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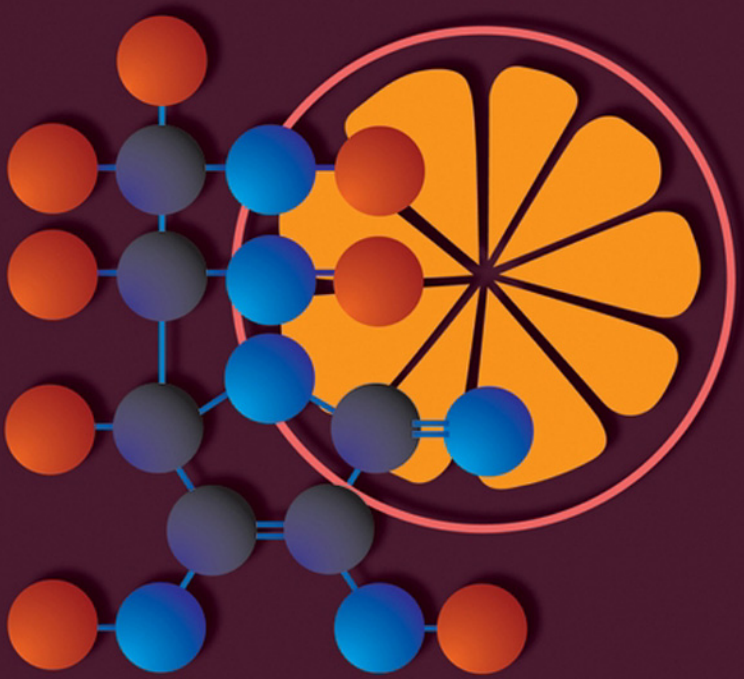
The Management of Chemical Process Development in the Pharmaceutical Industry



Derek Walker

THE MANAGEMENT OF CHEMICAL PROCESS DEVELOPMENT IN THE PHARMACEUTICAL INDUSTRY

DEREK WALKER
Schering-Plough Research Institute

AIChE 100

A JOHN WILEY & SONS, INC., PUBLICATION

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To my wife, Paddy and to my late mother, Elizabeth Florence Walker

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1

INTRODUCTION

Several very useful books on the subject of chemical process development have been published.[1] These have been written largely from the point of view of the bench chemist or chemical engineer. Emphasis in this collection of books is on the work needed to ensure that practical chemical reactions are created for scale-up, that the chemistry is understood, that the theory and mechanics needed to engineer scale-up are addressed, and that Safety, Environment and Food and Drug Administration requirements are met.

This book is about the management of the people, organization, and the main disciplines which have to be to be integrated to create and develop a chemical process to meet all the needs.

Management recognizes that people are the most important assets in their organization and that inspiring leadership provides the best driving force for success. The major requirements for such leadership are reviewed. In today's pharmaceutical industry, leaders need to be visionaries with the ability to motivate their scientist and engineer co-workers to express themselves, to take risks, and to harness sound judgment in fusing together the many components that form a chemical process. Personal examples are used throughout the book to illustrate this. A few of the

[1] (a) Lee, S., and Robinson, G. *Process Development*, Oxford University Press, Oxford, 1996. (b) Repic, O. *Principles of Process Research and Chemical Development in the Pharmaceutical Industry*, John Wiley & Sons, New York, 1998. (c) *Process Chemistry in the Pharmaceutical Industry*, Ed. Gadamasetti, K. G. Marcel Dekker, New York, 1999. (d) Anderson, N. G. *Practical Process Research and Development*, Academic Press, New York, 2000. (e) Griskey, R. G. *Chemical Engineering for Chemists*, American Chemical Society, Washington, D.C., 1997. (f) McConville, F. X. *The Pilot Plant Real Book*, FXM Engineering and Design, Worcester MA, 2002.

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frameworks through which people are recognized and rewarded for their achievements are described. People recognition and rewards are undertaken in partnership with the company Human Resources function.

Organization of the work of scientists and engineers and how this is integrated with other disciplines to provide the foundations for success in achieving defined missions is outlined. It is recognized that organizations need to be flexible and be prepared to change to meet the unexpected and also the different needs of different missions.

The main "outside" disciplines influencing the progress of chemical process development in the pharmaceutical industry are process safety, environmental considerations, and FDA regulatory affairs. The basic principles governing these disciplines and the major activities needed to meet the requirements in these areas are summarized. Beyond the regulatory disciplines, the vital importance of patenting and defending intellectual property is also emphasized. An outline of the chemical engineer's role in chemical process development is given with particular emphasis on chemical plant equipment requirements for the major unit operations.

Two case studies are provided to illustrate how the work of chemical process development is carried out and how this work is changing with time. Two essays describing technical excursions in two of the major fields I worked in, β-lactams and steroids, place chemistry in a historical perspective and provide a picture of the excitement and variety of challenges that come with a career in chemical process development.

The final chapter, on the future, provides a personal summary of a few of the major endeavors I believe should be pursued in order to address today's realities, including the consequences of past neglect. These endeavors require that we raise education—in our case, chemistry education and in particular its integration with the analytical, biological, and engineering sciences—to a much higher level of importance. They include finding ways to overcome the rising monster of intrusive regulation; to address the consequences of outsourcing; to increase the use of biological systems in synthesis; to simplify and contain chemical processes; to promote evaluation of newer technologies and reexamine some old ones; and to prevent and reduce waste. Preparing for the future also requires that all thinking people need to fantasize, in our case to stimulate debate on how the major chemistry challenges in the world should be tackled. Such debates must lead to the creation and funding of feasible programs—I offer one "starter," tongue-in-cheek fantasy of my own. By promoting new chemistry-based thinking, we might breathe new life into the old DuPont slogan "Better things for better living through chemistry," with the twist that "chemistry" be defined in the broader interdisciplinary context referred to above.

This book draws on my own experience and observations from over 10 years of working at the bench and over 30 years growing through the management ranks in chemical process research and development, the last 14 at the vice-presidential level. The book is thus a summary of the work of many co-workers, to whom I am forever indebted, and is written in the hope of stimulating others to create new futures.

Chemists and engineers joining chemical process development organizations quickly recognize that although we grow from our roots in chemistry or engineering,

we need to adapt quickly by embracing and incorporating all manner of inputs, sometimes unforeseen, into our work. We have to adapt to the turbulence that goes with practicing chemistry in the real world of tackling often urgent problems in R&D, in manufacturing and in pertinent business areas. Thus we have to accommodate the needs of government, secure intellectual property, and aid marketing, sales, finance, law, and so on, at the same time as providing supplies and information in order to bring new drugs to the market place as quickly as possible. The practical combination of these activities creates the life of a company more or less under the rule of imperfect and changing laws.

The chapters in this book started out as handouts for a series of talks prepared for students of chemistry interested in the possibilities of a career in the chemical process development field. Some were also presented to my manufacturing colleagues at Schering–Plough. The chapters are based on the work carried out during my employment at several pharmaceutical companies (Arapahoe Chemicals/Syntex, Glaxo, Bristol–Myers, and Schering–Plough) in both the R&D and manufacturing areas. This diversity of experience enabled me to appreciate the need to accommodate the different objectives and philosophies that drive each company, and frequently divisions within companies. Add to this the iterative nature of the drug development field and one soon understands the need for flexibility in progressing the work of any organisation. Above all, it is worth repeating that success in any organization is dependent on well-equipped people working together in a creative and disciplined environment to address the common need. People are the key. Creative individuals, working collaboratively in a team, which accommodates a little heresy, are more important than buildings, machinery, budgets, balance sheets and bureaucracies, and all the other components of any endeavor.

Although the core professional discipline in chemical process development is chemistry, success in finding the best chemistry to develop to a pilot plant and manufacturing scale is dependent on many factors and disciplines. In a chemical process development department that is part of a pharmaceutical research organization, the mission to produce the active pharmaceutical ingredients (APIs) and intermediates needed by one's research colleagues for their work to identify new drug candidates is the first priority. The early API supply mission usually comprises using research chemistry, often in a raw state (I refer to this as the *Recipe* stage), to produce needed supplies. To meet further urgent (usually larger) API needs, the *Recipe* stage evolves, for safe scale-up, into the *Method* stage. As the likelihood increases that a potentially marketable API is emerging, the chemical process development department works to cultivate a deeper understanding of what is needed to create chemical transformations that are practical and broadly acceptable, in safety, environmental, regulatory, and economic terms. This begins the real *Process Development* phase of a project. In this phase, one needs to give thinking people in the immediate organization—especially chemists, analytical chemists, and chemical engineers—increasing "space" to express themselves in building the research transformations, or new ones they can predict will be better, into the beginnings of a process.

As the momentum in this direction increases, the disciplines of chemical engineering, of patents, and of the regulations which guide process development work

(safety, the environment and FDA regulatory affairs) become increasingly important. In addition, one needs to seek the input of the manufacturing people in creating the manufacturing process and, as the project develops, to assist in process design and the implementation of a system of operations suited to the ultimate manufacturing process and manufacturing site. Integrating the sometimes seemingly conflicting activities of API supply with chemical process research and development inevitably creates a chaotic environment. However, chaos can be dealt with through proper staffing and with agreed prioritizations. In my mind the process that develops from integration of these activities is better than one that develops by separating API supply from process research and development. The simple reason for this is that gaining experience in the overall system enormously enhances the ability of scientists and engineers to see what is really needed in generating a manufacturing process.

This book is intentionally broad in scope. I recognize that some chapters may lack in depth, but I hope the collection will provide readers with human perspective on what is involved in chemical process development. I am aware that there are omissions, such as to the broad uses of computers and applications of statistics, which may intensify concealment of their value in developing chemical processes. I therefore urge practitioners to consult with their leaders for guidance on questions regarding other disciplines to accommodate in progressing their work.

The final reality is that every one of us working in chemical process development could write a different book drawing on their personal experiences. It would move the field along to a greater state of appreciation and understanding if more of us did.

2

PEOPLE: LEADERSHIP, VISIONARIES, ACKNOWLEDGEMENTS, AND AWARDS

The right people are the most important assets in any organization.

INTRODUCTION

The major factors I wish to address in recognizing the vital importance of people are leadership, the influence of visionaries, outstanding scientists and engineers, the value of consultants, and the recognition of the achievements of people through awards and a scientific/engineering ladder of promotion.

Organizations strive for success in their chosen businesses. To achieve success, nothing is more important and complex than finding, organizing, and keeping the right people to work in it and creating the environment for them to express their talents. The right people share the goals of a good organization and believe they are in a good place to meet their own needs. The leaders in the organization are, for their part, in general agreement with this assessment, especially in recognizing that both parties need to work to sustain their relationship and to accommodate changing circumstances.

The right people come from all walks of society, embracing everyone from the most gifted professionals to the cleaners. Understandably, it is visionaries and leaders

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and those who generate the successes who receive the most attention and publicity. However, it is vital that everyone understand that achievements also owe much to those working in the lower ranks of the organization, not forgetting those outside the organization who provide support, including families at home. All have an influence and need to feel that their contributions are appreciated.

Although this presentation is concerned with people in chemical process development organizations in the pharmaceutical industry, there is much that is applicable to people in almost all industries. First, it is worth placing people in the context of the most important element in an organization, leadership, recognizing that infinite variations are needed to suit infinite circumstances. Leadership sets the tone, evolving as objectives change.

Textbooks and educational courses may provide the principles of leadership, but it is human application and successes that identify the leader. Leaders are people who need to take responsibility for running an organization, at the same time as accommodating factors beyond their control.

In the scientific world it seems obvious that leaders in a given area should be highly qualified (or, rarely, just very, very experienced) in the major discipline they are leading and that they should understand the importance of related disciplines. In chemical process development a highly trained chemist leader needs to have experience in areas such as chemical engineering, biological sciences, and analytical sciences. Leaders of chemical process development may also come from these other sciences, provided they have the talent and supporting people to uphold their leadership.

LEADERSHIP

Leaders need many abilities:

- *The ability to identify the people needs of the organization and also to find, attract, develop, and keep real talent.* It is not enough to find someone for one immediate kind of work. One may need a specialist, but such a person in today's fast-moving risk-taking technical world must be able to adapt to changes and challenges that stretch his/her specialization and imagination. The final judges in the selection process need experience, and sometimes even an instinctive feel, in choosing their co-workers. It is necessary to ensure good mentoring and training to develop one's people resource over time. In the course of such a process, future leaders are identified.
- *The ability to delegate and trust.* These are important requirements in pursuing any endeavor. At the same time, especially early in a relationship, one generally needs to remain "unobtrusively interested" (e.g., through project review meetings) until progress reveals that the trust is well-placed.
- *The ability to be flexible and to act to correct one's failures on the one hand as well as to selflessly represent outstanding people on the other.* Leaders who fail to deal with poor performance do not inspire their subordinates. Leaders who neglect superior talent or hog their credit do a disservice to the organization, and ultimately to themselves. Leaders need to recognize and reward outstanding

ability. Salary is only one way. Organizational ladders of professional growth equal to managerial ladders is another. An awards system (see later) is yet another.

- *The ability to listen, communicate, promote action and collaborate, clearly, on the issues in a wide variety of situations.* Each issue may require its own mini-mission statement, worked out by the principals to define a needed objective, within the constraints of other commitments, and to marshal the resources to meet it. Given such definition, motivating the players needs enthusiasm and resolve and as good a grasp of the problems as can be mustered. This can be extraordinarily difficult if there is great uncertainty regarding the facts, or competing demands. Nevertheless, shrewd risk-taking needs to be encouraged, and, if unsuccessful, responsibility needs to be accepted. Keeping a wise focus on the essentials, including thorough project reviews, is often vital to success.
- *The ability to promote the scientific/engineering dialogue and project vision at as high a professional level as is feasible, or appropriate.* Scientists and engineers are usually very good at responding to technical challenges in an adventurous way, but wise counsel may occasionally be needed to avoid projects drifting far from addressing the core problem—still allowing that there is a chance for a maverick solution! The scientific/engineering dialogue extends beyond chemical development to require interactions with other disciplines, including pharmaceutical sciences and regulatory affairs, and it is in accommodating these interactions that listening ability, wisdom, and vision are most needed.
- *The ability to succinctly and modestly keep one's own superiors abreast of issues, progress, setbacks, and individual contributions.* In this arena, one needs to accommodate (although not necessarily always accept) the thoughts and advice of those with greater perspective.
- *The ability and courage to deal with project failure, usually without entirely abandoning the fight to salvage something useful.* Few events are more difficult to handle, especially if one has been personally committed. Mourning is brief for leaders since they need to take stock of the realities, reassess the facts, dissolve project teams, and redeploy resources on new initiatives. Leaders give credit for achievements in failed projects and encourage appropriate use or publication of worthwhile findings. Another positive is that failures give leaders the opportunity to show they care for individual workers.
- *The ability to continually adapt to an increasingly problematic regulatory world and persevere in efforts to improve operations and to deal with the bureaucracy.* Governments have, quite properly, reacted to the overly self-serving activities of some companies and individual entrepreneurs by creating strict rules of governance. Since breaching the rules leads to regulatory problems and causes business delays, industry has reacted by creating internal compliance groups to avoid such problems. Compliance groups, striving to help their company be "whiter than white," have set up internal controls and bureaucracies that, unfortunately, further stifle creativity and change. As a result, in the pharmaceutical industry, process development chemists and engineers are obliged to define an industrial process for producing an active pharmaceutical ingredient (API) at

the earliest possible development stage. Freezing or minimizing change, at say the IND filing stage, until the NDA has been approved by the FDA has greatly inhibited the creative drive for better processes, if not for new products. Given that rules impact on all phases of development and that the development phase of bringing an API to the market is the most costly phase, it is inevitable that if creative drive continues to be inhibited, the cost of drugs to the consumer will continue to be high. Thus, rules, lawyers, relentless media attention, the remorseless and often short-term demands of the financial markets and their analysts, and the increased politicization of the alleged obscene profitability of the pharmaceutical industry, at least in the United States, make for a difficult future.

