therapeutic Management (60% of the examination)
Domain 2: Generation, Interpretation, and Dissemination of Information (20% of the examination)
Domain 3: Guidelines, Policies, and Standards (15% of the examination)
Domain 4: Public Health and Advocacy (5% of the examination).

6. **Recertification**

Recertification for Board Certified Oncology Pharmacists (BCOP) requires assessment of a

practitioner's knowledge and skills through one of two methods:

- Achieving a passing score on the 100-item, multiple-choice objective recertification examination, based on the content outline of the certification examination
  OR
- Earning 100 hours of continuing education credit provided by a professional development program approved by BPS. In 2005, BPS approved a professional development program which is offered by the American College of Clinical Pharmacy (ACCP) in conjunction with the American Society of Health-System Pharmacists (ASHP), and the Hematology/Oncology Pharmacy Association (HOPA) that can be used by BCOP for recertification. Contact one of the organizations listed above for specific information about the program.
- A current, active license to practice pharmacy is required for recertification.

Ambulatory Care Pharmacy

1. **Supporting Organization(s)**: American College of Clinical Pharmacy, American Pharmacists Association, American Society of Health-System Pharmacists
2. **Year of Recognition**: 2009
3. **Description of the Specialty**:
   Ambulatory Care Pharmacy practice is the provision of integrated, accessible healthcare services by pharmacists who are accountable for addressing medication needs, developing sustained partnerships with patients, and practicing in the context of family and community. This is accomplished through direct patient care and medication management for ambulatory patients, long-term relationships, coordination of care, patient advocacy, wellness and health promotion, triage and referral, and patient education and self-management. The ambulatory care pharmacists may work in both an institutional or community-based clinic involved in direct care of a diverse patient population. Those who are granted certification in this specialty may use the designation Board Certified Ambulatory Care Pharmacist and the initials BCACP, as long as their certification is valid.
4. **Eligibility Requirements**
   The minimum requirements for this specialty certification are
   - Graduation from a pharmacy program accredited by the Accreditation Council for Pharmacy Education (ACPE) or a program outside the US that qualifies the individual to practice in the jurisdiction.
   - Current, active license to practice pharmacy in the US or another jurisdiction.
   - Completion of 4 years of practice experience with at least 50% of time spent in ambulatory care pharmacy activities (as defined by the BPS Ambulatory Care Content Outline)
     OR
   - Completion of a PGY1 residency * plus one (1) additional year of practice with at least 50% of time spent in ambulatory care pharmacy activities (as defined by the BPS Ambulatory Care Content Outline)
     OR
   - Completion of a specialty (PGY2) residency * in ambulatory care pharmacy.
     **Effective January 1, 2013, only residencies accredited by the American Society of Health-System Pharmacists or other BPS-recognized bodies are creditable for this purpose.*
   - Achieving a passing score on the Ambulatory Care Specialty Certification Examination.
5. **Examination Content**
   Domain 1: Direct Patient Care (50% of the examination)
   Domain 2: Practice Management (20% of the examination)
   Domain 3: Public Health (5% of the examination)
   Domain 4: Retrieval, generation, interpretation and dissemination of knowledge (15% of the examination)
   Domain 5: Patient Advocacy (10% of the examination).
6. **Recertification**
   Recertification for Board Certified Ambulatory Care Pharmacists (BCACP) requires:
   - Achieving a passing score on the 100-item, multiple-choice recertification examination, which is based on the same content outline as the certification examination

- Earning 100 hours of continuing education credit provided by a professional development program approved by BPS (to be developed).

Added qualifications process and currently recognized areas

In 1997, BPS approved a process for the recognition of Added Qualifications in an existing specialty. Added Qualifications provides a method to document further differentiation of practitioners within BPS-recognized specialties.[76] BPS issued its *Petitioner Information for Added Qualifications in Infectious Diseases* document in August, 1997. Conferral of the Added Qualifications credential requires submission of a $100 fee and a structured portfolio, which is reviewed by the pertinent BPS Specialty Council and scored in accordance with published criteria. Added Qualifications must be reaffirmed every 7 years, just as BPS certification in a primary recognized specialty.

In May 1998, the Society of Infectious Diseases Pharmacists submitted a petition for Added Qualifications in Infectious Diseases Pharmacotherapy. The petition, including the portfolio review process, was approved by BPS in March 1999. In March 2000, the American College of Clinical Pharmacy (ACCP) submitted a petition to BPS, requesting designation of cardiology as a second area of Added Qualifications within Pharmacotherapy. The petition, which incorporates the portfolio review process, was approved by BPS in October 2000.

As of 2012, 147 Board Certified Pharmacotherapy Specialists held Added Qualifications in Infectious Diseases, and 92 held Added Qualifications in Cardiology. More than 10,500 pharmacist specialists are currently certified by BPS.

The BPS specialty certification process

Currently, BPS specialty certification and recertification examinations are administered once annually, on the first Saturday in October. The application deadline is the preceding August 1. BPS administers specialty certification examinations at approximately 45 sites each year worldwide.

Additional, "alternate sites" may be established in other US and foreign cities, at the request of ten or more candidates. Complete examination information, including a Candidate's Guide, Specialty Content Outlines, current fees, and application materials are available upon request from BPS or at the website, http://www.bpsweb.org. First-time applicants are encouraged to apply online.

As previously described, each BPS specialty certification examination consists of 200 multiple choice questions, each having only one correct answer. Written recertification examinations consist of 100 questions. Short practice tests for each specialty are posted on the BPS website to illustrate the construction of the questions and their content.

Candidates are informed in writing of their performance on each domain of the examination, and successful candidates are awarded a BPS certificate. A BPS certification or recertification examination may be retaken, if necessary, at a reduced fee.

The value of specialty certification in pharmacy

As in other professions where specialty certification has become established, this rigorous process provides value and benefit to society, to the pharmacy profession, and to the certified individuals.

A. *Society*. The existence of pharmacists who have demonstrated an advanced level of practice knowledge and skill has clearly resulted in improved pharmaceutical care for patients. Numerous studies have investigated the positive impact of clinically trained pharmacists in inpatient and ambulatory care settings.[77–80] Pharmacists who are able to interact with other health professionals in planning and implementing therapy contribute special expertise in areas that complement the skills of their colleagues. As recognized "drug experts," they can also help to ensure that patients maximize the potential benefits of therapy. While there have been few direct studies of the impact of specialty certification in pharmacy (or in medicine, for that matter) on patient outcomes, available evidence suggests that training and experience are important determinants of the quality of care. Specialty certification provides an objective, independent measure of knowledge and experience against established criteria. High quality certification programs in

all areas of specialization maintain that their first obligation is to society, and ensure that these programs meet that goal.

B. *The Pharmacy Profession*. As the numbers of BPS-certified pharmacists have grown within the pharmacy profession, the value of this credential has been increasingly recognized just as in other health professions; increasingly, specialty board certification is viewed as an important qualification for clinical faculty in pharmacy schools.[81,82] BPS certification has also been accepted by Idaho State University as a measure of the clinical expertise of applicants to their non-traditional PharmD program. In the Idaho State University program, candidates may obtain academic credit via current Board Certification in Pharmacotherapy and shorten the didactic requirements for the degree. Specialty board certification is a respected model of clinical expertise in institutional settings where clinical privileges are required to perform some patient-care services.

C. *The Individual*. Specialty certification confers many potential benefits for the pharmacist. Positive recognition by patients, colleagues, and employers often brings psychological "enrichment" and reward to pharmacists who have worked hard to develop, maintain, and document their expertise. There are also increasing instances of monetary reward for specialty certification. Some examples include bonus pay for members of the uniformed services and pharmacists in many institutional systems; hiring or promotion preference, particularly for professionally challenging clinical specialist positions; reimbursement of costs for successful certification and/or recertification; and eligibility for participation in collaborative practice or other arrangements where payment for pharmaceutical services is possible. As specialty certification becomes more common in pharmacy, recognition of its value to the individual pharmacist will also increase, just as it has for medicine and other health profession specialists.

Other credentials in pharmacy

Specialty certification is but one of several options open to pharmacists seeking to advance professionally after their initial entry into practice. Other credentials available include

- Formal post-graduate degree programs
- Residency or Fellowship training
- Certificate training programs
- Multi-disciplinary certification programs (e.g., Certified Diabetes Educator)
- Non-specialty certification programs (e.g., Certified Disease Manager).