- *The ability to work for the love of it, as if the company is your own.* This is generally an inspiration to all around you. Such a commitment requires a complex combination of qualities, notably a personal passion for the job, wisdom, aggression, humility, creativity, a sense of humor, obsession, relentless drive, occasional ruthlessness, and the ability to stay hungry, inter alia. People working for the love of it generally have a passion to promote excellence.

A continuous search for leaders is a vital part of every company's mission. The following statement[1] by Charles D. Miller, Chairman and CEO of Avery Dennison, is illustrative:

> My personal specifications for successful leaders are very simple. I look for people who possess the character to succeed in a highly competitive environment; who have the courage to take risks; who speak candidly and with confidence; who exercise good judgement, often with little information; who think creatively and inventively; and who have a community spirit to work collaboratively in a team-supported environment. One of our most important challenges today is to nurture and develop our next generation of leaders who will be successful in diverse global environments and who will, in turn, develop other leaders to capitalize on the Company's many strengths.

In conclusion, leadership has never been more needed, in every area, to overcome situations and inertias that take an inevitable toll on the competitiveness of the advanced nations (see Chapter 11).

It is worthwhile for all of us to look back and reflect on the individuals who really made a difference to our professional careers. It usually begins with supportive parents and inspiring teachers, enabling one to emerge from university with the knowledge and certificates that are the tickets allowing you to travel. Once "on the road," it is up to you and to all the professionals around you. In most respects you find these professionals yourself in joining companies of people whom you feel are of like mind and whom you can convince would benefit from employing you.

Although most of the legion of people who made a difference to my own career are little known, except through their scientific papers and local recognition, it seemed

[1] Avery Dennison Annual Report to Stockholders, March 1, 1995.

to me worthwhile to introduce the most influential ones to you. These are the people who illustrate particular abilities needed to succeed in chemical process development projects. Perhaps these "sketches" will encourage readers to reflect on corresponding people in their own careers.

Of the many people to whom I reported, I found only a few to be exceptionally visionary and brilliant leaders. Five were the sort of leaders anyone would be privileged to work with; the sixth was more of a maverick superbly suited to particular situations and circumstances. While the visionaries were indispensable to all our successes, it was the hundreds of scientists and engineers who I had the good fortune to work with, and whose sustained technical achievements over many years created the chemistry and engineered the processes, who provided the company with benefits and breakthroughs. In completing this section of the presentation, I pay tribute to several of our consultants and particularly to three professors who consulted for us over long periods and who proved particularly inspiring.

VISIONARIES

These are the people who generally see, as part of their professional brief, that there must be opportunity for revolutionary as well as evolutionary approaches to "business" creation, development, and improvement. They have ideas of their own but are open to outside stimulation and willing to run with the ideas of others. Visionaries recognize the importance of giving talented people their head. In our field they encourage and support such people in their scientific enterprise and quest for scientific understanding. They are willing to give talented people time and resources and willing to beat back naysayers and senior managers who all too often call for short-term solutions or strict adherence to organizational boundaries. Visionaries believe in their people, they tolerate a little heresy, they possess personal courage and have the good judgement to know how far "vision" can be taken. Visionaries by their enterprise often acquire more than their normal fair share of luck and, as a result, are often responsible for many of the great advances in anything.

In my experience, process technology is advanced significantly under such leadership. This leads me to the people who, in the periods indicated, contributed so much to my own career.

Drs. Tom and Richard Waugh (1960–1966). These exceptionally adventurous and courageous brothers, together with an engineer, Oscar Jacobsen, raised the capital to found Arapahoe Chemicals in Boulder, Colorado, simply because they wanted to work there (rather than continue working with Standard Oil in Gary, Indiana). They perceived Boulder as a better place to raise their families, and they needed a workplace environment in which they could better express their technical abilities.

In founding the company, much thought went into tapping the most singular quality of the Colorado climate, its dry air. This led them to the production and sale of Grignard reagents and later other metallo-organics. They were willing to tackle all manner of hazardous chemical reactions, some of which led to fires and the loss of physical plant. The insurance money enabled them to learn from mistakes and

rebuild. In my time I recall the rupturing of a bursting disc following a runaway Grignard reaction—a large quantity of ethyl chloride had been added to slowly activating magnesium. A spurting jet of ethyl magnesium chloride blew onto an aggressively sited MacDonald's hamburger stand. Tom and Dick took the whole affair very seriously, paying for the cleaning and repair of damage to customer cars. But they couldn't gag the jokers who suggested that the hamburgers never tasted so good!

Arapahoe won the respect of major customers around the United States, not only for the custom work done for them by Arapahoe, but by reacting to quality issues in a fundamental way. Thus, by becoming aware of the instability of the *N*-bromoamides they made for others, particularly in the steroid industry, they continually improved and patented[2] their processes thereby producing stable *N*-bromoamides which became another foundation of Arapahoe's business. The culmination of this work was a process[2c] wherein a solution of the amide in a cold (5–15°C) freshly prepared solution of $HBrO_3$ was treated with bromine to give the *N*-bromoamide. The key step was to form $HBrO_3$ by passing a concentrated solution of $NaBrO_3$ through a column of a strong acid resin (Dowex 50W-X8). Bromide ion produced in the bromination was reoxidized to bromine. The process was particularly useful for the preparation of the relatively unstable *N*-bromoacetamide.

Product purity became a passion at Arapahoe Chemicals, as well as a formidable marketing tool. It became an unwritten trademark in all of Arapahoe's marketed products, including DDQ, organic scintillators, numerous pharmaceutical intermediates, and metallocenes.

The scientific environment at Arapahoe Chemicals was stimulating and successful. Tom and Dick supported scientists in their efforts to further their education through course work at Colorado University and by encouraging dialogue and consulting sessions with several of the chemistry departments professors. Their leadership and family orientation as employers owed much to their commitment to the company, their love of their jobs, their sense of purpose, their energy and enthusiasm, and their willingness to accept difficult projects and to listen to everybody's ideas for solutions. Not surprisingly, they attracted entrepreneurial people to the company. They also established a strong business/science culture. This was always evident at our frequent open-ended project reviews in which the responsible scientists presented their project work, fielded questions, ideas, and suggestions, and made appropriate accommodations in presenting an ongoing course of action. In the scientific arena we accomplished a great deal, even if it seemed small in the greater scheme of science. Tom and I made a useful contribution to the organic scintillator field with the invention of dimethyl-POPOP, a commercially successful more soluble successor to the original organic scintillator, POPOP.[3] We created practical chemistry, with

[2](a) Waugh, R. C., and Waugh, T. D. U.S. Patent 2,971,959, 1961. (b) Waugh, R. C., and Waugh, T. D. U.S. Patent 2,971,960, 1961. (c) Robertson, D. N. U.S. Patent 3,187,044, 1965 (to Arapahoe Chemicals, Inc.).

[3]Walker, D., and Waugh, T. D. *J. Heterocyclic Chem.*, 1964, **1**, 72. Dimethyl-POPOP is still on the market, 40 years after its invention.

Dr. Bill Coleman, for several chemical steps in Syntex's synthesis of the oral contraceptive chlormadinone. With Haldor Christensen, sodium dispersion chemistry led to a superior process for the manufacture of the Eli Lilly herbicide, diphenamid. We devised novel patented chemistry, with the inspiration of Dr. Martin Hultquist, for the manufacture of DDQ. The list could go on and on, but the essence is that in Arapahoe we became chemical process development chemists. We learned that there were no such chemists as steroid chemists, organometallic chemists, heterocyclic chemists, and so on. There are only process development chemists, capable of synthesizing anything. Being scientists in a small company we also learned to accommodate other disciplines and business requirements in creating our chemical processes.

As a result of its successes, Arapahoe Chemicals became a takeover target for Syntex. Once taken over, the ensuing changes disturbed the magic of the original company. It was not the same and many of us moved on. But all of us owed a debt to the genius and vision of Drs. Tom and Dick Waugh. I built on this unique experience for the rest of my career.

Dr. Arthur Best (1966–1975). Moving to the penicillin and fledgling cephalosporin production facility of Glaxo Laboratories in Ulverston, Lancashire, introduced me to the more structured rigors of the pharmaceutical industry. The Ulverston factory synthesized chemical intermediates and APIs as well as many dosage forms for the marketplace. The move from working in a small, fast-moving, free-wheeling, all-encompassing, practical chemistry organization to heading the chemistry component of a large process investigation department came as an immense shock. The chemical process challenges were enormous, but the whole thrust of the department—troubleshooting and improving existing processes with limited resources—severely restricted the opportunities for real process understanding, redefinition, development, and improvement. It was clear that we needed process revolution as well as evolution.

It was fortunate for Glaxo, as well as myself, that Dr. Arthur Best was the technical director of the Ulverston factory at the time and, moreover, that he subscribed to the view that only people on the ground in Ulverston could do the process development and process troubleshooting work he thought was needed. He saw that the process research and development people in Glaxo, Greenford, were much too involved in serving research needs for clinical supplies of the company's new APIs to have the time and effort to provide the dedicated technical power needed for all the process evolution/revolution opportunities in Ulverston. They were also far away and did not have the laboratory space to enable them to increase staff to meet the needs. He also perceived a conservatism in the Greenford process development department. Thus in selecting and developing a second process[4] for the manufacture of cephalexin,[5] the Greenford development group opted to develop Eli Lilly's chemistry in the belief that

[4]The first process, which was already in production in Ulverston (and, in part, in Montrose, Scotland), utilized the 2,2,2-trichloroethyl (TCE) group for the protection of the carboxyl group in the starting penicillin G sulfoxide acid; for more detail of the need to change, see Chapter 7.

[5]Eli Lilly was the discoverer of cephalexin. They used *p*-nitrobenzyl (PNB) protection of the penicillin carboxyl group in their manufacturing process. Glaxo had rights to this process, as well as to market

this would speed change to a new process in Ulverston and Montrose. We in Ulverston argued that the Eli Lilly chemistry was undesirable for safety and environmental reasons.[6] To the chagrin of some in the Greenford process development group, Dr. Best encouraged and supported (by approving the conversion of existing and available space in Ulverston to laboratories and adding scientific manpower and equipment) my proposal to explore and develop the DPM alternative to the PNB group despite enormous risks to himself.

Dr. Best's initiative set in place an unprecedented and competitive collaboration between the Greenford and Ulverston process development groups. This was administered through frequent technical review meetings in Greenford. Greenford concentrated on developing the chemistry to use the PNB group while we in Ulverston set about proving that use of the diphenylmethyl (DPM) group would give cephalexin yields equal to those obtainable via use of PNB and also generating the information to prove that the DPM group offered a safer, more environmentally friendly option.

Making the choice between the two protecting groups was accelerated by a letter received from Ciba pointing out that Glaxo's use of the TCE group was covered by a Woodward patent to Ciba. The final selection between PNB and DPM was made at a meeting in Greenford. Dr. Best's position, based on the equivalence of yields, cephalexin product quality, and the equal state of advancement of the two processes, was that it was unacceptable to introduce the Lilly-patented PNB process (despite our NRDC rights allowing us to use it) versus the Ulverston, Glaxo-patented DPM process when the Lilly process introduced so much more in the way of hazard and waste. We argued that the use of *p*-nitrobenzyl bromide, a proven vesicant, in introducing the PNB group and the hazardous waste produced in removing it were undesirable burdens in a manufacturing situation. In addition, cost calculations showed a marginal advantage in favor of using DPM protection. The decision to adopt the DPM process was made by Glaxo senior management after the technical meeting.

During the nine years I worked with Dr. Best he regularly demonstrated that an eloquently argued, well-supported case would generally overcome a weaker case, however passionately argued.

Dr. Robert A. Fildes (1975–1980). Bob Fildes was one of the most dynamic and controversial people I ever had the pleasure to work with, as a colleague in Glaxo (1968–1974) and in Bristol–Myers. As a biochemist in Glaxo, he saw the immense opportunities to be gained through "neutralizing" the amino group in the α-aminoadipoyl side chain of cephalosporin C using a D-amino acid oxidase (DAAO). He was years ahead of his time, but unfortunately his staff in Sefton Park and ourselves in Ulverston were not able to generate an economic process for the recovery of the product. Dr. Fildes no doubt feels somewhat vindicated today by the later adoption of his process by Farmitalia (now Antibioticos) as part of their successful technology.

cephalexin, through the blanket license agreements with the National Research and Development Council (NRDC), which owned all the patent rights to cephalosporins and derivatives thereof.

[6]We opted to develop diphenylmethyl (DPM) protection as an alternative to PNB. More detail of the chemistry is provided in Chapter 9.

They coupled Bob Fildes' DAAO-enzyme first step with an acylase-cleavage step to generate a commercially successful process for producing 7-aminocephalosporanic acid.[7]

When the senior management in Glaxo Laboratories changed (1974), a harsh compartmentalization of responsibilities occurred, wherein factories such as Ulverston were restricted to process investigation and troubleshooting and responsibility for process research and development was returned, fully, to Greenford. It seemed to me a form of organizational terrorism. Dr. Fildes left Glaxo to become Vice President of all development (primarily fermentation, chemistry, and chemical engineering) in the Industrial Division of Bristol–Myers in East Syracuse, New York. He persuaded me to join him. At the time, control of the Industrial Division was in the hands of a very tough Italian, Dr. Abramo Virgilio, whose mission for development was that they create process cost reduction and quality improvement as rapidly as possible, and whose mission for his marketing arm was that they pursue sales of existing products, notably 6-APA, ampicillin, amoxicillin, 7-ACA, kanamycin, and amikacin to meet agreed, but aggressive, targets. In defining "as rapidly as possible" for development, he required that any money spent on process cost reduction had to produce full payback in no more than 18 months! Bob Fildes provided the vital buffer between ourselves and the short-term thinkers in senior management and encouraged the science that led to the many successes of our chemical process development group. Our group was also funded to develop processes and to produce supplies of APIs for the Research Division's drug discovery and development programs. Our successes led to a close and harmonious relationship with the Research Division. However, neither the Research nor the Industrial Division would countenance delay of their programs by any perception that we were favoring one Division's requirements over the other's. Although we were well-staffed to meet the needs of both, we had to be careful and realistic in making promises to either. In reality, the careful balance of resource utilization was only seen to be acceptable if we exceeded expectations for both divisions! Bob Fildes proved to be masterful in handling the balance despite his many other roles which required that he travel extensively worldwide. He proved quite adept at managing all his responsibilities at 40,000 feet!