Detailed discussion of these opportunities is beyond the scope of this chapter. Attainment of some of these credentials may help prepare or qualify a pharmacist for BPS specialty certification.

Council on Credentialing in Pharmacy

Because of the multiplicity of credentials available to pharmacists, several of the major membership organizations in pharmacy joined to establish the Council on Credentialing in Pharmacy in 1997. The Council on Credentialing in Pharmacy provides leadership, guidance, public information, and coordination for the profession, of pharmacy's credentialing programs.

The vision of the Council on Credentialing in Pharmacy is that all credentialing programs in pharmacy will meet established standards of quality and contribute to improvement in patient care and the overall public health.

The Council has published resource papers on the following topics: credentialing in pharmacy, the scope of practice of pharmacists and pharmacy technicians, and guiding principles for certification of individuals and accreditation organizations, sites, or programs.[83]

In an era where there is greater emphasis not only on cost, but on healthcare quality and accountability, healthcare systems, payers, and patients will continue to demand greater knowledge and skill *and documentation of that knowledge and skill* from those professionals responsible for drug therapy management. In their document titled, *Guiding Principles for Post-licensure Credentialing of Pharmacists*, the Council on Credentialing in Pharmacy calls for

> a planned, coordinated effort by the pharmacy profession to educate pharmacists, other health professionals, employers, payers, and

> the public about all credentials held by pharmacists and their value to patients and the health care system. This effort should also advocate for the effective integration of pharmacists with post-licensure credentials into current and evolving health care delivery systems. Credentials should enable pharmacists to obtain specific patient care privileges and should not create barriers to the provision of any services pharmacists provide to their patients.[84]

From 1995 to 2010 the number of board certified specialists in pharmacy has grown by over 600% (i.e., from 1649 to 10,337); this number represents just 5% of practicing pharmacists. For those pharmacists that have sought BPS certification, the recognition and acceptance of specialization have increased. The future of specialty certification will ultimately be defined by many factors, including payment for medication therapy management services, continued development of collaborative prescriptive practices (i.e., currently, more than 40 states have such legislation), evolution of accountable care organizations and medical home models, further expansion of postgraduate training programs (including new degrees and specialty practice residencies), employer practices, and society's acceptance of new roles and practices for pharmacists. Over the past decade, the growth in pharmacy residents has been impressive, from 896 graduates in 2001 to over 2100 graduates in 2010.[85] As more and more students continue to seek postgraduate training to differentiate themselves from the typical graduate, the number of pharmacy practice residencies and specialty practice residencies must expand. Unfortunately, the development of new residency programs is currently lagging behind demand for this training. A new cadre of specialty trained practitioners will help drive the process of specialty recognition.

There has been consistent support for board certification by many of the profession's professional organizations, including the American College of Clinical Pharmacy,[82] the American Society of Health-System Pharmacists in their document, *ASHP Long-range Vision for the Pharmacy Work Force in Hospitals and Health Systems*[86] and through the ASHP's Commission on Credentialing accreditation standards for PGY2 residency program directors.[87]

While it is uncertain which areas of pharmacy practice will be recognized as specialties in the future, BPS is currently conducting role delineation studies in critical care, pain management, palliative care, and pediatrics. Each new specialty must satisfy all seven criteria for recognition by BPS, and this process maintains the high standards set forth by the visionaries who began this process nearly three decades ago.

Ambulatory care pharmacy practice

Ambulatory care pharmacy practice encompasses a broad range of patient care and public health activities conducted in settings where patients are responsible for administering their own medications and engaging in self-care behaviors.[88] According to the Board of Pharmacy Specialties, ambulatory care pharmacy practice is:

> the provision of integrated, accessible healthcare services by pharmacists who are accountable for addressing medication needs, developing sustained partnerships with patients, and practicing in the context of family and community. This is accomplished through direct patient care and medication management for ambulatory patients, long-term relationships, coordination of care, patient advocacy, wellness and health promotion, triage and referral, and patient education and self-management.[89]

Although commonly perceived to be a practice setting, ambulatory care pharmacy practice is not location-specific.[88] Indeed, ambulatory care pharmacists practice in community health centers, community pharmacies, employee health clinics, family medicine practices, physician offices, primary care clinics, specialty care clinics, and occasionally visit patients in their homes. Many ambulatory care pharmacists work in organized health systems like academic health science centers, health maintenance organizations, the Indian Health Service, military hospitals, ambulatory care centers, or Veterans Affairs Medical Centers. But a growing number of ambulatory care pharmacists are employed by national pharmacy chains and independently owned pharmacies. Some ambulatory

care pharmacists are self-employed independent practitioners. Thus, ambulatory care pharmacy practice does not occur in a specific location or specific employment model, but rather is a patient-centered practice where pharmacists interact directly with patients and their families over sustained periods of time to address health and medication-related issues. Many ambulatory care pharmacists devote a considerable amount of their time to wellness and health promotion activities, rather than focusing solely on disease management tasks.[90]

Chronic illnesses such as cardiovascular disease, diabetes, chronic respiratory diseases, and bone diseases are the leading causes of death and disability in the United States. The incidence of obesity and related complications is rising. By 2009, 145 million Americans, nearly half the population, lived with a least one chronic disease.[91] Nearly a quarter of the population has multiple chronic diseases. Furthermore, 84% of all healthcare expenditures are related to chronic care. In October 2007, the Milken Institute released a report indicating that the seven most common chronic diseases resulted in a $1.3 trillion annual cost to the US economy.[92] These costs are expected to exceed $6 trillion by 2050.

Medications play a significant role in the prevention and treatment of most chronic diseases.[93] Millions of patients are prescribed complex regimens with multiple medications taken several times a day and requiring special administration procedures.[88] With increasing medication use there comes a greater potential for medication errors, adverse drug events, and drug misuse. The negative consequences of poor medication use behavior are well documented.[94,95] Poor medication adherence contributes to poor outcomes, hospitalizations, and unnecessary costs.[96]

Numerous scientific publications have documented the significant reductions in morbidity and mortality when patients with chronic illnesses have access to the professional services of an ambulatory care pharmacist.[97–100] Clinical, humanistic, and economic benefits have been demonstrated in patients with asthma, chronic kidney disease, diabetes, dyslipidemia, hepatitis C, hypertension, HIV, stroke prevention, and venous thromboembolism.[98–107] By virtue of their education, training, and experience, ambulatory care pharmacists are better prepared than any other healthcare professionals to meet patients' medication-management needs.[88] Ambulatory care pharmacist specialists possess specialized knowledge and skills that enable them to meet the needs of complex ambulatory care patients with chronic diseases and to take responsibility for achieving desired medication therapy outcomes. As the profession of pharmacy has evolved and become more specialized, ambulatory care pharmacist specialists have become leaders in chronic and preventive care. They often implement patient care programs; educate and train other pharmacists to deliver innovative clinical services in ambulatory care settings; and participate in practice-based research. Moreover, they often serve as preceptors for the required advanced pharmacy practice experiences and the growing number of postgraduate residency programs.

Self care

Pharmacists and Self-Care with Non-prescription Products

In the matter of self-medication by the public with non-prescription (over-the-counter or OTC) drugs, pharmacists are in a unique position to provide assistance because of their education, training, and ready accessibility to the public. Experts estimate that the number of non-prescription products is in excess of 300,000.[108,109] In the United States, non-prescription product sales exceeded $16.8 billion in 2008.[110]

Like other businesses, pharmacies are in a fight for survival. Recent years have seen closings of many small, independent stores. Third-party plans have reduced prescription profits so drastically that some retailers have turned to high volume strategies in an attempt to survive. One unfortunate result of high volume is decreased patient interaction time. Pharmacists are forced to spend long hours behind the prescription counter with no scheduled lunch hour and little patient contact. Pharmacist-generated comments on websites detail these complaints.[111,112] Even though counseling is required, it can be cursory and hurried.[113] Management demands more work with less help, because hiring additional pharmacists and pharmacy technicians further reduces shrinking profits. This dismal picture is more prevalent in high volume chain stores.

Fortunately, some pharmacists realize that pushing for high volume is self-defeating in the long run

because it appeals to the patient who wants cheap products at the expense of services such as delivery. Some pharmacists have realized that another route to survival is to cultivate a specialty or "niche."[114,115]

There are several viable and profitable specialties, such as compounding. Unfortunately, articles in pharmacy journals and textbooks may advise specializing in products of unknown safety and efficacy, such as herbal supplements and homeopathic products. Perhaps pharmacists could focus instead on becoming self-care specialists, advising patients on the use of a wide range of FDA-reviewed non-prescription products that are ethical, safe, and effective.[116]

Marketing one's practice location as a center for self-care through intense counseling on non-prescription products and devices is a logical and profitable specialty. Self-care is especially appealing because of several factors:

- Non-prescription products are available in numerous non-pharmacy outlets where personnel lack medical training.[109] By contrast, most pharmacists have had a non-prescription products/self-care course as part of the professional pharmacy curriculum. Thus, the pharmacist with expertise and education in self-care of minor medical conditions can provide competent medical advice that the patient will not be able to obtain in non-pharmacy locations.
- The typical community pharmacy already stocks a wide range of non-prescription products and devices, so there is no need to purchase a special group of products or invest in costly equipment and remodeling (e.g., adding a clean room and laminar flow hoods).[109]
- The non-prescription market includes many ingredients and products lacking proof of efficacy and/or safety.[109] Pharmacist counseling helps patients choose products whose safety and efficacy is demonstrated.
- Effective counseling in the non-prescription area allows the pharmacist to extend the concept of pharmaceutical care.
- Many pharmacies locate non-prescription products away from the immediate location of the pharmacy. The pharmacist cannot advise patients who need help with these items, which seriously compromises their ability to offer self-care counseling. Those who choose to place non-prescription products in close proximity to the pharmacy enhance their credibility as experts in self-care.[109]
- In some community pharmacies, non-prescription products are positioned close to the pharmacy, but shelving is parallel to the pharmacy, rather than perpendicular, which also makes it impossible to see patients who need help. Choosing a store layout that allows the pharmacist to visualize the patients in the self-care aisles allows the pharmacist to render assistance when necessary.[109]

The pharmacist who wishes to develop this niche should obtain current information on the various self-treatable conditions, as well as all of the non-prescription ingredients and the many precautions associated with their use.

The Movement Toward Self-Care

During the 1960s, the United States experienced a growing distrust of established entities, such as the government, organized religion, and legitimate medicine. One of the consequences was a compelling consumer desire to rebel against the traditional provider–patient relationship, in which the consumer meekly and unquestioningly followed the directions of the provider. Patients began to demand a greater personal involvement and responsibility for healthcare maintenance and treatment, a trend that continues today.[117] Direct-to-consumer advertising of prescription products enhanced this trend by introducing a medical paradigm in which patients should demand specific prescription products from the physician based on advertisements. Consumers also feel competent to guide their own medical therapy based on past personal experience or anecdotal information from friends and relatives in regard to specific non-prescription products. This is partly due to the common myth that any non-prescription product or device advertised in the media is safe and effective for self-use without medical supervision. Further, some patients feel that the non-prescription product label contains all of the important information, denying the possibility that a pharmacist consultation can add any value to the purchase. Partially as a result of these various market forces and misconceptions, non-prescription products cause many episodes

of morbidity and mortality that might have been prevented with judicious pharmacist counseling.[109] It is an uncomfortable truth that patients who enter pharmacies with preconceived notions about a particular non-prescription product or course of action are often manifestly and profoundly incorrect, and it is in the highest tradition of pharmaceutical care that the concerned pharmacist correct those misconceptions and guide them to more appropriate self-care decisions.

The Prescription to Non-prescription (Rx-to-OTC) Switch

A second factor that greatly increases the validity of pharmacist counseling in self-care is the dynamic and ongoing switch of prescription products to non-prescription status.[109,118–121] During the past several decades, powerful new therapies have become available for self-care in widely divergent arenas. They include loperamide for diarrhea, ibuprofen and naproxen for pain, hydrocortisone for dermatoses, minoxidil for androgenetic alopecia, nicotine patches and gum for smoking cessation, ophthalmic antihistamines for allergic conjunctivitis, histamine-2-blockers and proton-pump inhibitors for heartburn and gastroesophageal reflux, non-sedating antihistamines for allergic rhinitis, and pyrantel pamoate for pinworm.[122–124] Unfortunately, due to widespread opposition, there is no "third class" into which switched medications move prior to their unsupervised release to the American public. This leads to the uncomfortable realization that a particular medication awaiting a switch is only available under a physician's prescription, requiring pharmacist counseling and refill authorization until midnight the day before the switch occurs. At 00:01 hours on the day of the switch, the ingredient is suddenly deemed safe enough to be sold to any consumer in any location at any time, with no professional monitoring or advice being necessary.[109] The products can be purchased in any gas station, beauty shop, airport lobby, or hotel vending machine. Since there is no legal requirement for professional counseling prior to purchase of non-prescription products, the manufacturer assumes the full burden of communicating proper use, precautions, risks, and other information by creating an appropriate label.

Can Patients Read Non-prescription Product Labels?

Another major rationale for pharmacist involvement in self-care is the issue of patients' ability to read and/or comprehend non-prescription product labels. The FDA requires that each OTC label clearly communicate to patients all information required for safe use of that non-prescription product. However, pharmacists add value to the purchase of non-prescription products by acting as a "learned intermediary." In this role, the pharmacist points out specific contraindications to use of certain products, answering questions about dosing, adverse effects, and appropriate use.

Many patients are unable to properly read and/or interpret the label. Some suffer impaired vision (e.g., glaucoma damage, detached retina, macular degeneration) that does not allow them to read small print. Some suffer from tremor or other conditions that make it difficult to hold the container still for reading prior to purchase. Other patients cannot understand the terminology used on labels, perhaps because English is not their primary language. Still other patients have limited reading comprehension or may be completely illiterate. In all of these cases, pharmacist counseling can be of immense value.

How Patients Choose Non-prescription Products and Devices

Persons do not always seek the advice of a physician with every illness. Symptoms of the ailment may be deemed minor enough to treat with a non-prescription product. In fact, 60% of all medications purchased by Americans are non-prescription products.[108] The decision of the patient concerning which product to purchase is based on such input as prior experience with the product, advice received from a neighbor or relatives, or advertisements. However, the pharmacist supersedes all of these, being the only expert in self-care with non-prescription products and devices. Pharmacists can develop an enduring self-care specialty by making defensible patient triage decisions that are based on scientific principles. Through this practice, it is often necessary to guide incorrect patient purchase decisions into a more suitable and appropriate path.

Diagnostic self-care

In 2010, the medical device market was worth $94.9 billion, 3.65% of the total spent on healthcare ($2.6trillion, about 17.7% of GDP). Diagnostic devices have revolutionized the self-care industry. Consumers benefit from their easy accessibility. Some examples of these devices include blood pressure monitors, home blood glucose monitors, HIV exams, cholesterol exams, and home tests for colorectal cancer. They help monitor chronic diseases, diminish doctor visits and associated costs, decrease hospitalizations, and allow consumers to become an active part of their own healthcare.[125] With the trend toward pharmaceutical care and preventive medicine, the pharmacist can perform a vital public health role by counseling the consumer on newer diagnostic devices, contributing to a reduction in deaths from colon cancer, helping patients monitor blood glucose, and aiding in the detection of drug abuse.

Even though they have become more user friendly, patients may still encounter problems with even the simplest devices. Consequently, pharmacists are often summoned to educate patients on proper use and the validity and application of the results. It is essential that pharmacists ask questions about the disease or exam and make any appropriate recommendations based upon the available information. The pharmacist should remind the patient that any information attained as a result of counseling shall remain strictly confidential. The pharmacist should also mention that these test kits/devices must be used in collaboration with healthcare professionals, who can interpret and discuss the test results and their implications.

Diagnostic aids and tests are complex to use. Patient comprehension is maximized when a pharmacist is involved in the purchase and use of these products. If these products are purchased in a non-pharmacy outlet, the consumer does not have the opportunity to ask questions or receive reliable recommendations from an educated professional, increasing the chance of product misuse.[125]

Pharmacist-assisted care has direct benefits to the patient. The pharmacist is a highly educated drug information specialist in OTC products. This, in conjunction with practical experience, makes the pharmacist the only health professional who understands the limitations of self-treatment with OTC products and who is also uniquely positioned to encourage the patient to seek the professional advice of a physician, when necessary

Complementary and alternative medical healthcare

Nearly 40% of adults in the United States use some form of complementary and alternative medicine (CAM) therapy.[126] There is a growing interest in CAM as individuals become more interested in health and fitness and disease prevention. CAM therapies are gaining popularity, in part due to rising prescription drug costs, side effects of conventional medicine, distrust of and frustration with the healthcare system, and increased public access to information. Some patients use CAM techniques like meditation[127] and prayer[3] to cope with chronic and untreatable diseases.