Our workload became more realistic for a while when Dr. Virgilio was posted to manage Bristol–Myers' Far Eastern Division, and Dr. Filippo LaMonica took over. This continued for a couple of years when numerous changes occurred. Dr. Irwin Pachter, Vice President of Research, retired and Dr. Julio Vita took over. Dr. Virgilio returned to take over the Industrial Division and Dr. LaMonica left. Bob Fildes moved on to become President of Biogen and later Cetus. Dr. David Johnson replaced Bob and I moved to take Dr. Johnson's place as director of development chemistry and engineering. Dr. Vita decided that Research should control its own API supply and began building his own facility—there was no Bob Fildes to argue against this.

Dr. Fildes' courageous, persevering British bulldog approach to problems and issues was admired and needed. He was never afraid of controversial combat, including with the FDA. Unfortunately, the bulldog image was seen by many as

[7] See Chapter 9 for an account of this work.

metamorphosing into that of a Rottweiler. Nevertheless, his career flourished in a different way beyond Cetus.

Dr. David Johnson (1975–1982). Of all my senior managers, Dave Johnson was the one who knew most about organic chemistry and synthesis. He was a hard-driving chemist with a "nose" for practical solutions to process development problems. Being a student of Professor John Sheehan, his knowledge of β-lactam chemistry was extensive. Indeed he was called on to represent Bristol-–Myers in its many patent battles with Beecham in which Bristol–Myers staked out its own patent position covering ampicillin and amoxicillin trihydrates.[8]

Dave Johnson generated many outstanding synthesis proposals during our frequent technical meetings—he always tried to stay involved—and stimulated the thinking of all around him. He had a synthesis vision that he promoted through in-depth discussion of specific chemical reactions and brainstorming with our chemists and me in intense sessions. No problem ever seemed insoluble to him, and as a result we all rose to the occasion. I particularly remember Dave's exhortations on the problem of overcoming Beecham's patent on amoxicillin synthesis, a patent that, if it could not be overcome, would shut down Bristol–Myers' efforts to gain a share of the lucrative Japanese amoxicillin market. Dave was relentless in goading us to search for a newer/better way of acylating 6-APA (preferably solubilized in an organic solvent) with *p*-hydroxyphenylglycyl chloride hydrochloride. There is no doubt that his efforts to stretch our minds to the limit, search our imaginations, and rummage in the most abstruse literature, for this newer/better synthesis were chiefly responsible for the practical success we finally achieved—which evolved from a finding in an obscure Russian journal.[9] I have no doubt that this success would not have arisen without Dave Johnson's perseverance.

Above his chemical vision, Dave Johnson was both a friend[10] and a mentor for me and many of my staff during the period of organizational upheaval at Bristol–Myers described above. Dr. Vita's initiatives broke up the chemical development organization and resulted in Bristol–Myers losing many fine scientists and engineers. I was fortunate to be identified by a headhunter and recruited by the Schering–Plough Research Institute to become their Vice President of chemical development. This coincided with the time when Schering–Plough was seeking revolutionary changes under the exceptional and inspiring leadership of their CEO, Robert Luciano. I joined them reporting to Dr. Hal Wolkoff, Senior V.P. of all development operations, including pharmaceutical sciences, analytical chemistry, organic chemistry and biotechnology.

Dr. Hal Wolkoff (1982–1992). My years reporting to Dr. Wolkoff were the most exciting, productive, and satisfying of my entire career. Hal Wolkoff was, to me,

[8]Once, while on a fishing trip by flying boat into northern Canadian Lakes, he was desperately needed to aid a patent action. Dr. Roy Abraham, at headquarters in New York, was able to call out the Canadian Mounties to find him—true to the legend they again got their man!

[9]See Chapter 7 for detail of this work.

[10]Inter alia he introduced my boys and me to the bone-chilling "sport" of ice-fishing on lakes Cazenovia and Oneida.

the most level-headed yet courageous visionary of all the people I worked for. He saw the big picture and agreed that chemical process development was not about chemistry alone. However, he needed a good case justifying our vision of what a modern chemical process development organization should look like. We had to convince him that the additional functions we wanted to adopt would fit with all the components of his larger development organization and also with the relevant groups in other parts of the company. He needed to know how we thought all the new functions we proposed adding would actually work, both together and in the larger organization. Although he might have needed to make a few leaps of faith, Dr. Wolkoff accepted the overall logic of our proposals and gave his unstinting support. He backed and often represented our case to senior management. Slowly a new comprehensive chemical process development function emerged.

As a result of Dr. Wolkoff's efforts, the following initiatives were supported by the company:

- Headcount was increased by recruiting many high-quality people into Chemical Process Development.
- Funds were secured for modern laboratory and pilot plant, equipment.
- In-house support groups were funded (Analytical, Safety, Environmental, and Regulatory Affairs).
- A chemical biotransformation group was introduced.

These initiatives are described in more detail in Chapter 3.

These enhancements took several years, in all, to introduce but provided the backbone of technical power that had so much impact on company operations, in both manufacturing and research.

Dr. Wolkoff deftly handled his position of power within the Schering–Plough Research Institute. His grasp of what was needed to achieve desired goals and his ability to distill the essentials from complex information and then to make concise and focused decisions that went to the heart of a problem were rare and admirable qualities. In keeping with my other visionaries, he recognized that people were the most important assets in any organization, and his efforts to acclaim what his people had achieved were widely appreciated. Also, he did not shrink from constructive criticism. I always knew where I stood.

OUTSTANDING SCIENTISTS AND ENGINEERS

These were the people who provided sustained scientific/engineering leadership in the pharmaceutical company settings I worked in.

To quote Stephen Mulholland,[11] "Scientific leadership is a useful and necessary drive in those industrial scientists who have it in them to make an impact on their organization through their own achievement. Scientific leadership requires the

[11] *South African Times*, January 17, 1999.

assumption of risk, the acceptance of failure, and the determination to overcome it when it strikes."

"What is useful to bear in mind is that very few people are willing to assume leadership in the sense of being prepared to assume risks and assume responsibility. Many of course desire the fruits of leadership but only a tiny proportion of people are willing to expose themselves to the risk of failure. An even smaller proportion truly wish to have responsibility. The hard truth is that the vast majority, notwithstanding their almost universal desire for recognition and the fruits of success, are not chosen, or they hang back, because they are not well-equipped for leadership."

Scientific/engineering specialists in the field of chemical process development need to acquire a complex blend of skills. Scientists and engineers may be well-endowed intellectually and by training to imagine synthetic schemes for the preparation of an API, and go into the laboratory to test them. They may have the right gifts of curiosity and imagination. They may have the energy, tenacity, and skills to implement imagination, but that is seldom enough. Some of the most overlooked additional requirements for becoming a successful chemical process development chemist are gaining experience, recognizing and cultivating practical solutions to problems, satisfying the regulatory disciplines, and accommodating the bottom line. To prepare for leadership in chemical process development, one needs to draw on an apprenticeship integrating chemistry with pertinent disciplines in a practical fashion.

The following pays tribute to a few of the people who made the most memorable contributions to the shaping of my own chemical process development career.

Dr. Martin Hultquist (1960–1966). Martin Hultquist was one of the most gifted, practical, ingenious, and generous process development chemists I ever met. He worked for American Cyanamid in Bound Brook, New Jersey, for many years, but his dream (like the dreams of Tom and Dick Waugh) was to return to Colorado (he was born in the tiny hamlet of Laird close to the Nebraska border). To that end, he pursued Arapahoe Chemicals for years, ultimately persuading them to give him a job. My own "training" was immeasurably enhanced by Martin's amiably intense and imaginative approach to chemical process development and scale-up. His vast experience was a technical resource for all of Arapahoe's laboratory scientists. Chemistry thoughts and advice were given unstintingly and always with a view to enhancing the Arapahoe mission. His work bench may have been a mind-boggling jumble of glassware, as though an earthquake had passed through, but, diving through it for a thermometer or a dropping funnel or anything else, he demonstrated he knew where everything was! He was a master of speed, convenience, and multi-tasking, often to be found smoking a pipe and watching a reaction going on a hotplate while exploring ideas for new reactions with his trademark test-tube experiments—generally a prelude to his next flask-sized experiment. It all seemed like wizardry—a power of transforming something common into something special.

Martin Hultquist had a rare instinct for organic chemistry and a "green thumb" that provided an education for us raw young chemists. Many simple solutions came from his work. He found ways to work in water as a solvent whenever he could. He would often acidify basic solutions of acid-sensitive compounds with methyl formate.

He encouraged the use of isopropyl acetate (b.p. 89°C) instead of ethyl acetate (b.p. 77°C) because of its reduced water solubility and greater stability to hydrolysis. He preceded the phase transfer catalysis era using detergents to speed reaction rates and increase yields. His bag of tricks, as he would whimsically refer to his armory of techniques, was an eye opener for his more conventional disciples.

Whenever he had a spare moment, he could be found thumbing through the latest chemistry journals. Martin Hultquist had an infectious passion for chemistry and was an inspiration to the entire laboratory staff. Most of all, when your experiments failed, he was always there with an encouraging word, a story of his own tribulations, and a few good thoughts and suggestions.

Glaxo Co-workers (1966–1975). There were many co-workers in Glaxo who contributed significantly to the successes of our laboratory, pilot plant, and plant programs. The following were kindred spirits in our efforts to break out of the conventional mold and do something new and better:

Brian Clegg led our chemical engineering department and later the entire development department. His chemical engineering training, his exploratory spirit, and his judgment and leadership were vital assets during our pilot plant and plant work to prove that the diphenylmethyl (DPM) group for carboxyl protection was a safe and practical option. Brian Clegg, convinced by our laboratory data, enthusiastically endorsed scale-up of our initial process which involved handling hundreds of kilos of peracetic acid and the separate preparation of hundreds of kilos of diphenyldiazomethane (DDM). Many were nervous about the risk of a runaway reaction, or an explosive decomposition.[12] Subsequent to this work, Brian Clegg made many enormous contributions to process engineering and process safety in Glaxo over many years, most noteworthy being his work with Hans Weibel of Rosenmund AG which led to the development of better filters. Later, Brian Clegg played a vital role in Glaxo's plant engineering projects both in the United Kingdom and in Singapore.

Dr. Ted Wilson added considerable technical strengths to our Ulverston chemical process development group when he, along with Glaxo, Greenford, colleagues, Drs. Brian Laundon, and George Taylor, decided to leave Glaxo Research and join us in Ulverston. Ted Wilson demonstrated his practical creativity in his work to generate a phase transfer catalyst approach to the preparation of DDM. He defined the structural requirements in the phase transfer catalyst for the best yields of DDM. He made other notable contributions, particularly in discovering penicillin G 1(S)–oxide acetone solvate, a compound that could be produced in a very pure state. Ted Wilson's scientific leadership was recognized as an important asset in his further career development—he later went on to head the Greenford process development group, and a few years after that he moved to Bristol-Myers to take over the post I vacated!

Dr. Roy Bywood no doubt made many contributions to Glaxo's Evans Medical Division before this unit's research effort was shut down. We were fortunate to engage Roy Bywood. His persnickety, quantitative approach to organic synthesis contributed

[12]Fortunately, thanks to the work of our Gerard Gallagher and Drs. Ted Wilson and Roy Bywood, in particular, we were later able to create a process using DDM generated and consumed in situ.

much to many of our Ulverston projects, but he will be most remembered for his unraveling of the role of iodine in the oxidation of benzophenone hydrazone to DDM, a discovery that enabled us to explain previous yield vagaries and that set the DPM process on a firm foundation.

Others. There were many others in our Ulverston laboratories to whom both I and Glaxo owe debts of gratitude for their valuable contributions to laboratory and pilot plant programs. Several moved on to production roles, notably Drs. George Taylor, Brian Laundon, Jim Patterson, David Eastlick, Colin Robinson, Phil Chapman, and Mr. Chris Dealtry. One of our most effective laboratory chemists, especially on our DPM ester project, was Gerard Gallagher. I can also pay tribute to two other bachelor's degree chemists, Ray Holligan and Eric Thompson, and two with no formal chemistry qualifications, Harry Stables and Gordon Bottomley. Their practical creativity progressed many Glaxo projects. Lastly, I would be remiss in not mentioning Dr. Eric Martlew, an unsung scientist with formidable analytical skills whose passion for chromatography proved invaluable in our projects and whose willingness to test out new ideas gave us some insight into the potential for polymer-supported synthesis (see Chapter 11).

Dr. Gordon Gregory. Apart from Dr. Arthur Best, Dr. Gordon Gregory ("Greg" as he was affectionately known) was my other mentor in Glaxo—he worked in Glaxo Research in Greenford. I had previously reported to him when we both worked in Britain's Atomic Weapons Research Establishment in Aldermaston (1955–1957). In addition to our many scientific discussions, mostly about cephalosporin chemistry, Greg provided wise counsel on ways of working with the Glaxo Development group in Greenford. His insights into the personalities in Greenford was extraordinarily helpful; and his rapport with his supervisors—Dr. Joe Elks and, to a lesser extent, Dr. Tom Walker and the director of all research, Dr. B. A. Hems, FRS—undoubtedly contributed to my being a better-known quantity than might otherwise have been the case. I was a fairly frequent visitor to Greenford, which helped to create the understandings that developed, especially during the competitive phase of our PNB//DPM ester interactions. Through Greg, I was also introduced to several of Glaxo's consultants, notably the formidable Professor Derek Barton (Imperial College) and Professors E. R. H. Jones (Oxford), Maurice Stacey (Birmingham), and Malcolm Clark (Warwick). Occasionally, I was invited to selected consulting sessions. All these consultants visited us in Ulverston, lending to the credibility of science on the Ulverston site.

Bristol-Myers Co-workers (1975–1982). Scientific life in Bristol's East Syracuse Industrial Division was driven by hard-nosed practical considerations and financial realities. Chemists and engineers adapted well to being perennially on the front line in fielding process yield and product quality problems. There was, however, thanks to Bob Fildes and Dave Johnson, time to spend on ideas for process improvement under the 18-month payback rule set by Dr. Abramo Virgilio, and, as in most major organizations, there were several chemists and engineers who rose to the challenge in both Syracuse and our major manufacturing facility in Sermoneta, Italy. The enthusiastic

leadership of Drs. Bob Fildes and David Johnson created the environment enabling a few people to emerge as successful doers and leaders of important scientific/business projects.

Dr. Chester Sapino applied NMR instrumentation to the solution of intricate problems with a verve, tenacity, and brilliance that even doubters of his strategy agreed was worth pursuing, for a while. Eventually, as a result of his outstanding achievement in working out and optimizing the chemical transformation of L(+)-glutamic acid into L(−)-4-benzyloxycarbonylamino-2-hydroxybutyric acid (BHBA, the N-blocked side chain for Amikacin) in D_2O in an NMR tube, he gained the credibility needed to apply dynamic NMR, as we called it, to other major projects. Probably the most important of these was his application of NMR to the identification and characterization of the trimethylsilylcarbamate obtained by gassing bistrimethylsilyl 6-APA with CO_2 (see Chapter 7). This finding was vital in enabling Bristol to market amoxicillin in Japan.

Dr. Ettore Visibelli, as head of the process investigation and development group in Sermoneta, Italy, was the "spiritual leader" of our chemical process improvement efforts in our Italian plant. His scientific ability and leadership role seemed at times under siege in the intense rough and tumble promoted by the hard-headed leaders of this prime manufacturing location. Ettore was a major player in cost reduction efforts and played a vital role in implementing the technology transfers needed for the Sermoneta factory to meet production targets. Dr. Visibelli became the beacon for science in Sermoneta; indeed his scientific skills, coupled with his talent for diplomacy became crucial in the area of implementing the systems essential for meeting environmental regulations and liaising with government officials on environmental matters.

Glenn Johnson became the chemical engineering process automation guru for Bristol–Myers during my time there. He introduced me to the power of computer-driven process control with his pioneering work in the East Syracuse plant. His principal achievement was in creating the computer program for automating the PCl_5-mediated cleavage of penicillin V to 6-APA and the corresponding cleavage of the *N*-isobutylcarbamate of cephalosporin C to 7-ACA. This program was particularly demanding in requiring precise operation at low temperatures (−30°C) and in needing that all process steps be adapted to eliminate physical handling; thus solid PCl_5 was prepared in situ by adding chlorine to PCl_3. The same process plant was used for producing both 6-APA and 7-ACA. Because this usage raised regulatory concerns associated with the possibility of contaminating one product with another, the cleaning of the plant between campaigns was regarded as an essential part of the manufacturing process. Glenn was able to build an efficient automated process for clean-out between campaigns by simply running the entire cleavage process through the plant without using any penicillin or cephalosporin.

Others. In any appreciation of the work of a department, one can always identify many dedicated, hard-working chemists and engineers who played important roles in the department's technical achievements. Among the people who made my seven years at Bristol-Myers so successful were chemical engineers Walt Williams, Bruce Shutts, Stephen Yu, Dave Warner, and Dave Angel and chemists, Drs. Chester Sapino,

Chou Tann, Marty Cron, and Messrs. Glenn Hardcastle, Herb Silvestri, Mario Ruggeri, Nikki Rousche, Steve Brundidge, Jack Ruby, Kenny Shih, and J. S. Lin. I was later flattered to have four of these join me when I moved to Schering-Plough (see below).

In addition, there was always a good collaborative spirit between ourselves in chemical process development and fermentation process development, thanks to excellent rapport with Drs. Richard (Dick) Elander, David Lowe, and Leonardo Cappelletti.

Schering–Plough Co-workers (1982–1996). It was clear, even before I joined Schering-Plough, that the company was on a mission to revolutionize the way it did business, largely seen in the appointment of the dynamic Robert Luciano to the post of CEO. Major changes in senior management, decisions to increase funding for Research, inter alia, and decisions to lure in a new cadre of leaders augured well for the future. Mr. Luciano created an adventurous climate and urged on the subsequent progress by encouraging and inspiring employees to rise to the new challenges which inevitably developed. Many great people from the outside saw the opportunities and joined the company. Change was easier to introduce in chemical process development when Bruce Shutts, Dr. Chou Tann, Steven Yu, and Mario Ruggeri joined us from Bristol–-Myers and Dr. George Love joined us from Merck. These people, along with like-minded people already in the organization (notably Drs. Marty Steinman and Doris Schumacher and Messrs. Ray Werner and Bob Jaret), were instrumental over a relatively short time in changing the culture of our organization to one more focused on science and the fundamentals of process engineering. The latter was key. Prior to the arrival of Bruce Shutts and Steven Yu, no chemical engineers had been hired for more than 15 years—chemists (who had lower salary requirements) were believed to be perfectly satisfactory substitutes!

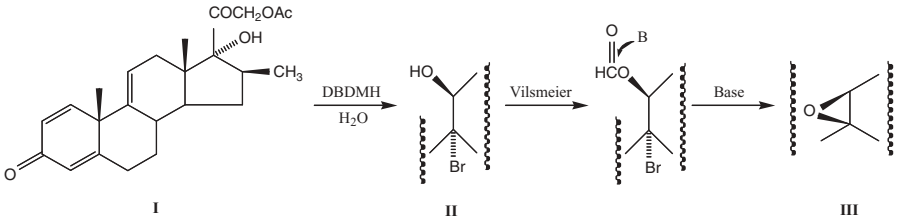
Bruce Shutts, like his supervisor at Bristol, Walt Williams, was born and raised in Pittsfield, Massachusetts, and was schooled in chemical engineering at Cornell University, New York. The Cornell chemical engineering program provides a comprehensive chemistry training as well as an excellent training in the core chemical engineering discipline. As a result, Bruce proved quite conversant in both chemistry and analytical chemistry. He quickly picked up the skills needed to run analytical instruments, notably NMR instruments, and, in the days before his managerial talents were recognized, he was frequently to be found in the laboratory carrying out the experiments needed to define a pilot plant process. This hands-on approach served him well in his dialogue with chemists and enabled him to appreciate and help them in creating processes. He used his training effectively, and often brilliantly, in the chemical engineering aspects of process development. He pioneered, within Schering, the technology of process containment and became as familiar with the nuances of operating a controlled environment room as in identifying, and spearheading, Schering's investment in process equipment wherein the plant itself served as the controlled environment room (introduction of the Kraus–Maffei Titus system to Schering—see the case study on Dilevalol Hydrochloride–Development of a Commercial Process — was entirely Bruce's brainchild). Bruce played major roles in both (a) running process

development projects for preparing APIs and (b) our programs with manufacturing (identifying process equipment needs for particular chemical reactions and aiding Puerto Rico in its programs to raise steroid process yields and reduce costs). Over time, Bruce worked hard to familiarize himself with the main Regulatory disciplines, safety, environmental and FDA regulatory affairs. Bruce Shutts became a well-rounded and adventurous engineer/scientist/manager asset and played a major role in our successes.

My almost two decades of working with **Dr. Chou-Hong ("Joe") Tann** was undoubtedly the most scientifically productive and successful period of my career. Chou Tann served with the military after graduation from university in Taiwan. He gained his doctorate from Catholic University in Washington, D.C. with Professor John Eberhardt and went on to "post-doc" with Professor Steven Gould. I hired Chou to work in our development groups in Bristol–Myers to augment our efforts to use NMR to understand the chemical transformations going on in process development work. Initially, Chou worked with Dr. Chester Sapino, his mentor and first supervisor, and raised the science of using NMR (both in process research for leads and in the development and optimization of processes) to a level well beyond anything previously achieved. Also, it was not just Chou's NMR skills in analyzing chemical reactions that set him apart. He joined my Schering-Plough chemical process development team in 1983 and quickly demonstrated a creative ability much needed both in rapidly searching for new approaches to the synthesis of Schering's new APIs and, equally important, in the revolution of long-standing manufacturing processes. Chou also proved he had a gifted approach to people selection and attracted many fine young scientists into our organization (Drs. T. K. Thiruvengadam, Xiaoyong Fu, and Junning Lee all introduced major advances in several projects). The group worked as more than just a team; in fact, it worked as a family striving to rise in the world.

Many examples of the successes of Chou Tann and his team are detailed in the following pages. His impact on the manufacturing operations of Schering-Plough, especially in Puerto Rico and Mexico, was truly immense. I can mention one contribution to manufacturing which demonstrated the value of his attention to detail and his zeal to *fully* understand what was going on in a chemical reaction.

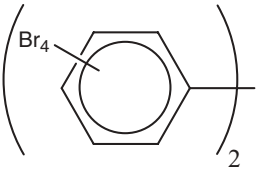
Chou had brominated steroid I with 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) to give the bromohydrin, II, which in turn was formylated (Vilsmeier reagent) and treated with base to give epoxide III:



I II III

This reaction scheme had been successfully carried out in the laboratory, giving III of high purity (ca. 99.5%). Before the process was introduced into the plant in Puerto

Rico, Chou and his team undertook a number of large-scale runs in our Union, New Jersey, pilot plant using Puerto Rico intermediate I and their new batch of DBDMH (a batch not yet used by Puerto Rico) received from our normal supplier. Chou observed, in all of the pilot plant runs, that the yield of epoxide was as expected but was puzzled by the purity number (99%), which was consistently 0.5% lower than typically found. Chou Tann and his team undertook many laboratory reactions with different lots of intermediate I, different lots of DBDMH, and different solvents in an attempt to resolve their quality finding. This led them to undertake a mass spectral analysis of the new DBDMH which revealed the presence of the fire-retardant, octabromobiphenyl (**IV**), as a trace contaminant.



IV

This very insoluble compound accumulated in product III at a low level but proved to be undetectable in the final betamethasone product. Despite this, Schering decided that no betamethasone should be made using DBDMH contaminated with IV on the grounds that polybrominated biphenyls are known to concentrate in body fat and that hexabromobiphenyl was implicated in a large-scale poisoning of dairy cattle in Michigan in 1973.[13,14] Other steroid manufacturers used this DBDMH, unaware of the contamination, and later were embarrassed into multimillion dollar recalls of their products from the marketplace. In short, Chou Tann's vigilance and high standards saved Schering from a similar fate.

Chou Tann was mostly responsible for numerous other innovations in other projects. Picking up on the trimethylsilylation approach to solubilizing aminoglycosides (see Chapter 7), Chou and his team created new processes for the selective acylation of polytrimethylsilylsisomicin and polytrimethylsilylgentamicin B which led to the current manufacturing processes for the preparation of netilmicin and isepamicin. During this work he created a valuable new formylating agent, formylmercaptobenzthiazole, a reagent that deserves wider attention. The very significant contribution he and his team made to improving Schering-Plough's steroid manufacturing operations are summarized in Chapter 9.

Chou Tann's selfless ability in encouraging his co-workers to express themselves provided the environment leading to Dr. T. K. Thiruvengadam's invention of the

[13]I had earlier encountered this probably worthy philosophy at Bristol–Myers when Joe Bomstein, our QC Director, dismissed efforts to completely segregate Kanamycin production from penicillin production with the words "If you cannot detect penicillin in Kanamycin, your test in no good!"

[14]*Sax's Dangerous Properties of Industrial Materials*, 8th edition, R. J. Lewis, Sr., Ed., Van Nostrand Reinhold, New York, 1982, p. 2830.

process for the manufacture of Schering-Plough's highly successful cholesterol absorption inhibitor, ezetimibe (see Chapter 9).

Looking back over my 43 years working in the pharmaceutical industry, I can unequivocally say that Chou Tann was the best chemical process development scientist I ever had the privilege of working with.

Ray Werner obtained his degree in chemical engineering at the New Jersey Institute of Technology and was already established when I arrived. Ray was one of our greatest assets in advising us on the way the organization worked at the time and thus became an invaluable resource in enabling us to climb out of the era of chemist domination of pilot plant operations. To his credit, Ray quickly recruited chemist and analyst help to supplement his engineering skills in creating pilot plant procedures. Our takeover of the manufacturing operations of the Union site and adaptation of the large-scale equipment would not have happened in the desired time frame without Ray's evaluations and advice. Ray continued to be a major asset and chemical engineering resource with respect to our programs in the Manufacturing Division.

Steven Yu obtained his chemical engineering training at the Massachusetts Institute of Technology and honed with it an incredible work ethic, a can-do attitude, and an ability to see how his engineering skills needed to be applied in any project. His affable and outgoing personality brought people together, even under the most harried of circumstances, qualities that promoted him into significant management roles within the chemical development organization. Steven welcomed dialogue with the many chemists who sought his advice before writing their pilot plant procedures. He was also much in demand as an evaluator of plant equipment needs for the Union, Puerto Rico, and Singapore sites. His initiatives, in seeking further education in the regulatory requirements associated with chemical and API processes, led to his becoming responsible for the Union-site manufacturing operations. Steven became an important asset in the organization as well as being recognized as a chemical engineer's engineer.

Dr. Ernst Vogel came to lead our Swiss Chemical Development Operation in Schachen, near Lucerne, with both impressive credentials (Ph.D. from ETH, Zurich, and postdoctoral experience with Professor David Evans at Caltech in California) and industrial experience working in the Vitamins Division of Hofmann LaRoche. Some would say his genes were also right. His father was a co-founder of the chemical supply house Fluka. Ernst led his organization with gentlemanly courage and enterprise and made many scientific contributions to numerous projects, especially in the areas of preparing and/or outsourcing intermediates for such as our penem, ACE inhibitor, and antifungal projects. He also played a major role in setting up the Schering Biotechnology program in Switzerland.

Ernst could always be relied on, greatly relishing adventurous projects. He was personally involved in transferring the chemistry for producing the sulfur-containing fragment of our Spirapril (ACE inhibitor) project to Schering's Mexican plant (and climbed Popocatapetl ($\sim$19,000 ft) while waiting for plant engineering modifications!). He took on new technology, in setting up plant to run a process at -80°C, when my Union colleagues got "cold feet." This equipment was then very

successfully used in carrying out a chiral hydroxylation of an olefine using a chiral dichlorocamphorylsulforyloxaziridine (discovered by Franklin Davis at Drexel and made "practical" primarily by our Dr. Dinesh Gala—see Chapter 4). Once installed, this equipment became very useful in several other projects that required low-temperature chemistry.

Ernst Vogel built on the support of several outstanding direct reports, notably by Ruedi Bolzern, his plant engineer (highly regarded, and always on top of every imaginable kind of engineering project), Dr. Ingrid Mergelsberg (an experienced chemistry "all-rounder," especially talented in techniques for producing chiral molecules), and Kurt Jost (who managed the pilot plant with impeccable thoroughness and was "ahead of the curve" in waste disposal and environmental matters).

Dr. Doris Schumacher graduated from Gettysburg College, Pennsylvania, gained her master's at Johns Hopkins, Baltimore, Maryland, and continued her further education in part-time study while working for Schering. It took her eight years, working with Professor Stan Hall at Rutgers University, New Jersey, to complete her Ph.D. Doris' career owed much to her incredible sense of purpose, towering determination, and hard work. These qualities, infused with humility, a common touch, and a willingness to pick up on the ideas of others, served her extraordinarily well during her long career, which was rewarded by scientific recognition (Presidents Award) and promotions. Doris was a wonderful role model for other aspiring people. She and her co-workers made a number of very important contributions to Schering-Plough programs. The key steps of the Schering manufacturing processes for Loratadine and Florfenicol were invented by her and her team. She showed enormous tenacity in pursuing chemical transformations she believed should work, her ultimate achievement being to demonstrate that a previously unsuccessful attempt to use Ishikawa's reagent, for the step of converting CH_2OH to CH_2F in Florfenicol manufacture, could indeed be made to work—in nearly quantitative yield (see Chapter 7).

Finally, to underline Doris' restless quest for further education, she completed a law degree at Seton Hall University, New Jersey, in 2004!

Dr. George Love brought a vital discipline, physical organic chemistry, to our organization. He studied with Professor Harold Hart, Michigan State University, for his Ph.D. and did postdoctoral work with Professor Robert Moss at Rutgers University, New Jersey. He went on to Merck and gained valuable experience in chemical process development work before joining Schering. George was one of the key figures in changing the Schering way of thinking in two key areas. One was to persuade Schering's manufacturing people in Puerto Rico and Mexico to provide theoretical yield data in addition to the weight/weight yield data they used in their accounting. This was achieved by their acquisition of purity data, especially on intermediates, enabling us to make better sense of every step in each process. George's effort, supported by the Manufacturing V.P., Jim Confroy, was no mean feat considering the expense of adding people and modern analytical instrumentation to the manufacturing site. The effort was absolutely vital in enabling us to provide a scientific basis for yield improvement, especially in the steroid manufacturing processes. The other change in the way of thinking was in the Regulatory Affairs area. George was seconded to the Regulatory Affairs Department for several months, where he acquired the insights

needed to enable Chemical Development to gain a real voice in decisions on what technical information should be included in our INDs and NDAs. On his return from this "sabbatical," his efforts enabled us to preserve some flexibility in our written submissions to the FDA, especially in submitting information on the early steps of a process. We were able later to accommodate crucial, if sometimes seemingly only minor, process changes in our operating procedures through mechanisms agreed with our regulators.