Patients and practitioners are increasingly interested in integrating CAM therapies with conventional medical treatments. These therapies include acupuncture, chiropractic, herbal medicine, dietary supplements, homeopathy, mind–body techniques, faith healing, massage, and a number of others. While many CAM therapies have not been rigorously tested and evaluated, knowledge and understanding is growing. Evidence-based resources on CAM[128–132] compile and analyze the available evidence in this field. Open dialogue should exist between healthcare professionals and patients about the use of CAM products and practices to ensure safety and coordinated care.

Preventive care

Introduction

Routine follow up with primary care physicians and other healthcare professionals can aid in the early detection of many medical conditions (e.g., cancer, diabetes, hypertension), and can encourage healthy habits that prevent the development of other conditions (e.g., lung cancer, obesity). This section seeks to point out areas of preventive care that are wide-reaching to the general population, and are areas that pharmacists of all practices should be aware of when interacting with patients.

To begin with, it is appropriate to provide some definitions of prevention. Primary prevention refers to preventing a disease from occurring (such as childhood vaccinations). Secondary prevention refers to trying to reduce morbidity in pre-symptomatic subjects with established disease by its early detection and treatment (such as screening of asymptomatic women and early treatment of detected cervical cancer). Tertiary prevention is implemented on patients with a view of cure, palliation, rehabilitation, or prevention of recurrence or complications (such as treatment of symptomatic cancer). There are numerous interpretations among individual practitioners about these three definitions, and their use is not recommended by all.[133] Instead, it has been suggested clinical interventions be defined by their objective, target population, and type ("reduction of mortality by increased use of statins in patients with a history of myocardial infarction") instead of by level of prevention ("tertiary prevention of myocardial infarction").

Health promotion and disease prevention were not always priorities of healthcare. It was not until 1979 that the *Healthy People: The Surgeon General's Report on Health Promotion and Disease Prevention* and *Promoting Health/Preventing Disease: Objectives for the Nation* were published. Since that time, regular updates to the Healthy People recommendations have been made, the most recent being *Healthy People 2020*, released in 2011. *Healthy People 2020*, from the US Department of Health and Human Services, is considered the master plan for improving the health of the American population over the next decade, and covers 42 topics and nearly 600 objectives. There are 12 key topics, 24 key objectives, and 24 leading indicators to go with Healthy People 2020 (Box 13.2).[134] The intent is to increase the quality and years of healthy life, and to eliminate disparities among the overall health of various communities, ethnic groups, and classes.

Providing cost-effective healthcare throughout the country is a huge challenge, and is being undertaken by the US Preventive Service Task Force (USPSTF). This task force is an independent panel of experts in primary care and prevention convened by the Agency for Healthcare Research and Quality that systematically reviews the evidence of effectiveness of, and develops recommendations for clinical preventive services. The first task force started working in 1984 to 1989 to develop recommendations for primary care clinicians on the content of periodic health exams. It published the *Guide to Clinical Preventive Services* based on this work. In 1990, the second

Box 13.2 *Healthy People 2020* topic areas

- Access to health services
- Adolescent health
- Arthritis, osteoporosis, and chronic back conditions
- Blood disorders and blood safety
- Cancer
- Chronic kidney disease
- Dementias, including Alzheimer's disease
- Diabetes
- Disability and health
- Early and middle childhood
- Educational and community-based programs
- Environmental health
- Family planning
- Food safety
- Genomics
- Global health
- Health communication and health information technology
- Healthcare-associated infections
- Health-related quality of life and well-being
- Hearing and other sensory or communication disorders
- Heart disease and stroke
- Human immunodeficiency virus infection
- Immunization and infectious diseases
- Injury and violence prevention
- Lesbian, gay, bisexual, and transgender health
- Maternal, infant, and child health
- Medical product safety
- Mental health and mental disorders
- Nutrition and weight status
- Occupational safety and health
- Older adults
- Oral health
- Physical activity
- Preparedness
- Public health infrastructure
- Respiratory diseases
- Sexually transmitted diseases
- Sleep health
- Social determinants of health
- Substance abuse
- Tobacco use
- Vision

USPSTF updated these recommendations for preventive services, and released the second edition of the guidelines in 1996 and the third in 1998. The *Guidelines to Clinical Preventive Services, 2010–2011 Recommendations of the USPSTF*, released in 2010, can be found at http://www.ahrq.gov. These recommendations are modified by individual health plans for their use, endorsed by the American Association of Health Plans, incorporated into HEDIS (Health Plan Employer Data and Information Set), and may result in changes in laws regarding health coverage. Part of the challenge of the USPSTF is to make recommendations for care based on cost-effectiveness. Accordingly, they have developed ratings for their recommendations, based on the levels of evidence, which are listed in Table 13.5.

Screening for Disease Prevention

Disease screening is effective when the screening test can detect a disease or its precursor before it becomes symptomatic, and when early treatment can improve the patient's outcome. Effective screening tests should be highly sensitive (i.e., correctly identifying a high proportion of persons with the disease) and highly specific (i.e., correctly identifying a high proportion of persons without the disease). Effective screening tests should not cause harm from the test itself. These should also be of an acceptable cost burden to society so as to be utilized by the patients who need them.

Disease Prevention Interventions

The first method of prevention for a particular disease is to eliminate the risk factors that a patient possesses. When one considers risk factors to disease, these are often broken down into modifiable and non-modifiable risk factors. Modifiable risk factors are actions that the individual can make to change his/her own behaviors, such as smoking cessation, weight loss and dietary changes. Non-modifiable risk factors often include the presence of genetic risk factors, concomitant disease states, and abnormal laboratory values, and cannot typically be changed by the actions

Table 13.5 USPSTF recommendation definition

A	Strongly recommends that clinicians routinely provide [the service] to eligible patients. (The USPSTF found good evidence that the service improves important health outcomes and concludes that benefits substantially outweigh harms.)
B	Recommends that clinicians routinely provide [the service] to eligible patients. (The USPSTF found at least fair evidence that the service improves health outcomes and concludes that benefits outweigh harms.)
C	No recommendation for or against routine provision of [the service]. (The USPSTF found at least fair evidence that the service can improve health outcomes but concludes that the balance of benefits and harms its too close to justify a general recommendation.)
D	Recommends against routinely providing [the service] to asymptomatic patients. (The USPSTF found at least fair evidence that the service is ineffective or that harms outweigh benefits.)
I	Evidence is insufficient to recommend for or against routinely providing [the service]. (Evidence that the service is effective is lacking, of poor quality, or conflicting and the balance of benefits and harms cannot be determined.)
The US Preventive Services Task Force (USPSTF) grades the quality of the overall evidence for a service on a 3-point scale (good, fair, or poor)	
Good	Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes.
Fair	Evidence is sufficient to determine effects on health outcomes, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies; generalizability to routine practice; or indirect nature of evidence on health outcomes.
Poor	Evidence is insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.

of the patient. A key element to preventive care is to make patients aware of the risk factors that exist for various diseases and to minimize the presence of these risk factors.

Chemoprevention

Chemoprophylaxis is the use of natural or synthetic compounds to block, reverse, or prevent the development of a disease or undesirable outcome. Increasing evidence in the literature supports the role of chemoprevention to prevent the development of various diseases, such as the use of tamoxifen to prevent breast cancer development. For patients that are at high risk for the development of a disease because of underlying risk factors, consideration of drug therapy to help prevent the development of a disease may be necessary. Typically, clinicians think of antibiotics and antivirals because of their evidence against several infective illnesses; for example, isoniazid for tuberculosis, amoxicillin for dental prophylaxis against subacute bacterial endocarditis, and antiviral agents after needlestick injuries to prevent HIV transmission.

Clinical Guidelines

Many organizations provide guidelines for screening of various diseases, actions to prevent disease, and effective chemoprevention methods. These recommendations can be found at the National Guideline Clearinghouse web site at http://www.guidelines.gov/index.asp, which is sponsored by the US Agency for Healthcare Research and Quality in partnership with the American Medical Association and the American Association of Health Plans. Interested readers can also search the Internet home pages of major national organizations, such as the Centers for Disease Control and Prevention, American Diabetes Association, American Heart Association, and the American Cancer Society, or perform Medline searches for the individual recommendations. Readers are encouraged to search these guidelines routinely, because they are updated on a regular basis, as new research and evidence become available.