By approaching his chemical process development work from a quantitative analytical point of view, George was one of the key people, along with Chou Tann and a few others, who demonstrated that fundamental understanding of the process chemistry and identification of the impurities in every process step was essential to yield improvement. The process improvements made through these efforts, especially over the years in the steroid processes, were worth millions of dollars to the company both from yield increases and in avoiding the need for capital investment in additional processing equipment to meet the requirements of our growing steroid markets.

Dr. Junning Lee was one of several outstanding people in Dr. Chou Tann's organization, in addition to Drs. T. K. Thiruvengadam and Xiaoyong Fu. I had the opportunity to work closely with Junning Lee for about 4 years in the area of finding better chemistry for the manufacture of Ceftibuten, licensed by Schering-Plough from Shionogi (see Chapter 9). He was seconded to work directly with me and with the several other parties also involved in the project, namely, Colorado State University in Fort Collins, Antibioticos in Milan, and the Electrosynthesis Company near Buffalo, New York. Dr. Lee proved to be not only a gifted laboratory experimentalist but also superb in liaison initiatives with the other three laboratories. His scientific insights, business acumen, and ability to get the right work done at the bench level were major factors in the technical success of the project.

Although **Dr. Ashit Ganguly**, Vice President of Schering's Drug Discovery operations on the Kenilworth site, was in the research arm of the Schering-Plough Research Institute, he was an extremely important collaborator. His genius has been well-recognized in numerous awards for his many avant-garde scientific achievements. He was an organizational peer of mine but, with respect to meeting his research needs for API supplies and for chemical intermediates, my role was a subordinate one. In short we did everything possible to help him move his research programs along as rapidly as possible. We also worked closely on the chemistry aspects of a few of the projects assigned directly to development, where we played the lead role in the efforts to find a lower cost process for the manufacture of Ceftibuten. The liaison and rapport that we built with his research group was enhanced during the period when we occupied laboratories alongside those in his organisation. We benefited greatly from interactions with his people, notably Drs. Girijavallabhan (Giri), Stuart McCombie, Mike Green, Elliot Shapiro, Paul McNamara, Adrian Afonso, Vince Gullo, John Piwinski, and more. A particularly strong and invaluable rapport was also established with Dr. Ganguly's structural chemistry colleagues, specifically Dr. Birendra (Ben) Pramanik (see Case Studies—Temozolomide). Research also benefited from Chemical Development's discoveries that we freely passed on through ongoing scientific dialogue—for example, our Dr. T. K. Thiruvengadam's brilliant chiral β-lactam

synthesis (see Chapter 9). Dr. Thiruvengadam's synthesis became the vehicle through which research synthesized many new cholesterol absorption inhibitors. The team spirit was also enhanced by the several consulting professors we shared, notably Professors Sir Derek Barton, Ronald Breslow, and Paul A. Bartlett.

The close interactions between our two groups led to the acquisition of several of our best contributors from the Research organization. Before my time, these were Drs. Marty Steinman, Dick Draper, and John Jenkins, and later Drs. Shen-chun Kuo and David Andrews. One of our Development team, Dr. Nick Carruthers, even went the other way, with considerable success.

Others. Our chemical development organization was driven, in every sense of this word, by the enormous enthusiasm, commitment, and professionalism of all of our personnel. I owe a great deal to Dr. Marty Steinman, who, especially in the early days, selflessly advised me through the intricacies of the changes I needed to make. He served as a sounding board, restrained some of my excesses, and went on to demonstrate steady leadership in managing a large section of our laboratory operations. Marty later played an important role in our outsourcing mission.

Drs. Don Hou and **Nick Carruthers** joined us from Professor Paul A. Bartlett's Group in the University of California, Berkeley. Don proved diligent and creative in learning the "development trade" and made outstanding contribution to many projects. His ingenuity in identifying an avant-garde synthesis of our D_2 antagonist CNS drug (Sch 39166) and his work on enantioselective alkylation (Farnesyl Protein Transferase Inhibitor Project) provided outstanding examples of "out-of-the-box" thinking. Nick Carruthers had earlier worked for Roussel–UCLAF in the United Kingdom on penem syntheses. More than most, he demonstrated that chemistry training enables one to be comfortable undertaking chemical process discovery and development in any field of chemistry. His synthesis contributions to the transformation of 9α-hydroxyandrost-4-ene-3,17-dione into intermediates useful for Schering's manufacturing processes were particularly creative (see Chapter 9). Several of our Ph.D. chemists had a hand in our steroid process discovery and improvement programs. Notably, **Dr. Richard Draper** made many visits to Mexico City and provided valuable insight and inputs into their operations. The two who later did the most work in Mexico City were **Drs. Donal Maloney** and **David Tsai**. Donal was seconded from Schering's process R&D operation in Rathdrum, Ireland, and spent a couple of years working in our Mexican production plant before joining our chemical development organization in Union, New Jersey. Donal's chemistry and analytical inputs into the processes being run in Mexico City demonstrated the inestimable value of seconding a high-powered scientist, and especially one with production experience, to work on the ground at the plant site. David Tsai traveled numerous times to Mexico City and became a respected visitor who, like Dr. Maloney, did much to bring new chemistry, new analytical techniques, and better process understanding to the site. These efforts enabled us to make rational changes to the plant processes. As a result of this work and the efforts of all the support people on the Mexico City site, process yields improved and product costs declined substantially over the years.

There were others who contributed greatly to our programs to improve plant steroid processes. **Dr. Xiaoyong Fu**, in collaboration with Drs. Chou Tann, **T. K. Thiruvengadam** (T.K. for short) and **Junning Lee**, was one of the principal architects in our successful introduction of our new process for "dehydrating" 11α-hydroxysteroids to $\Delta^{9,11}$-steroids (see Chapter 9). T.K. proved to be very special and one of our most gifted scientists from the very beginning when Chou Tann recruited him into his group. Although T.K's lovely exploitation of the Passerini reaction, to create albuterol, never did take off his brilliantly successful ezetimibe synthesis did (see Chapter 9). T.K. made many other contributions—for example, to Schering's aminoglycoside processes. **Anantha Sudhakar**, who is not just another Ph.D., demonstrated extraordinary creativity in utilizing allene chemistry in two of our projects, one to establish 9α-hydroxyandrost-4-ene-3,17-dione as a starting material for Schering's anti-inflammatory steroids (see Chapter 9), and the other in our highly successful program to create a manufacturing process for the chiral left hand fragment of Schering's superior new antifungal, Posaconazole (see **Scheme 1** in Chapter 8). When I graduated (retired), it was clear that Anantha's accomplishments and talents would lead him on to greater things. Also in this category was **Dr. George Wu**, whose highly creative chemistry and irrepressible enthusiasm bore fruit in several synthesis challenges, particularly in Schering's florfenicol and farnesyl protein transfer inhibitor projects. In the latter, his creative use of a variant of the Heck reaction (converting a 2-bromopyridine to a carboxyanilide with CO and aniline in the presence of a Pd catalyst) led to a highly efficient commercial process. **Dr. Dinesh Gala** broke new ground for us on many projects, with the chiral hydroxylation of olefins at very low temperature being one of the most memorable. Dinesh was one of the few who made time to write papers and publish his work. (The problem is partly, if not mostly, of management's making, resulting from pressing people to move on quickly from one "completed" project to a new one.) Bill Leong should be mentioned along with Junning Lee, for their efforts within the American Chemical Society, New Jersey local section, and the Sino-American chemistry society, respectively, to promote the profession of chemistry on the larger stage outside the internal activities of their employer.

We were fortunate in employing many very talented, hard-working bachelor's and master's degree chemists without whom we could not have succeeded. **Bob Jaret**, despite being labeled early on as "outspoken," was recognized rather late in his career as a person with a considerable grasp of the broad requirements needed to synthesise an API. He came into his own when we promoted him to lead our pilot plant operation. Bob had a practical "bottom line" vision as well as a great appreciation of the people needs in organizing the work of engineering and implementing a chemical process on a pilot plant scale. He became a valuable asset, and the flow of APIs from his pilot plant was testimony to his leadership. **Lou Herczeg** blossomed as a chemist working in George Love's group. He quickly picked up on George's fervor for process understanding: One outstanding achievement was his isolation, identification, and quantification of all the impurities produced in manufacturing the final steroid intermediate produced in our Mexico City plant. He was a frequent visitor to Mexico, greatly aiding their process improvement efforts—he survived the 1986

Mexico City earthquake with vivid memories of the walls of his hotel cracking open! Lou later used his acquired knowledge and skills to take on the task of writing our Development Reports (essential for our interactions with the FDA). **Mario Ruggeri**, with his Sicilian flair, perfectly mirrored the picture of Mt. Etna on his office wall. He was seconded to our manufacturing plant in Puerto Rico, where he worked long hours to introduce them to the routine use of HPLC to gather the fundamental information needed for process control and improvement. I personally appreciated the work Mario did to lay the groundwork for later successes. I also remember him for his incredible tomato plants, which grew over the roof of his Puerto Rico house but set no fruit! We lost an enthusiastic chemist and a great character when he was headhunted away to manage the plant of a generic penicillins manufacturer in Columbia, Maryland.

There were many, many more bachelor's/master's chemists deserving of thanks. **Richard Rausser** (el barrelito, as he was referred to in Mexico City), **Pete Tahbaz** (who, it seemed, could do anything), **Tim McAllister**, **John Chiu**, **John Clark**, **Michael Green** (all quiet, reliable, technically accomplished, hard-working doers), **Cesar Colon**, **Kim Belsky**, **Jan Mas**, **Bruce Murphy**, **Gene Vater**, and on and on. One person deserving special mention is **Alan Miller**, who worked with passion and energy in pilot plant scale-up. His motto is "If you enjoy what you do you never need to work!" In regard to environmental matters, our operations were fortunate to be in the hands of our most experienced chemical engineer, **Bob Emery**. Environmental Compliance became more difficult with time, and we came to be dependent on the competent, conscientious, and exacting **Liz Dirnfeld** to keep us "clean."

Our process safety people, notably **Dr. Rick Kwasny** and **Messrs. Joe Buckley**, **Bob Giusto**, **Howard Camp**, and **Jay Marino**, proved wise and dedicated professionals who thoroughly educated us in calorimetry, the tests to run, and the practices to adopt to ensure we met the requirements for safe operation.

Our successes owed much to the rigor of the analysts in our chemical development analytical team who worked vigorously and tirelessly to ensure we met the set quality standards and who worked collaboratively to resolve issues. Their responsiveness at times seemed superhuman. I particularly recall **Paul Sandor**, **Robert Strack**, and **Paul Johnston**, who in turn relied on the dedication of co-workers including **Fred Roberts**, **Alicia Duran-Capece**, **Jian Ning**, and others. In the larger analytical context, our colleagues in the separate, core analytical department were true colleagues in their enormous efforts to help progress our projects—**Gene McGonigle**, **Nick DeAngelis**, **Van Rief**, **Don Chambers**, and **Caesar Snodgrass Pilla**, to name only a few. Their commitment and involvement were essential to our progress.

Our biotransformation group (**Drs. David Dodds**, **Alex Zaks**, and **Brian Morgan**) contributed to most of our chiral synthesis projects, although in most cases enzyme-based routes were not selected over chiral induction or classical resolution processes for the short-term needs in API synthesis. This area, however, remains one of huge promise with the prospect of working in water being one of its most appealing attractions.

The quality and professionalism of our large-scale work improved significantly through the hiring of several gifted engineers, **Bruce Shutts**, **Steve Yu**, **Al DiSalvio**, **Noel Dinan**, **"Perry" Lagonikos**, **Joe Cerami**, **Vince Djuhadi**, **Andy Ye**, and, later,

Guy Gloor and **Anthony Toto**, to add to the able hard-pressed people already in the organization, **Bob Emery**, **Ray Werner**, **Don Beiner**, **Lydia Peer**, and **Ron DeVelde**, conscientiously assisted by a chemist-turned-engineer, **Stan Rosenhouse**. One of our big plusses was our employment of an electrical engineer, **Tom Brennan**, who proved to be an invaluable asset in many projects. Successful operation of our pilot plants and large-scale plant depended on our forepersons (notably **John Junio**, **Ed Coleman**, **Al Regenye**, **Dan Simonet**, and **Al Winkelman**) and operators. Good operators are well-trained, experienced, proactive and reliable. They show a shrewd understanding of plant equipment and often ran a procedure on the knife edge of operability with the critical eye needed to improve it. Good operators never allow stressed equipment to become a problem. They behave as if they were owners, developing an instinct for what looks, sounds, feels, and smells like normal. They continually involve others in getting things right and, as needs change, which in a development situation is all the time, they are the people who adapt, learn, and do. They briefly mourn the loss of failed projects and generate the enthusiasm and drive to move on to new challenges. There were dozens of process operators and support people on whom successful operation depended. I talked to many of them fairly regularly in the course of "rounds" of our facilities and in reviewing projects on the "shop floor." All appreciated being appreciated! A few I can recall, many years later, are **Al White**, **Khalif Rashid**, **Elvie Cooper**, **Bill Hood**, **Bill Fee**, **Dan Coakley**, **Lewis Balcom**, **Al Fiers**, **George Dietrich**, **Henry Hill**, **Steve Zimenoff**, **John Czerwinski**, and our diligent maintenance leader **Tony Meyer** and his assistant **Pete Ruffo**.

The entire operation of a plant is dependent on the supply and warehousing of chemicals. Here the dedication of talented professionals (**Jeff Samuel** and **Jenny Dong**) provided a vital service in ensuring the timely delivery of quality materials. For the warehousing and stringent documentation covering receipt, storage, and distribution, we were fortunate to be in the hands of **Dennis Von Linden** and his staff.

No people acknowledgment would be complete without paying tribute to the enormously talented and well-organized administrative assistants I relied on, especially in my Schering years, to ensure that the organization ran smoothly. They were called secretaries, but they took on a much more proactive guidance role, beyond the routine definition of secretary. Those who had the greatest impact, over many years, were **Elaine Piete**, **Janet LaMorte**, **Gina Alcaide, Lavonne Wheeler**, and **Kathy Torpey**.

On the larger stage, our interactions with the Schering manufacturing organization were strongly supported by **John Nine**, President of Worldwide Manufacturing, and his vice presidents, **Jim Confroy** and **Michael Monroe**. They enthusiastically encouraged our collegial rapport with the technical movers and shakers in all their major manufacturing plants in Rathdrum, Ireland, in Mexico City, in Manati, Puerto Rico, and, later, in Singapore.

Of all the technical people in manufacturing, the greatest concentration of talent was in our Rathdrum, Ireland, facility. **Drs. Brian Brady**, **Henry Doran**, and **Maurice Fitzgerald** provided an enthusiastic and extraordinarily creative technical

resource. Their practical genius enabled them to design manufacturing processes that were simple, efficient, productive, and economical. It was essentially their chlorpheniramine process which convinced Schering that purchase of their originally tiny company was a good investment—and it was. During our 15 years of close association with them—including the frequent visits of people, both ways, to promote practical chemistry and technology transfer—we made tremendous progress in all the projects we handled together. Their "chemistry" (between people as well as at the bench and in the pilot plant) had a practical elegance that had a major impact both on their own processes and on manufacturing scale operations all over the Schering organization, notably in Singapore. Brian Brady was the consummate leader—he had grown up, as I had, exceeding the offerings of his home chemistry set, carrying out experiments such as the spectacular Thermit reaction in his own back garden. Because he was given responsibility for the Analytical/QC function, as well as the chemistry R&D function, he harnessed the combination to the benefit of Rathdrum synthesis programs as well as in the exquisite resolution of many impurity problems. Henry Doran possessed a nearly incandescent practical creativity and needed Brian to temper the ardor of his fertile mind—he had wonderful and invaluable insights in process chemistry and was an engaging companion in discussing chemistry anywhere.[15] Maurice Fitzgerald was one who just got on with the business of chemistry. He was quite the reverse of Henry in demeanor but no less a powerful practical chemist whose incredible persistence wrung chemical processes out of the most unyielding situations. In broad terms the Irish group was one of exuberant creativity which employed an abundance of great characters. **Tony Smith** was the affable general manager for many years and magically overcame his English heritage in being embraced as a virtual Irishman. **Stephen Barrett**, whose other passion was sporting dogs, took over on Tony's retirement. **Conor O'Brien** was their marvelously crusty and colorful purchasing manager, as well as a collector of Irish silver.

My only regret with the Irish was that I did not get them involved sooner in polishing Chou Tann's Albuterol process. If the Irish sodium borohydride process for the final triple reduction step (see Chapter 5) had been proved earlier, Albuterol would be being produced today using it. We wasted too much time expecting a third party to come through employing the original reduction using borane-dimethylsulfide, such that both process justification and momentum were lost. It was my failure. I also wish that more of the work of the Irish had been published. For one, Professor Lawesson would have been delighted that his quirky reagent (for converting –CO to –CS) had actually been adopted by Rathdrum on a commercial scale!

Puerto Rico was, culturally, quite different and, although the production support scientists and engineers did not have the entrepreneurial spirit of the Irish, given our technical support and the enthusiastic encouragement of their Polish-American leader, **Rich Murawski**, they played a large part in helping us to introduce better technology. In particular, Puerto Rico was Chou Tann's "field of dreams," where he and his staff, working with Puerto Ricans **Dr. Yvonne Lassalle**, **Ms. Iliana**

[15]I recall our last uproarious dinner at my house before I "graduated" when Henry consumed more than anyone else of five Grand Cru Bordeaux's. At the end he was found drinking the last of the bottle, heavy tannins and all, of a memorable 1989 Chateau Figeac, or was it the 1990 Lynch Bages, or . . .?

Quinones, and **Messrs. Luis Rios**, **Luis Gil**, and **Kenny Llaurador**, broke new ground in both aminoglycoside and steroid projects. Our interaction with our plant in Mexico City was probably the most intense. **Ing. Miguel Escobar**, our Mexico City general manager, persuaded his own senior management and ourselves that their process issues needed urgent attention. This began a long and fruitful period of collaboration, some of which is outlined under "Excursions in Steroid Chemistry." The Mexico City plant did, indeed, have much to contend with. Quite apart from chemistry/engineering issues, our nervous corporate security people worked with Miguel Escobar to avoid his being kidnapped, and they made draconian changes to the security system after payroll robbers, armed with a machine gun, broke into the factory at a time he was not there. Despite his heavy administrative duties, especially in finding, hiring, and keeping staff to support his core of long-serving people and dealing with the trade unions, Miguel Escobar made a special point of being involved in our technical discussions whenever he could. Of his technical staff, two stood out: **Dr. Gilda Morales**, for her outstanding technical abilities, and **Mr. Sergio Sanchez**, who proved to be a reliable, always-interested contributor over many years. But it was Miguel Escobar's grasp of the ever-changing global nature of the steroid raw material supply situation and his constant effort and pressure to create safe processes, and to secure cost reduction, year after year, which became his greatest legacy to Schering.

Consultants. The value of consultants can sometimes be difficult to quantify. To me they were an indispensable component of our organization. It was not just their analyses of our process strategies, their contribution of ideas or critiques, or their ability to refer us to literature which we might not have seen, but it was also the stimulus that outside minds, with none of the inside "baggage," provided which lifted us to contribute at a higher level.

Over the years we benefited from visits by many consultants, but it was the Professors I referred to as the three great B's of our chemistry who stimulated us the most. These were **Professors Paul A. Bartlett** (University of California, Berkeley), **Professor Sir Derek H. R. Barton** (Imperial College, London, and Texas A&M, State College), and **Professor Ronald Breslow** (Columbia University, New York). They each brought different qualities to aid us in our work.

We interacted with Professor Bartlett both at the time of his visits and whenever we needed to follow up on any problem with any of the projects under discussion with him. He worked with us through a preset agenda and written progress reports that we sent to him prior to his visits. He wrote detailed reports on our projects and his ideas following his visits. His modus operandi created a disciplined structure for our engagements with him and made all his visits extraordinarily successful. Anecdotally, the success of many of his avant-garde ideas reflected a risk-taking creative style that was evident both in his own research and in the adventurous sky-diving/hang-gliding activities in his leisure life! Professor Sir Derek Barton was of altogether a different stripe. Our scientists were in awe[16] of his enormous intellect—he invariably could

[16]When I worked in Glaxo, awe was more like dread. Especially after he won his Nobel prize, many saw him as tyrannical, especially if they inadvertently erred in presentation and explanations of their chemistry.

offer several solutions to synthesis problems to our one, and he would refer you to papers, authors, dates, and once even a page number from his stupendous memory bank. In his later years he was a delight to work with, but the chemists coming to our consulting sessions had usually "burned the midnight oil" to ensure that all their data were "bulletproof" and that they were prepared to answer deep and searching questions. There was no doubt that Sir Derek "raised the level of the game" of everyone who worked with him.

Professor Ronald Breslow's vast knowledge of steroid chemistry, and natural products in general, coupled with extensive experience in consulting with totally different industries (such as General Motors), brought a perspective to our consultations with him which was without equal. His flair for the practical aspects of synthesis and his appreciation of the accommodations needed to meet the requirements of impacting disciplines (pharmaceutical sciences, safety, engineering, etc.) enhanced his comment and suggestions. The many years he worked with us were testimony to the enormous value of his consulting visits.

Over my many years in the chemical process development "business," I encountered several invaluable consultants. Notable were those in Glaxo (in addition to Sir Derek)—Professors ERH Jones (Oxford University), Maurice Stacey (Birmingham University), and Dr. (later Professor) Richard Stoodley (Newcastle University and University of Manchester Institute of Science and Technology). The latter visited us more in a lecturing capacity but was always scrupulously careful in what he said about penicillin chemistry since he also consulted for Glaxo's then arch rival, Beecham.

We first benefited from consultations with Professor Paul A. Bartlett at Bristol-Myers and were fortunate to engage him to consult with us in Schering. Another consultant of note at Schering, in addition to the three great B's, was Professor Jerry Meinwald (Cornell University), who brought an enthusiasm and a sense of joy to his and our chemistry. Although not everyone I encountered believed in the merit of engaging consultants, I have no doubt that our own track record of process discovery and the rate of progress of our projects was enormously enhanced by their presence.

Awards. The recognition, appreciation, and advancement of people is one of the most important activities in a successful organization. Intelligent people know their strengths, weaknesses, and desires and recognize that everyone cannot reach the very top. However, they need to see that those who do reach the top are worthy of the position. They also need to see that there are many "tops," other than the very top, which they can aspire to reach. Periodic (usually annual) salary increases provide only one way of recognition and appreciation. They often follow difficult (and occasionally debasing) performance appraisals. Top companies usually attract top people who have never suffered the indignities that go with comparison with similar peers. For this reason, top companies understand that performance appraisal and salary increases must be only one of many ways of recognizing talent. Nor

Later, when he came to consult with us at Schering, post his time at Gif-sur-Yvette, he had mellowed considerably. Over a luncheon one time, he even shared with Dr. Ganguly and me that "Glaxo was the only company that ever fired me!"

is a performance appraisal system, usually an annual event, adequate to account for a whole year's work. Great leaders make performance appraisal a continuum and build other systems to recognize and appreciate what all of their people do. A caring approach by leaders for the welfare of their co-workers needs to be created. This may be through first-name greetings, periodic walk-abouts, thanks for jobs well done at project reviews or in meetings, and so on. Knowing the people and people knowing their leaders is an essential part of good management. If your people understand the reasons for company difficulties, as well as successes, they better accommodate the realities of company life for themselves. Open communications (perhaps including through a company newspaper) make people aware of reasons for company restraint (thereby avoiding the appearance of stinginess, or, in the unfortunate case of layoffs, giving the company a draconian hard-nosed image). Whenever possible, in good times and bad, companies should be continually striving (and to be seen as doing so) to promote other dimensions and definitions of "top" in order to recognize and reward the people whose work will take the company out of a bad position or raise the prospects for enhanced company performance—at all levels.

In the scientific/engineering arena, encouraging publication and the presentation of papers at professional meetings promotes a good image of the company and enhances the prestige of individuals. Such an exercise may make an employee as valuable to the outside as he/she is within the company, thereby making it even more important that the company recognize individual talent. Awards and a technical ladder of promotion help to meet the needs and create a good image of the company.

Dr. Ganguly established a President's Award to recognize outstanding achievements in his drug discovery organization, and we defined an equivalent award for all of Development, including analytical development, biotechnology development, chemical development, and pharmaceutical development.

In brief, the President's Award for Development was created to recognize outstanding achievements (by individuals or a team) in the discovery and development of innovations that measurably contributed to the advancement of company projects and business.

A committee of three expert reviewers, drawn from the above development areas, supplemented by one reviewer each from drug discovery and research administration, was set up to judge the submissions. Most of the reviewers were vice presidents.

Guidelines were created and published for the use of potential candidates who were made aware that successful submissions would be for exceptionally creative and meritorious, as well as complete, pieces of work that were beyond normal performance expectations. The criteria used for judgment were based on creativity, novelty, value, the difficulties faced and overcome, and the level of cooperation evident in advancing the achievement.

Candidates were required to provide perspective with a review of the problem (including an analysis of competing situations and literature references). The novel solution of the problem had to be shown to be truly innovative (and probably patentable—see Chapter 7—or publishable in a major journal). The weighting given to innovation was generally 35–40% of the total score.

The innovation also had to be shown to be of significant value to the company. The weighting given to value was set at 30–35%, with novelty and value together comprising 70% of the total score.

The magnitude of the technical challenge overcome had to be convincingly demonstrated. This element was given a weighting of 20%.

The remaining 10% of the score was given for participative openness in the advancement of the project.

All four categories above were scored by the "expert reviewers" on a 1–5 basis:

Acceptable	Fair	Adequate	Good	Very Good	Excellent	Outstanding
1.0–2.0	2.0–2.5	2.5–3.0	3.0–3.5	3.5–4.0	4.0–4.5	4.5–5.0

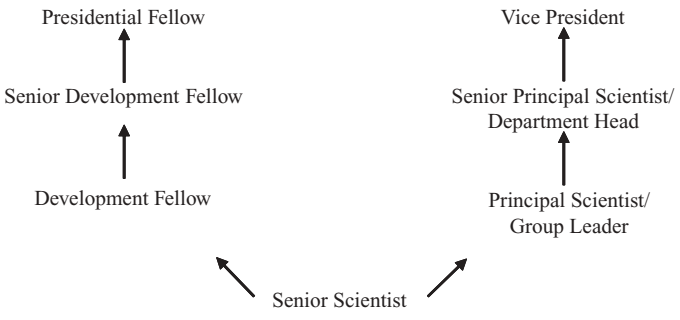
Addition of the scores, corrected for weightings, gave a final score in the 1–5 range.

Generally, our evaluations only awarded those with scores exceeding 4.0. This was because a separate award, called the Impact Award, could be given if a more senior person or champion of the project could make a case that the submission was worthy of a separate, albeit lesser, award. No one could be given both awards.

It was recognized that some employees would regard the President's Award as somewhat elitist, open to relatively few. On these grounds the Impact Award gained wider significance being open to all personnel. In practice, nominations were generally submitted through lower-level supervisors on behalf of the submitters, though self-nomination was also permitted. Every effort was made to avoid trivialization of Impact Awards.

Awards may also be given to employees who obtain patents from which the company benefits financially—such recognition is often long after the President's or Impact Awards have been made.

Promotions. It seems obvious that some scientists/engineers are not suited to, or not interested in, taking on a management role. In order to recognize the importance of significantly creative individuals, many companies have developed a ladder of promotion parallel to that leading to the vice presidential rank. This may be along the lines of the following:

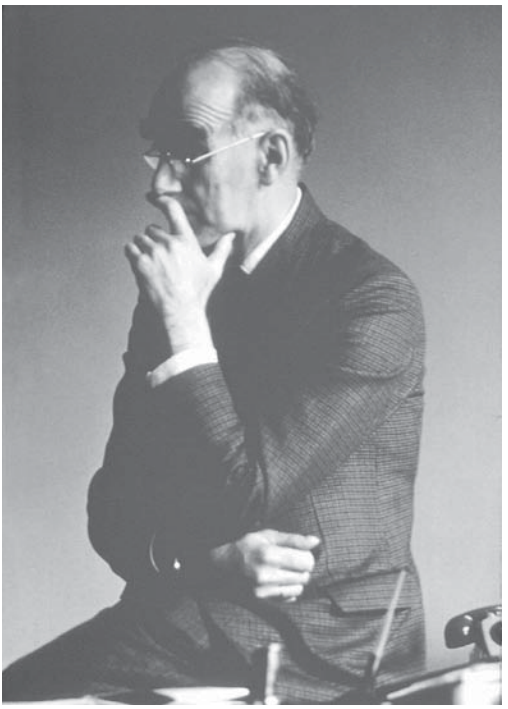


As with all organizations, rising to more exalted positions is not necessarily permanent. One's standing in all positions has to be earned. Thus a Development Fellow needs to demonstrate, year after year, a sustained level of scientific/engineering performance in terms of innovation and the implementation of innovation. The higher the position, the higher the bar. A presidential Fellow, for example, would have to be well-recognized outside the company, both in industry and academia, as well as within it, for his/her technical achievements, thereby earning national/international standing.

Put simply, people are everything in any organization. They provide the leadership, the character, the vision, the technical innovations, and the day-to-day effort necessary for the discovery, development, and progression of an organization's mission. In the chemical process development field people create the collaborative mechanisms needed to bring together the various disciplines required to effectively advance science and technology into plant operation. People express the social concerns needed to meet and exceed the standards set by regulatory authorities (in safety, environment and FDA regulatory affairs). People, through their achievements, gain personal satisfaction and recognition. People also recognize for themselves the vital importance of continuing education in order to stay "at the top of their game."