Substance abuse care

Substance abuse and drug addiction permeate our society today, irrespective of one's socioeconomic status. Estimated lifetime prevalences of alcohol and drug dependence were estimated to be 12.5%[135] and 2.3%,[136] respectively, of the population in the United States in a 2001–2002 study. Alcoholism was estimated to be responsible for 85,000 deaths in 2000.[137] In 2007, the estimated direct and indirect costs of illicit drug use in the United States exceeded $193 billion.[138] Even with these staggering numbers, substance use disorders are frequently overlooked as healthcare issues that pharmacists can impact. Co-occurring mental health disorders such as depression and anxiety disorders are frequently seen in those with drug dependencies and can significantly complicate therapy and outcomes.

As healthcare professionals, pharmacists are well positioned to take a major role in the disease management of substance use disorders and other comorbid conditions.[139] Pharmacists have knowledge of the pharmacology, pharmacokinetics, mechanisms of action, drug interactions, and adverse events associated with prescription medications and abused substances.[140] Therefore, taking an active responsibility in assessing patients and assuring the appropriate use of treatments for substance use is another opportunity in the ever-increasing role of the pharmacist.

Emergency medicine pharmacy practice

Although Emergency Medicine (EM) pharmacists are becoming increasingly common in Emergency Departments (EDs) across the country, their role is still evolving within clinical pharmacy practice. For over 30 years, EM pharmacists have been providing decentralized services in EDs.[141,142] When EM pharmacists first established services in the ED setting, they primarily facilitated medication distribution and inventory control, while providing limited clinical services.[142,143] Initially, clinical services offered by EM pharmacists were met with resistance in the fast-paced ED environment. However, over time, EM pharmacists have slowly but surely gained ground in providing clinical consultation, preventing medication errors, and establishing a collaborative practice with healthcare providers in order to optimize care across the spectrum of ED patients. By demonstrating their value through clinical intervention

documentation along with advancement of the specialty practice area at the national level, EM pharmacists have grown in number, particularly over the past 10 to 15 years.[144,145]

EM pharmacists have worked diligently to develop their clinical practice and expand the types of services they offer in the ED setting. Many EM pharmacists not only provide clinical expertise in medication therapy management, but also play a vital role in supporting educational and research efforts in the ED, providing insight and expertise in policy development and disaster planning, and assisting in quality improvement initiatives.

Pediatric pharmacy practice

Introduction

Medication use in children remains a challenge in many ways. Many prescription and nonprescription medications are not approved by the FDA for use in children under 12 or 18 years of age. Safety of medication used in children is a public health concern; however, the prevalence of data on medication use in children is limited, and thus the actual impact of proper or improper medication use is not well described.

Based on the Slone survey published in 2009, for the 7 days preceding a randomized phone interview, 56% of children had used more than one medication, with 20% taking prescription-only medications and the majority taking non-prescription medications.[146] Fifteen percent of the participants reported taking two, 7.1% taking three, 3.1% taking four, and 1.9% taking more than five medications.[146] The survey included questions differentiating the use of prescription, non-prescription, and herbal medications (less than 5%).[146] According to IMS Health, besides occasional use of medications such as antibiotics, more than 25% of children and teenagers in the US are taking prescription medications on a daily basis for chronic conditions including diabetes, hypertension, depression, insomnia, and hypercholesterolemia.[147] Many of the medications used for such chronic conditions are not FDA approved for use in children, and limited clinical trials are available to determine proper dosages, efficacy, and safety. With ongoing physiologic developmental changes throughout childhood and adolescence, interpretation of clinical trial data conducted on pediatric patients must be carefully analyzed and evaluated with this special population's characteristics in mind.

Over the past two decades, more comprehensive literature guiding clinicians on effective use of medication in children, including dosing recommendations, has become available. However, it is imperative to use standardized age definition (Table 13.6) to ensure safety and avoid medication mishaps, errors as well as omissions.

Challenges in pediatric drug therapy

Significant improvements for addressing incomplete pediatric clinical pharmacology data in the US have been made in the past two decades, largely due to the Best Pharmaceutical for Children Act (BPCA), Pediatric Research Equity Act (PREA), and the National Institutes of Health Pediatric Pharmacology Research Unit (PPRU) network.[149–151] The BPCA provides pharmaceutical manufacturers additional 6 months of market exclusivity when pediatric trials under the direction of the FDA are completed.[149] The PREA mandates the studies of new and marketed medicines in children when use is applicable for children.[149] Despite these advances, certain medication dosage recommendations may be conflicting in

Table 13.6 Age definitions[148]

Terminology	Age
Premature neonate	Gestational age ≤37 weeks
	Postnatal age ρ month
Full-term neonate	Gestational age ≥37 weeks
	Postnatal age ρ month
Post-term neonate	Gestational age ≥43 weeks Postnatal age ρ month
Infant	1–12 months
Child	1–11 years
Pubescent or adolescent	12–16 years

children in situations of continued incomplete pharmacology data and differences in established off-labeled prescribing practices.

Due to the lack of pediatric friendly dosage forms, several commercially available oral and intravenous medications require reformulation by pharmacists. Oral forms such as clonidine, metronidazole, and spironolactone lack commercially available oral liquid forms and require extemporaneous compounding by pharmacists for children who are unable to swallow tablets or capsules. Extemporaneous oral formulation databases are available with product stability information but lack clinical absorption data.[152] If no oral liquid formulation exists, powder papers (aliquots and titrations of tablets or capsules) or the intravenous dosage form for oral administration serve as alternative methods for oral drug delivery. Available concentrations of commonly used intravenous medications for premature infants often require dilutions to assure accuracy of dose delivery. *In vitro* simulations of intravenous drug delivery for a 1 kg neonate have shown the potential for overdoses up to twice the desired dose when using commercially available drug concentrations and measuring devices that make measuring smaller dosage volumes (<0.05 mL) impossible and inaccurate.[153] In addition, administration of undiluted hypertonic/hyperosmolar oral and injectable medications may result in gastrointestinal irritation and phlebitis or intraventricular hemorrhage in preterm infants, respectively.

Table 13.7 summarizes pharmaceutical excipients that are known to cause adverse events in children.[154] Benzyl alcohol, a common preservative found in many multidose intravenous products, is an example of a pediatric therapeutic misadventure. In the early 1980s there were several reports of neonates developing a gasping syndrome with severe metabolic acidosis and encephalopathy resulting in fatalities when receiving intravascular flush solutions containing 0.9% benzyl alcohol. Premature/newborn infants lack mature metabolic pathways to fully metabolize benzyl alcohol, which may result in the accumulation of benzoic acid, an intermediate metabolite, leading to the development of the aforementioned adverse effects.[155] In addition, intravenous cephalosporins, such as ceftazidime and cefepime, contain L-arginine as a buffering agent and exposure to children with a rare form of arginase deficiency may result in severe progressive neurological decompensation.[156]

Potential drug delivery issues for children include difficulties with initiating and maintaining the patency of intravenous lines (especially in preterm neonates); incomplete flushing of intravenous and oral lines to assure complete dose delivery; inadequate shaking of oral suspensions resulting in potential under- and overdosages; and poor tasting oral medications.[157]

Table 13.7 Adverse effect potential of pharmaceutical excipients[9]

Excipient	Adverse effect
Benzyl alcohol	Severe metabolic acidosis, encephalopathy, respiratory depression with gasping in premature neonates[7]
Propylene glycol	Contact dermatitis, cardiac arrhythmias, hypotension, CNS depression, lactic acidosis and seizures
Lactose	Abdominal intolerance and diarrhea
Coloring agents and sulfites	Hypersensitivity reactions
Alcohol	CNS depression
Sugar	Dental caries
Aspartame	Contraindicated in phenylketonuria (PKU)
L-Arginine	Contraindicated in arginase deficiency[8]

Although the use of flavoring agents may be helpful in increasing the palatability of poor-tasting oral liquid medications, use of this adjuvant should be used with discretion as overuse may result in potential future behavioral issues by which a child will take their medicines only if it is a certain flavor that they desire. Also, using a flavoring agent may negatively affect the medication's stability and absorption characteristics as supporting data in this area are often incomplete.