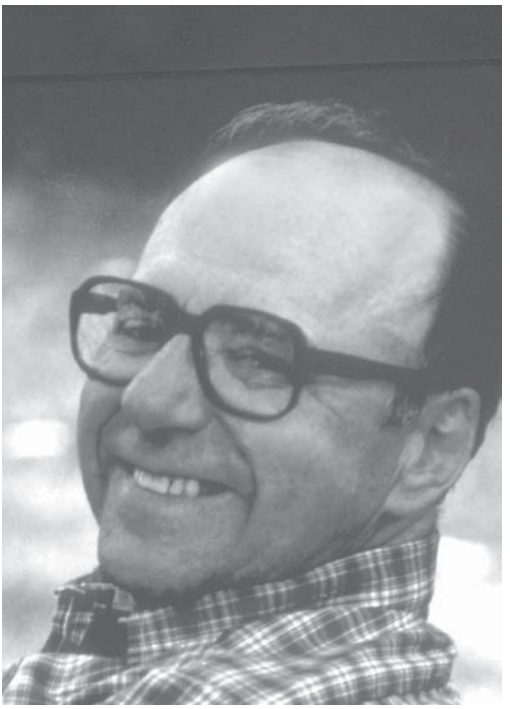
My abiding memories spring from the richness of the people component of the companies I have worked in, as well as from recollection of the many chemistry/engineering successes we created over the years. It is a source of reassurance for the future to realize how technically oriented people from all over the world can come together to produce solutions to problems and implement them in all manner of settings.

Drs. Tom and Richard Waugh with engineer Oscar Jacobsen

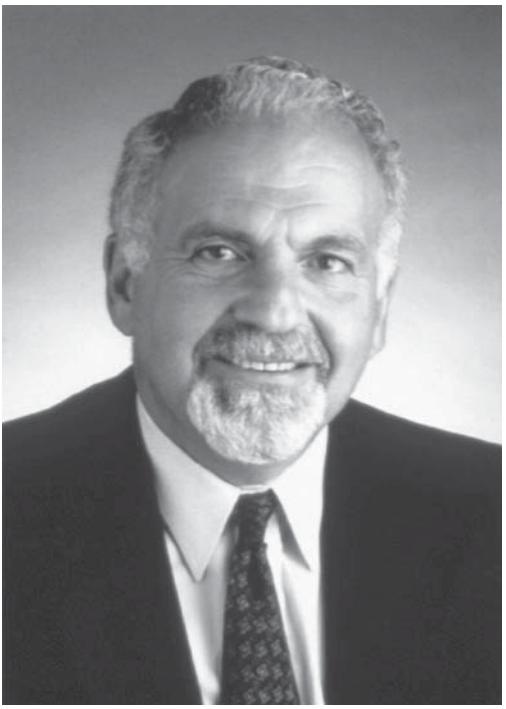


Dr. Arthur Best

Dr. Robert A. Fildes



Dr. David Johnson



Dr. Hal Wolkoff

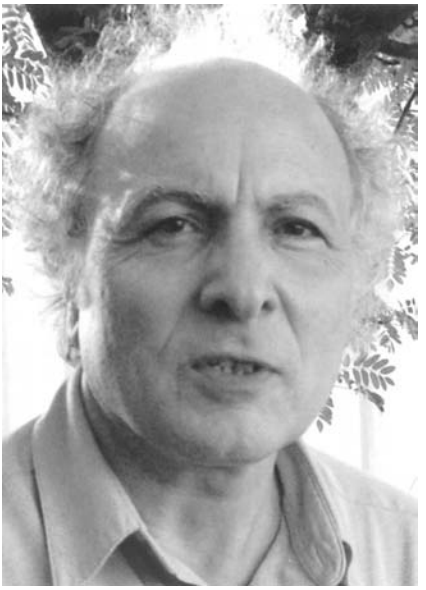
Dr. Martin Hultquist

Dr. Chou-Hong Tann

Engineer Brian Clegg

Dr. Ted Wilson

Dr. Ettore Visibelli



Mario Ruggeri

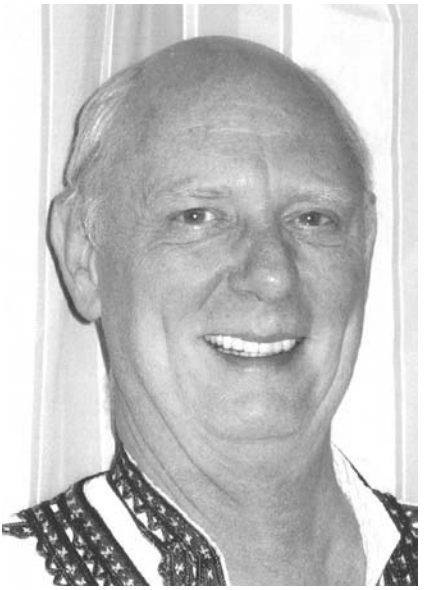
Engineer Bruce Shutts

Engineer Steven Yu

Engineer Ray Werner

Dr. Martin Steinman

Dr. Ernst Vogel



Dr. George Love

Dr. Doris Schumacher

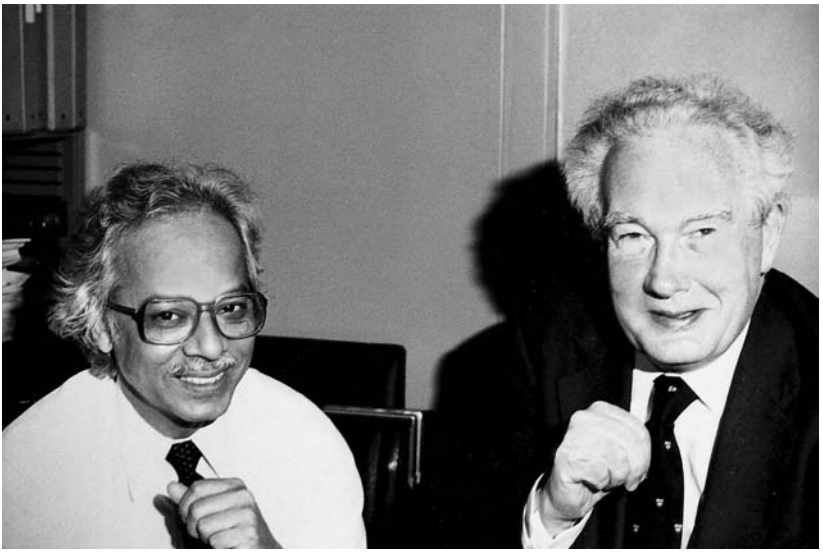
Dr. Junning Lee

Dr. T. K. Thiruvengadam

Dr. Birendra Pramanik

Dr. Brian Brady

Ingeniero Miguel Escobar



Dr. Ashit Ganguly with Professor Sir Derek Barton

Autographed British Postage stamp honouring Nobel Laureate, Professor Derek Barton

3

ORGANIZATION

A formal people structure is needed to effectively create, implement and continually update collective strategies and tactics in pursuit of a mission.

INTRODUCTION

Organizations are assembled from diverse human resources to achieve defined missions through orderly action plans. In industry, organizations and their people are generally in perpetual competition with others in their effort to "create profit." They strive to find pathways to distinguish themselves from competitors in the expectation of generating opportunities for company and personal growth within the social system. Robert Frost eloquently illuminated opportunities for distinction in his poem "The Road Not Taken," which ends:

Two roads diverged in a wood, and I —
I took the one less traveled by,
And that has made all the difference.

Although Frost's words crystallize the spirit of adventure, in encouraging a journey by a less-traveled route, they do not speak to the possibility of encountering setbacks. Thus the adventurer may, later, need to deal with the unexpected by products of his/her adventurous spirit. President John F. Kennedy, in the 1960s, recognized the issue with words to the effect that when you scientists invent something new, I have to invent a way of dealing with it. In short, organizations built to create something new

The Management of Chemical Process Development in the Pharmaceutical Industry by Derek Walker
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seldom deal with all the consequences of their actions. As a result, and perennially lagging behind, they have to address the need to continually retool their organizations to try to meet the overall needs. In this way, responsible organizations react to their failings and work to accommodate a broader (including social) approach in their organizational thinking. Thus organizations, like people, continually evolve in order to stay alive and prosper. Unfortunately, in recent years, pharmaceutical organizations in general seem to have lost their way in addressing social (public) setbacks.

Organizations undertaking drug discovery, development, and marketing are often taken for granted as sources of cures for illnesses. As a result, the general public mostly forms its impressions of pharmaceutical organizations not through the valuable contributions the discovery and development components make to treating and curing disease, but through the more visible marketing component (the major player in setting drug prices) and associated media and stock market analyst attention. The United States media, for instance, pays disproportionate attention to United States drug price differentials versus other countries, to market withdrawals due to adverse medical revelations, to aggressive drug company advertising, to alleged bribes and shady financial practices, to large payouts to failed executives, and so on. Most of the good works in terms of discovering life-saving drugs, in extending and improving the quality of life through drugs, in reducing costs by reducing patient time in hospitals, in donating drugs at times of world crises, in making orphan drugs available, in doing everything reasonable to minimize animal testing, and in sponsoring educational, arts, and social programs, and so on, are suppressed by the cacophony of adverse publicity.

Although pharmaceutical organizations are not blameless, the media and stock market analysts share in the responsibility for the poor image of pharmaceutical organizations. For instance, all three seem to conspire in creating all too frequent public statements on research findings that can skew the merits and gloss over the uncertainties in drug research and development. The quarterly reporting of progress for stock market analysts seems much too aggressive for a complex industry that advances only slowly. Some calming in the frenzy for information (affecting stock prices, inter alia), as well as curbing marketing excesses, would seem in order to allow pharmaceutical organizations time to rethink, retool, and reconfigure the many components that go into creating a new drug and pricing it for the marketplace. Without such time to build a coherent position and to harmonize ideas on how drug research and development should be funded in the world as a whole, pharmaceutical organizations will remain on the knife-edge of credibility risking government price controls. Price controls will only curtail the expensive wide-ranging research spirit of inquiry, which is the cornerstone of future success, and is needed to enable the knowledge societies to advance at a harmonious rate, at the same time as adapting their systems to accommodate a changing world and the emergence of new knowledge societies.

In general, pharmaceutical organizations and the Pharmaceutical Research and Manufacturers Association (PhRMA) do an unconvincing public relations job in providing believable explanations of their activities—in particular, why it is so difficult (expensive) to discover new drugs, why it takes so long to bring new drugs to the

marketplace, why better drugs reduce overall treatment costs, and what goes into making drugs so relatively costly. To compound their problems, pharmaceutical organizations often seem flat-footed in responding to criticism, such as in countering suggestions that they may be covering up adverse information on their drugs. Unfortunately, the public perception of the pharmaceutical industry is not unlike that of some of the disciplines, certainly the chemistry discipline, that are needed to produce new drugs. Chemistry, for instance, also has a poor image in the eyes of the public, often being seen as spawning an industry that is dirty, odorous, dangerous, and environmentally harmful. To digress further, chemistry is also seen as a difficult subject in which to gain a university degree. Small wonder that the number of young people in Western countries wishing to pursue a career in chemistry has proportionately declined over the decades and that funds are presently not there to support university chemistry departments, leading to a few chemistry departments being closed in the United Kingdom.

Recent signs are more encouraging as Chemical Societies, individuals, and industrial companies work to publicize the vital importance of the sciences to civilization and particularly how important science is to the economic life of the advanced (developed) nations. Much of this appears in learned journals and scientific society magazines. Efforts to reach out to the public through the mainstream media seem to be increasing,[1] but scientific organizations and industrial companies still have much to do to help those at the interface with the public rebuild the valued image they once had. Fortunately, the organizational crisis at the marketing interface with the public is virtually absent at the Discovery/Development level. There is therefore plenty of opportunity for pharmaceutical organizations to improve their image.

Therapeutic Teams and the Chemical Development Role

In contrast with the turbulence at the top of pharmaceutical organizations, the organizational situations at the Research and Development level are challenging in a different way. In Research and Development the task is to build a team of organizations that can work together to meet the requirements for successful drug discovery and development. The chemical development organization is usually considered to be a part of the Research drug discovery organization, although it can also work as part of a forward-thinking Manufacturing organization provided that Manufacturing can ensure dedicated, enterprising, visionary, collaborative, and supportive leadership.

The discovery and early development of APIs is handled in a variety of ways by pharmaceutical companies. This presentation is limited to describing a Research organizational structure I have worked in and which continues to work well. The most important element in making drug discovery and development effective is to have visionary open-minded people in the important leadership roles, especially from the discovery point of view, and in the conceptual areas (also involving marketing, and a business development organization assiduously screening third-party prospects).

[1]For example, the *New York Times* Tuesday Science Section and BBC and American TV programs of the Discovery type.

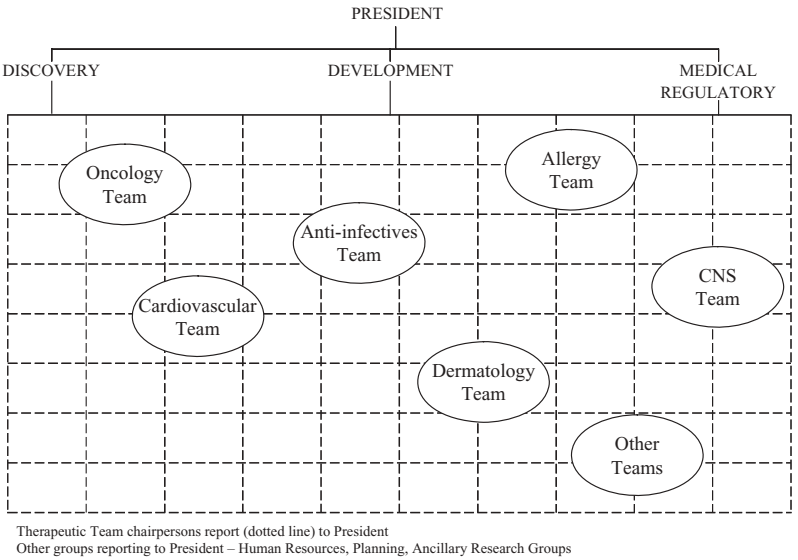


FIGURE 1. Matrix organization for the drug discovery and development process.

Chemical process development's early role is usually to provide quality API as rapidly as possible, often using the research department chemical methodology (the *Recipe*) for the earliest supplies.

In most major pharmaceutical organizations, Therapeutic Teams are created to shepherd the discovery and development process. Each of these Teams is responsible for a given therapeutic area—for example, anti-infectives, cardiovascular, oncology, and so on. Each Team creates a mission statement to formalize its objectives. To meet its objectives, each Team draws its pertinent human and physical resources from the Research line organizations, Discovery, Development, and Medical. The people drawn from the line organizations are those with full authority to speak for their particular discipline. Therapeutic Team leaders are generally experts in the field they lead, and they are of high standing (e.g., Vice Presidents) in the overall organization. A representation of such an organizational structure is provided in Figure 1.

It will be clear that conflicts of resource availability and utilization will occur. Conflict resolution and overall guidance of the various Therapeutic Team programs is handled by a committee of the most senior executives in the research organisation, if conflicts cannot be resolved at a lower level.