Current medication delivery support systems such as electronic prescribing, smart intravenous infusion pumps, and pharmacy computer systems are currently being developed to foster safe and efficient use of mediations for children.[158–161] Existing commercial systems are typically adult-based systems that are not compatible for children and require the input of well-trained and experienced pediatric pharmacists to incorporate the necessary modifications.

Transplant pharmacy practice

Over the past 60 years, the field of transplantation has evolved significantly with improvements in medical diagnostics, procedures, surgical techniques, and pharmacotherapy. With the development of new immunosuppressive medications and the use of complex pharmacologic regimens, the opportunity has arisen for pharmacists to become more involved in the management of transplant patients. In today's clinical practice, transplant pharmacists are integral members of multidisciplinary transplant teams.

Pharmacogenomics in pharmacy practice

The field of pharmacogenetics and pharmacogenomics attempts to examine the interindividual differences in drug response.[162] Pharmacogenomics is defined as "the genome-wide analysis of genetic determinants of drug efficacy and toxicity."[163] This is in slight contrast to pharmacogenetic approaches that generally examine variations within single genes. Upon completion of the Human Genome Project in 2003, the field of pharmacogenomics and "genomic medicine" rapidly expanded with the advent of new technologies.[164] Such technologies include high-throughput DNA sequencing, gene mapping, and bioinformatics. This has resulted in genomewide association studies, whereby hundreds to thousands of polymorphisms are studied in the content of potential disease associations in a patient population.[165]

DNA sequence variation that is present in more than 1% of the population is defined as a polymorphism.[166] The most common polymorphism is known as a single nucleotide polymorphism (SNP). The resultant single base-pair change (e.g., substitution of adenine for guanine) may or may not change an amino acid sequence. The thiopurine methyltransferase (TPMT*3A) is an example of a nonsynonymous SNP. The adenosine-triphosphate binding cassette protein B1 (*ABCB1*) 3435 C>T is an example of a synonymous SNP. The cytochrome P450 [CYP] 2C19*3 polymorphism is an example of a point mutation involving a premature stop codon that results in termination of protein synthesis. Other polymorphism types include a gene deletion (e.g., CYP2D6*5) or gene copy number variant (e.g., CYP2D6*2N), both of which involve large segments of the DNA sequence. Certain polymorphisms will affect gene expression, protein function, and activity. Of note, alterations in gene expression can also occur in the absence of DNA sequence variation (e.g., epigenetics).

Prior to establishing a pharmacogenomics clinical practice, a systematic approach to understanding polymorphisms is recommended.[167] Identification of the polymorphism type and the protein that is affected by the polymorphism is important. Affected proteins can include an enzyme, drug transporter, or receptor. Polymorphisms may differ in functional effect, population prevalence, and clinical relevance.[167] Population variation may exist, whereby a polymorphism is present in a higher frequency in a specific ethnic group.[168] For example, the human leukocyte antigen (HLA)-B*1502 allele is associated with a carbamazepine-induced hypersensitivity reaction.[169,170] The prevalence of the HLA-B*1502 allele is higher in certain Asian populations, compared to Caucasians and African-Americans.[171,172] Consequently, HLA-B*1502 testing is recommended in all patients of Asian descent prior to initiating carbamazepine therapy. With respect to clinical relevance, drug dosing, selection, efficacy, toxicity, pharmacokinetics and/or pharmacodynamics may be affected by the polymorphism. Finally, a polymorphism may

influence disease prognosis and susceptibility, or be used as a screening test for certain diseases.[173]

Critical care pharmacy practice

Over the past two decades, numerous advances in diagnostic testing, technological intervention, and pharmacotherapy have led to substantial improvements in the outcomes of patients who require admission to the intensive care unit (ICU).[174] At the same time, the care provided to critically ill patients has steadily increased in complexity and intensity. Perhaps the most important strategy that has evolved over the past 30 years to address these changing paradigms of ICU care is the intensivist-led, multidisciplinary ICU team.[175] This model of care, supported by major critical care organizations and increasingly being implemented in ICUs across the United States, advocates that a board-certified intensivist-led team of nurses, pharmacists, respiratory therapists, nutritionists, and physical therapists work together in a multidisciplinary fashion to optimize the delivery of safe and effective care in the ICU.

Drug therapy plays a key role in the management of critically ill patients. The average patient admitted to an ICU receives 30 different medications throughout his or her stay. Critical care clinicians are faced with numerous decisions each day regarding drug selection, dosing, administration, and monitoring strategies and must consider how each of these decisions may influence patient outcomes and healthcare costs.[176] Even if the correct medication is chosen for a patient, a suboptimal dose or route of administration may result in either therapeutic failure or drug toxicity. Most dosing regimens employed in the ICU are extrapolated from clinical trials completed in non-ICU individuals, or even healthy patients, and therefore usually do not account for the substantial pharmacokinetic, pharmacodynamic and pharmacogenomic variability seen in this population.[177–179] Failure to account for these alterations when initiating medication therapy in the ICU may lead to unpredictable drug effects, undesirable clinical outcomes, and increased drug toxicity.

Adverse drug events (ADEs) are common in the ICU and often result in increases in both morbidity and mortality and healthcare costs.[176] The true rate of ADEs is unknown, because most institutions rely on voluntary reporting mechanisms. However, some studies have reported rates as high as one or more ADEs occurring on 17% of all patient days,[180] and a rate of ADEs nearly twice that of non-ICU patients.[176] In many cases, patients experience more than one ADE during their ICU stay.[181] A number of unique factors account for the high number of ADEs detected in critically ill patients, including disease complexity, the presence of end-organ dysfunction, the urgency with which underlying conditions must be treated, the distractions inherent in the intensive care environment, the use of complex (including high-risk and narrow therapeutic index) drug regimens, and the frequent use of intravenous infusions.[182] Increasingly, health information technology such as computerized physician order entry, clinical decision support systems, barcode technology, and electronic surveillance systems are being implemented in the ICU in an effort to reduce medication error and improve the efficiency and quality of care.[183] However, this technology is expensive, requires a dedicated multiprofessional team to implement, and currently is supported by only limited evidence regarding its benefit in the ICU.

Infectious diseases pharmacy practice

Despite the advances in antimicrobial therapy made over the past 50-plus years, the burden of infectious diseases in the United States and worldwide remains significant. According to 2004 data published by the World Health Organization (WHO), communicable diseases are the cause of three out of ten deaths worldwide, whereas six of ten deaths are due to noncommunicable conditions such as cardiovascular diseases. [184] Nonetheless, approximately 15 million individuals die annually secondary to infectious diseases, and in low-income nations, infectious diseases such as malaria are the leading causes of death.[184] Furthermore, of the 20 leading causes of death across all age groups worldwide, six include conditions that are infectious in nature, while communicable diseases account for 50% of all deaths in children under the age of 5 years.[184]

Several factors are responsible for the ongoing battle against both old and evolving infectious pathogens.

Gastrointestinal diseases caused by *Salmonella* species and other bacteria are a major cause of global mortality and are particularly prominent in poor and crowded populations with inadequate sanitary practices, while foodborne outbreaks of infection also occur in developed nations.[185–187] Infections with certain pathogens are associated with an increased risk of co-infection with additional infectious illnesses, as in the case of the association between human immunodeficiency virus (HIV) infection and malaria.[188] Disadvantaged populations that lack access to healthcare resources are disproportionately affected by a variety of communicable diseases, as seen in Africa, where a particularly significant impact of HIV infection is observed.[189–191] Compounding this inequity, drug development targeted toward neglected diseases is insufficient.[192] Moreover, even in developed nations the burden of diseases such as HIV infection may be greater in certain disadvantaged or underserved populations, such as females, racial minorities, and children.[190,191] Finally, deficiencies in immunization rates lead to the ongoing dissemination of certain vaccine-preventable diseases. Studies have shown that as few as 9% of children receive recommended vaccines at the appropriate ages and that trends in childhood vaccination coverage, while on the rise, have not reached national goals in all cases.[193,194] Furthermore, refusal of vaccinations, based on mistaken beliefs regarding the safety or efficacy of vaccinations, adversely impacts immunization rates.[195]

Of even greater concern is the ongoing development of antimicrobial resistance, which poses a grave public health threat. Bacterial resistance to antibiotics has been observed since the introduction of penicillin, and clinically significant resistance to an antimicrobial agent often develops just a few years after introduction of that therapeutic agent.[196] One of the more problematic resistant bacterial species, methicillin-resistant *Staphylococcus* aureus (MRSA), kills more patients in the United States than HIV, Parkinson disease, and homicides combined. Hospital-acquired infections, the majority of which are caused by resistant pathogens, kill more than 90,000 Americans each year.[197] Infections caused by resistant organisms are associated with increases in morbidity and mortality, lengths of hospitalization, and cost. Infections caused by resistant pathogens are associated with increases of $6,000 to $30,000 in total costs when compared to infections caused by susceptible pathogens;[198] the annual attributable cost in the United States is estimated to be upward of $34 billion.[197] While infections caused by resistant micro-organisms were once largely confined to hospitalized patients, in recent years a marked increase in community-acquired infections caused by resistant pathogens has been observed. In the late 1990s the first reports emerged of patients who had acquired MRSA in the community.[199,200]

Even more concerning is *Clostridium difficile*, a Gram-positive, anaerobic, spore-forming, toxigenic bacterium, which now rivals MRSA as the most common health care-associated infectious organism, contributing to a cost in excess of $3.2 billion annually in the United States.[201–203]

Since 2000, there has been a dramatic increase in the frequency and severity of *C. difficile* infection throughout North America, Europe, and Asia that has been associated with an epidemic strain. This hypervirulent strain, known as BI/NAP1/027, has enhanced resistance to fluoroquinolone antibiotics and is characterized by increased toxin production, sporulation, morbidity, and mortality.[204,205]

A significant factor that drives the ongoing emergence of antimicrobial resistance and other phenomena such as *C. difficile* infection is antimicrobial use. It is generally accepted that antimicrobial consumption leads directly to antimicrobial resistance. Humans use an estimated 3 million pounds of antimicrobial agents annually; the majority of this use occurs in the community setting, and one half or more of outpatient prescriptions are prescribed inappropriately for such conditions as viral infections.[206] A direct link between prior antimicrobial use and colonization or infection with antimicrobial-resistant bacteria has been shown for a number of antimicrobials and pathogens; examples include associations between fluoroquinolone use and fluoroquinolone resistance in nasally carried coagulase-negative staphylococci, fluoroquinolone exposure and acquisition of MRSA, as well as correlations between exposure to a variety of antimicrobials and bacteremia caused by extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae.[207] Antibiotic use has also been linked to increases in both antimicrobial resistance and mutation frequencies in bacteria commensal to the human flora, such as *Escherichia coli* and enterococci.[208] One of the more notable studies to

demonstrate a relationship between antimicrobial use and resistance showed that a nationwide reduction in outpatient macrolide use in Finland led to a decline in the frequency of erythromycin resistance in group A streptococci.[209] An additional contributing factor to antimicrobial resistance is the widespread use of antimicrobials in the food-animal industry.[210]

Given the ongoing emergence and dissemination of antimicrobial-resistant pathogens, the development of novel antimicrobial agents is of paramount importance. Unfortunately, the pharmaceutical industry's commitment to the development of novel antimicrobials is on the wane (Fig. 13.4). In the 1970s, 1980s, and 1990s, no novel antimicrobial classes were approved, and new antimicrobials were instead versions of existing agents. Between 2000 and 2004, only two novel antimicrobial classes were approved; between 2006 and 2009, only one antimicrobial was approved, doripenem, which belonged to an existing class of antimicrobials.[211,212] A number of factors are responsible for this lack of antimicrobial development, including failures in the drug discovery process, an emphasis on developing "me-too" versions of existing compounds, and the targeting of research efforts only toward existing resistant pathogens.[213,214] The current stagnation in the antimicrobial pipeline has led to the formation of advocacy initiatives designed to enhance antimicrobial development in Europe and the United States.[211,215] The Infectious Diseases Society of America (IDSA) has recommended a number of strategies to enhance antimicrobial discovery, including provision of financial incentives to entities that undertake such development, and regulatory guidance designed to encourage antimicrobial research and development.[197,211] The ongoing crisis of antimicrobial resistance, coupled with the lack of novel antimicrobials, supports the idea that the role of pharmacists in the field of infectious diseases is more important than ever.

Pain and palliative care

Background

Our experience with death and disease has changed dramatically over the last 150 years, and with it our expectations for care at the end of life. In previous centuries, death usually was caused by sudden illness or trauma. Infections, childbirth, and even dental procedures were dangerous. Today, the development of vaccines, discovery of antibiotics, and other innovations in modern medicine have significantly improved our health and increased our lifespan.

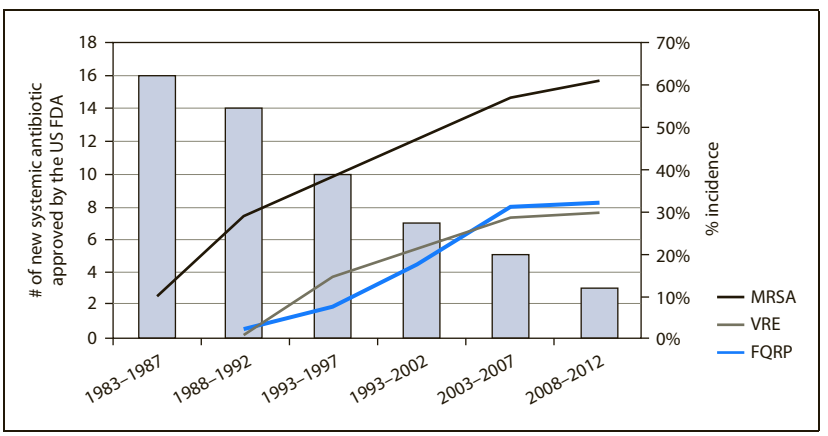

Figure 13.4 Inverse trajectory of declining antibiotic drug development, superimposed by the increase in the prevalence of three concerning bacteria: methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), and fluoroquinolone-resistant *Pseudomonas aeruginosa* (FQRP). (Data based on estimates collected from intensive care units of hospitals that participate in the CDC's National Nosocomial Infections Surveillance System and adapted from Boucher HW *et al*., Bad bugs, no drugs: no ESKAPE! An update from the Infectious Diseases Society of America. *Clin Infect Dis* 2009 48: 1–12.)

These advances also have raised important questions about what we truly want in end-of-life care. Intensive medical treatments often are invasive and can be painful and debilitating. Patients often give up quality of life now, to be placed on a ventilator or to go through surgery, with the expectation that their medical care will resolve the illness and provide quality of life for years to come. Unfortunately, chronic illnesses often cause a slow functional decline that can be difficult to predict or treat. Ultimately, many patients reach a point where modern medicine can no longer improve their condition. At this stage, patients and their families face difficult decisions. Further intensive treatments may cause more debility and reduce quality of life without providing any benefits. For these patients, hospice and palliative care programs have been developed to provide quality care focusing on the relief of symptoms rather than the removal of disease.

The History of Hospice

The word *hospice* derives from the Latin *hospitium*, or hospitality. Its use dates from medieval times, when hospices were resting places for travelers and pilgrims.[216] Later, the term was revived by religious orders, who used it to denote homes that cared for the sick and destitute.

The modern hospice movement traces its origins to the opening of St. Christopher's Hospice in London in 1967.[216,217] Founded by Dame Cicely Saunders, St. Christopher's developed new standards for the field and incorporated education and research into clinical practice. Researchers at St. Christopher's pioneered investigations into understanding the pharmacokinetics of opioids and developed new strategies for symptom management, all while alleviating what Dame Cicely Saunders described as "total pain" – the combination of physical, emotional, and spiritual suffering often experienced by the terminally ill. [216,217]

Typically, patients admitted to hospice are cared for at home by a family member or other caregiver. Hospice staff are available at all times and assist with regular visits and by providing medications and other supplies. The environment usually is an interdisciplinary one, where physicians, nurses, pharmacists, social workers, clergy, and others work together to develop individualized care plans.

The Palliative Care Model

Modern palliative medicine arose, and is shaped by, its origins in hospice. Its goal is "to prevent and relieve suffering and to support the best possible quality of life for patients and their families, regardless of the stage of the disease or the need for other therapies."[218] As with hospice, palliative care focuses on symptom management and improving quality of life. But palliative care programs recently have begun to extend outside the scope of traditional hospice practice.

In this new model, as chronic disease develops, palliative medicine works together with life-prolonging therapy, with palliation becoming a more prominent focus as the disease progresses (Fig. 13.5). The result is a model of comfort care that is distinctly different from, yet integrated with, hospice. Palliative care programs can be found in hospitals, long-term care facilities, nursing homes, and ambulatory clinics. Like hospice, palliative care often is provided by a multidisciplinary team, including physicians, nurses, pharmacists, social workers, and chaplains committed to a patient-centric model of care. Palliative medicine incorporates aggressive symptom management with psychosocial, cultural, and spiritual factors to address

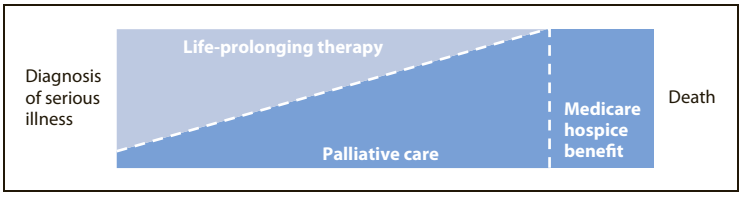

Figure 13.5 The role of palliative care and hospice in serious illness. (Adapted from National Consensus Project for Quality Palliative Care. *Clinical Practice Guidelines for Palliative Care*, 2nd edn., 2009. http://www.nationalconsensusproject.org.).

physical as well as emotional suffering. But unlike hospice, palliative medicine is a model of symptom management at all stages of disease.

Pain and Palliative Care Pharmacy

Pharmacists are uniquely positioned to meet the challenges associated with pain management and palliative care. Medication management in these patients often is complex and requires specialized attention to understand the interactions of disease, medications, and comorbid conditions that will achieve the desired therapeutic response. According to the American Society of Health-System Pharmacists *Statement on the Pharmacist's Role in Hospice and Palliative Care*,[219] pharmacists have a wide array of responsibilities, including:

- Assessing the appropriateness of medication orders and ensuring the timely provision of effective medications for symptom control
- Counseling and educating the hospice team about medication therapy
- Ensuring patients and caregivers understand and follow the directions provided with medications
- Providing efficient mechanisms for extemporaneous compounding of nonstandard dosage forms
- Addressing financial concerns
- Ensuring safe and legal disposal of all medications after death
- Establishing and maintaining effective communication with regulatory and licensing agencies.

Assessing pharmacy-related quality of care

Defining quality

Quality has many definitions in the context of healthcare, and it is essential that individual healthcare organizations determine for themselves what quality means to their organization. Donabedian proposed that there are seven "pillars" of quality: efficacy, effectiveness, efficiency, optimality, acceptability, legitimacy, and equity.[220] In 1990, the Institute of Medicine (IOM) defined quality "as the degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge."[221] The US Department of Health and Human Services has defined quality as "the degree to which a health or social service meets or exceeds established professional standards and user expectations."[222] Quality of healthcare is viewed as a multi-component concept that involves common elements: provision of services that yield better patient outcomes. We can apply this concept to quality in pharmacy practice and provide patients what they want and need to improve outcomes in accordance with established standards of excellence. As healthcare professionals, pharmacists are responsible for guaranteeing the quality of the services delivered and ensuring continuous quality improvement.

Why is quality so important in healthcare? With the mounting emphasis on the safety of the healthcare system, cost containment, coordination of care, pay-per-performance, patient-centered care, health information technology, public reporting, and healthcare reform, quality serves as a framework to guide endeavors in our "value-driven" healthcare.[223] For example, the Centers for Medicare and Medicaid services (CMS) and the US Department of Health and Human Services National Quality Strategy established their central goals, known as the "Triple Aim," to transform the US healthcare system. The Triple Aim entails better care for individuals, better health for populations, and reduction of *per capita* costs.[224]

Achieving better patient outcomes is not the only benefit of ensuring quality of healthcare services; the potential financial impact of improved quality can be immense. Research shows that better quality of care may generate healthcare cost savings.[225,226] For every US$1.00 spent on a prescription, approximately US$1.33 will be spent on complications and drug-related illness.[227] In 2008, a study that measured the frequency and costs of US medical errors estimated that the annual cost of the harm produced by errors amounted to US$17.1 billion.[228] Adverse medication events cause more than 770,000 injuries and deaths each year, and the cost of treating patients who are harmed by these events is estimated to be as high as US$5 billion annually.[229] Improved quality of care can reduce medical expenditures for patients and their employers and improve productivity due to decreased job absence.

In order to oversee the quality of care delivered and plan for continuous improvement, it is essential to measure quality. Quality measurement can identify system problems and monitor the impact of quality improvement activities.

Long-term care

The need for long-term care in the United States will continue to grow in the coming decades as the "baby boomer" population of US residents born during and immediately after World War II attain retirement age and as advances in medicine contribute to longer lives. In 2009, the number of US residents aged 65 and older was approximately 39.6 million or 12.9% of the total United States population, with a projected increase in this population to 72 million people by 2030. The number of individuals aged 85 and older is expected to grow from 4.2 million in 2010 to 6.6 million in 2030.[230] The number of nursing homes in the United States has decreased over the past decade by more than 1000 facilities, with the number of beds in nursing homes also falling by nearly 100,000.[231] While this trend may seem alarming, given the aging population increase, this shortfall in nursing home beds is countered by the increase in assisted living facilities and use of home healthcare as desirable alternatives to most individuals. This shift in healthcare is highlighted by the fact that occupancy rates in nursing facilities nationwide has continued to average about 83%.[231]

Rates of chronic medical illnesses in the older population have increased over the past decade. Diabetes, hypertension, and cancer diagnoses continue to climb, while individuals with these diagnoses are living longer, due to improved medical treatments for these conditions. The proportion of individuals aged over 65 years with poor glycemic control fell 72% during this time period, while the use of statin medications for hypercholesterolemia rose to 40 to 50% of the over 65 population, resulting in significantly lower cholesterol. The use of drug therapy as a primary means to manage chronic conditions is highlighted by epidemiological data showing no significant change in tobacco use in the older population, as well as low rates of regular exercise (less than 10%). The Centers for Disease Control (CDC) estimated that in 2008, more than 65% of people over age 65 took at least three routine prescription medications daily and nearly 75% took at least one daily supplement.[231]

The pharmacist, whether in the community, consultant, or clinical setting, plays an important role in aiding the older patient with management of medications, including appropriate use, drug interactions, and adverse effects. The Omnibus Budget Reconciliation Act of 1987 (the Federal Nursing Home Reform Act), and the subsequent Act in 1990 (OBRA 90), require that a pharmacist provide a systematic drug regimen review that encompasses appropriate medication use, including unnecessary drug use, and that this review be performed on a regular basis.[232] The pharmacist can employ the principles of OBRA 90 patient safety and medication review to any long-term care treatment setting.

Chronic wound care

The prevention and treatment of wounds are vital aspects of caring for patients in diverse settings including the disabled elderly at home, non-ambulatory hospitalized patients, and those who have undergone surgery. During recent years, interest in wound care has increased with entire surgical subspecialties now devoted to it. There are still, however, too few clinicians skilled in this area and it remains a unique area in which pharmacists can play an important role as a part of a multidisciplinary approach. Pharmacists can aid in the selection of cost-effective topical and systemic therapies, and dressings, and help maintain the vigilance required for preventing and treating wounds.

The provision of wound care incurs an excessive burden to society, the healthcare system, and its patients. In a detailed analysis on the burden of skin diseases in 2004, the prevalence of skin ulcers and wounds was 4.8 million accounting for direct costs of $9.7 billion. Indirect costs, due to lost patient and caregiver workdays, and restricted activity, accounted for an additional $2.2 billion.[233] Each chronic wound requires a great deal of time and finances to change dressings, apply topical therapies, and provide in-patient surgical and medical therapy as needed. Chronic wounds have also been shown to significantly reduce quality of life.[234,235]

Despite such a large burden to society, little research has been done to improve wound care. Although there has recently been a surge in the number of products available for wound care and increased attention by the medical field, there still remains a paucity of adequate randomized controlled clinical trials that demonstrate which products work and which work best. This only adds to the frustration and confusion of patients, caregivers, and clinicians, who are often forced to use a trial and error approach to treating wounds. This also leaves the practice of wound care open to overall trends supported by the prevailing theories of the day rather than by rigorous scientific clinical research.

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