The Drug Discovery, Medical, and Development organizations incorporate the usual interacting disciplines needed to meet their objectives. Drug Discovery incorporates chemists, biochemists, microbiologists, structural analysts, drug metabolism scientists, and toxicologists. Medical incorporates physicians, FDA regulatory affairs (mixed disciplines), drug safety specialists, statisticians, and medical writers. Drug Development incorporates biotechnologists, microbiologists, biochemical engineers, chemists, chemical engineers, pharmacists, pharmaceutical engineers, and analytical

chemists (QC). Numerous other disciplines are intended to be included—for example, virologists, geneticists, bioethicists, computer scientists, QA, and crystallographers, inter alia. Legal, human resource, finance, business, and other administration disciplines are also incorporated, as needed, in setting up and running Team programs.

To ensure the broadest reach, Therapeutic Team members are also generally coopted from the Marketing and Business Development organizations. They also draw members from company International divisions to provide world perspective. The Team organizations can only be effective with the very best people in leadership roles and the very best people from the line organizations to do the work, all collaborating and coordinating with each other to move programs along in an agreed time frame.

As indicated, the Chemical Development organization provides the APIs for Therapeutic Team programs. Once some credibility regarding the value of a drug lead is established (this can often take many years—more than 10 years in the case of Schering–Plough's Loratadine), programs are projected by the Team to provide some kind of order enabling contributing parties to properly plan their inputs. It is recognized that no program can be definitely spelled out; all depends on the issues encountered as each information gathering phase progresses. An indefinite drug development program, outlining the major activities, is sketched out in Figure 2. It will be appreciated that since so many activities are going on at once, a setback in any activity will slow (or even terminate) any program.

The timing of Chemical Development's involvement is generally determined by Drug Discovery's conclusion that a given API is a drug development candidate. Once a candidate has been accepted, estimates of kilo requirements and the timing of deliveries can be made. Often these projections are quite aggressive such that Chemical Development is best served by working with Drug Discovery at an early stage in order to get a head start and, discretely, provide information on potential scale-up issues foreseen in the preparation of large quantities of emerging API candidates.

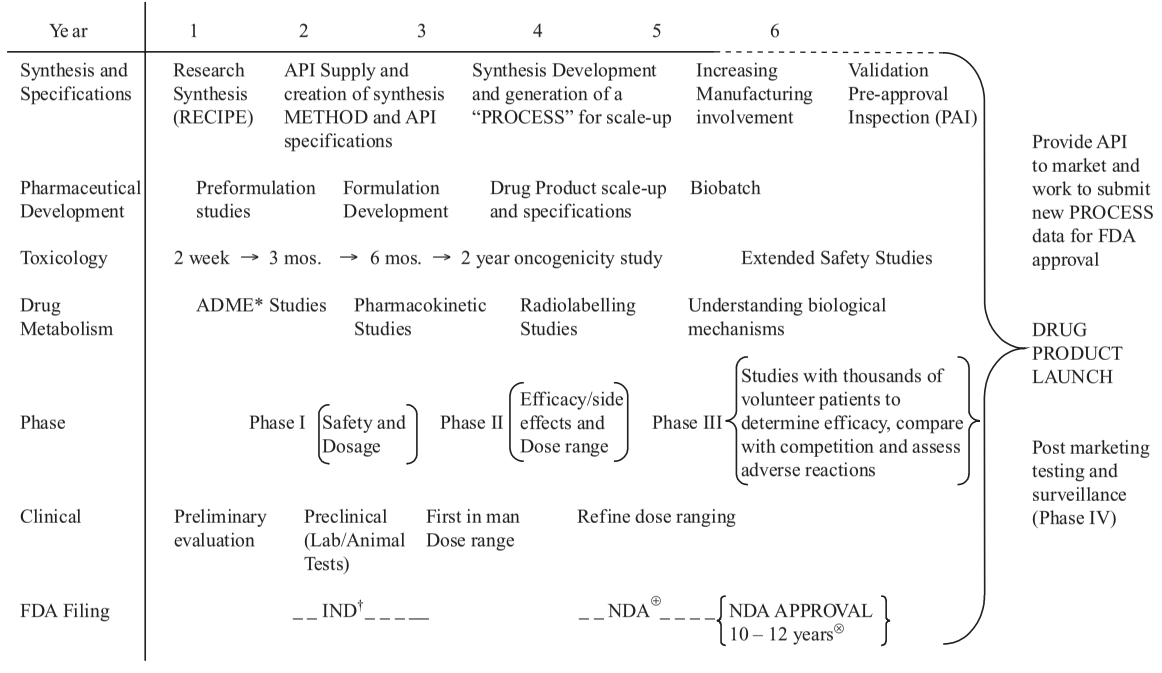
It is usually more difficult to decide that a developing API is really not worth pursuing and to terminate the program. This is often a major factor in terms of efficient utilization of the organization's resources.

The Chemical Development Mission and Structure

In my time in Schering–Plough the Chemical Process Development organization was given a dual role in being staffed to support both the Research drug discovery/development organization and the Schering–Plough Manufacturing organization. This arrangement owed much to the fact that Chemical Development was ceded the entire Union site manufacturing operation, and responsibility to continue manufacture of a few residual small volume APIs, when manufacturing moved offshore. Our mission statement reflected this unique state of affairs.

Chemical Development Objectives

- Chemical Development's primary objective is to provide quality active pharmaceutical ingredients (APIs) for company Therapeutic Team programs, on time



*ADME–Absorption, Distribution, Metabolism, Excretion
†IND–Investigational New Drug application
⊕ NDA–New Drug Application
⊗ From Inception –break through API's may be fast-tracked

FIGURE 2. Indefinite drug development program.

and in a cost-effective manner, at the same time as meeting all Safety, cGMP, and Environmental Regulations.

- The following objectives are integrated with the primary objective as the API develops to a marketed product:
  - Provide support for Therapeutic Team activities and Manufacturing.
  - Create and optimize safe, well-engineered commercial chemical processes by Phase III meeting all cGMP, Environmental, and cost-of-goods requirements—usually involving Manufacturing.
  - Engineer a total technology package suitable for designing a production facility elsewhere—with Manufacturing.
  - Where justified, undertake manufacture of early launch bulk actives for Marketing, allowing the company to delay capital investment until the market needs are fully known and the best process technology is worked out.
- Transfer Technology to company and/or third-party production plants.
- Hire, and work to keep, the critical force of capable people needed to meet the above objectives, and provide support and training to keep them up-to-date.

In the course of meeting its objectives, Chemical Development provides the bridge between new drug discovery and Manufacturing.

The above objectives deserve qualification and further explanation:

Remarkably, we were mostly able to meet the primary objective, with very few supply glitches, largely because of our early involvement with Research and our emphasis on quality and rigorous attention to detail (see Chapter 6). It took us some time, starting essentially at ground zero, to assemble and tune the systems needed to meet all the Regulatory requirements (see later).

Support for the Therapeutic Teams was wide-ranging, covering such items as the identification and preparation of API impurities for analytical and toxicity work, analyses of supply quantities and timelines, and, later, projections on possible API manufacturing strategies and the cost of goods, and so on. Support for Manufacturing is illustrated in Chapter 9.

The creation of a safe, well-engineered commercial process by phase III was seldom a task that could be completed to our satisfaction, even with the early involvement of our manufacturing colleagues. We could always create a practical method (interim process) for manufacture, usually with careful attention to outsourcing raw materials and intermediates (see Chapters 4–6 and 8).

Our chemical engineering staff, in collaboration with their manufacturing counterparts, rose wonderfully to the challenges of creating manufacturing technology packages, a task made more difficult by all the ongoing, sometimes excruciating requirements to show that the proposed package would meet all FDA requirements (see Chapter 6 and 8).

Undertaking manufacture of early launch bulk actives for Marketing was always controversial. It occurred in one case (see presentation on dilevalol hydrochloride) and, as it happened, the early launch manufacturing strategy saved enormously, by

avoiding capital investment in a manufacturing plant, when the drug had to be withdrawn shortly after its market launch. Today manufacture is often undertaken, at least for intermediates, using third parties. Third-party involvement brings its own problems: in the diversion of resources to meet the needs for confidentiality and intellectual property agreements, technology transfer, process support, and administration.

In today's climate, where everyone seeks to accelerate the supply of API [and all other activities leading to the filing of a New Drug Application (NDA)], technology transfer starts very early in the API supply program. It usually commences with efforts to outsource early intermediates and ensure the production of a quality product. Technology transfer requires that attention be paid to all the problems cited in the previous paragraph (see also Chapter 6).

Hiring and keeping the best people for the work needed is the most important mission in any organization (see Chapter 2).

Chemical Development Organization

It will be readily apparent that given the foregoing mission, a Chemical Process Development organization needs core skills in chemistry, analysis, and chemical engineering, and it also needs people with the ability to interact effectively with those in many other areas and disciplines (Figure 3).

From the outset our mission, enhanced by manufacturing responsibilities, required that our organizational structure should not be solely that of a service department for the Therapeutic Teams, and Discovery and Development departments, even though this was our primary mission.

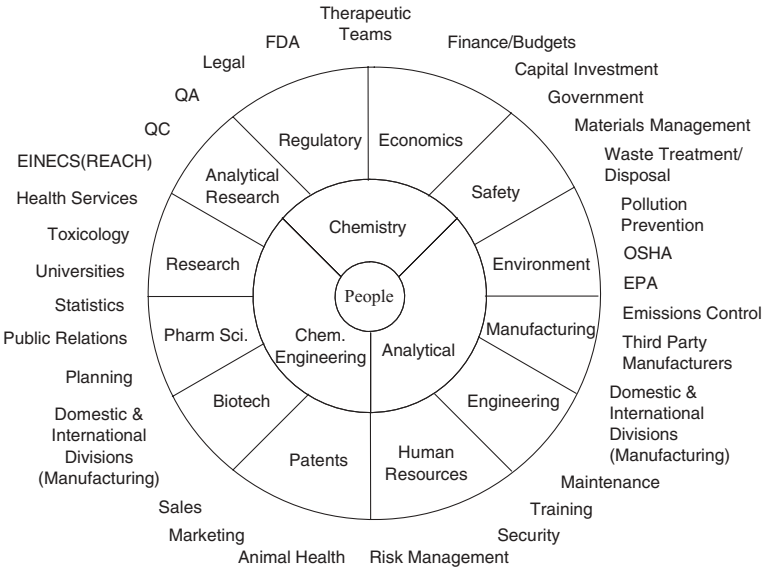


FIGURE 3. Chemical development interactions.

In meeting our primary mission, the need for close interaction with our Discovery colleagues was paramount. In this regard the positioning of some of our laboratories adjacent to those in Discovery was especially helpful in securing strong dialogue and liaisons on a scientist to scientist level. Interactions with the overall Development organization's Analytical Research and Development (QC) organization was also vigorously promoted (they created the first analytical methods and specifications and carried the responsibility for quality control on all APIs). Interactions with the Pharmaceutical Development organization were also strong. Our collaborations with them ensured that the API being produced was suitable, particularly in its physical form, for their dosage form preparations. Chemists were the primary people involved in the Discovery and Analytical liaisons, with chemical engineers being heavily involved, aided by the chemists, in interactions with Pharmaceutical Development and Manufacturing.

Our interactions with Biotechnology Development and the company Safety and Environmental departments depended on the project. The Safety and Environmental Departments were particularly involved when new chemicals were being handled. Interactions with Patents department were always strong, if intermittent, since the creation of patentable intellectual property was a frequent outcome of our work.

At the time I joined Schering–Plough (1982), the Chemical Process Development department was minimally staffed and equipped and unable to carry out all the duties it shouldered. Fortunately, our visionary leader of all Development, Dr. Hal Wolkoff, shared our view of the need to introduce small Analytical, Safety, Environmental, Regulatory Affairs and also Biotransformation functions into the Chemical Process Development organization and was instrumental in successfully making the case for funds for the following:

- Headcount, primarily chemists, chemical engineers and analysts, was increased to meet the needs of the added functions.
- Buildings were modified and upgraded to accommodate modern laboratories, analytical instruments and some pilot plant equipment.
- An in-house process safety group, with its own laboratory and calorimetry equipment, was introduced, in agreement with the existing company Industrial Safety and Hygiene group. Our in-house group became a resource for the broader company organization, especially Manufacturing, and its efforts led to wider recognition of the need for some of the same calorimetry capabilities on Manufacturing sites.
- An in-house process and intermediate chemicals analysis group was created, for liaison with the central Research analytical chemistry and quality control organization (housed in the Development component of the Research organization).
- An environmental scientist was recruited to liaise with the company's existing environmental affairs organization—the role grew to enabling chemical process development personnel to better "translate" environmental regulations into working practice in the chemical development organisation.
- One of our senior scientists was seconded to the Regulatory Affairs department in the Research organization to become conversant in the process for writing

and submitting the CMC (Chemistry, Manufacturing and Controls) sections to the FDA (as part of their IND and NDA submissions). On his return to Chemical Process Development, he became a vital asset enabling us to make more effective contributions to Regulatory Affairs and in enabling Regulatory Affairs to better represent the Chemical Process Development position in creating their CMC sections.

- A chemical biotransformation group was created to harness opportunities for the enzyme-mediated synthesis of chiral intermediates needed in our API programs. Later this group also went on to aid Research's evaluations of metabolism and chiral chemistry issues in progressing API candidates.

Over the course of time, our organization became fully fledged, as outlined in Figure 4.

One of the most difficult tasks was to create the operating structure to enable the organization to work as seamlessly as possible. In my time leading the organization, the Process Research and the Biotransformations functions in Figure 4 were in laboratories adjacent to those of the Discovery Research scientists' laboratories. Research's laboratories were nearly three miles away from the pilot plant/production site where all other functions, except the Swiss operation, were situated. The Swiss operation based near Luzern overcame their distance away from the core site by virtue of frequent interactions through their key personnel, all outstanding people (see Chapter 2).

The most important vehicles for ensuring strong interactions were monthly project reports, manufacturing plant visits (for our manufacturing role), appropriately timed technical meetings, and internal, in-depth symposia. The internal symposia were international in scope and usually lasted for about three days. They were attended by selected senior technical personnel from the major manufacturing sites, principally Ireland, Mexico, and Puerto Rico (and later Singapore), and key technical people from these sites who were involved in particular programs. The major players from our Swiss operation were always present. Program reviews usually included contributions providing invaluable perspective from the Coordinators of the pertinent Therapeutic Teams. The main contributors to the symposia programs, in addition to our people from Chemical Process Development, were the people from Research (drug discovery), Pharmaceutical Sciences, Analytical Research and Development, and often Patents department. The most important document (needed to promote preparation for the symposium and to provide the framework for the technical meetings) was a carefully crafted agenda based, principally, on important current development projects involving all relevant disciplines, including analytical, pharmaceutical sciences, and manufacturing (technology transfer). Research often provided an introductory overview of a major project, which could include a review of how a drug candidate was faring in a toxicological study or in the clinic. Technology transfer and manufacturing issues always had a significant place in the agendas. The impact of safety, environmental, and FDA regulatory affairs was included where pertinent. Although the symposia were usually held in the United States, they were occasionally

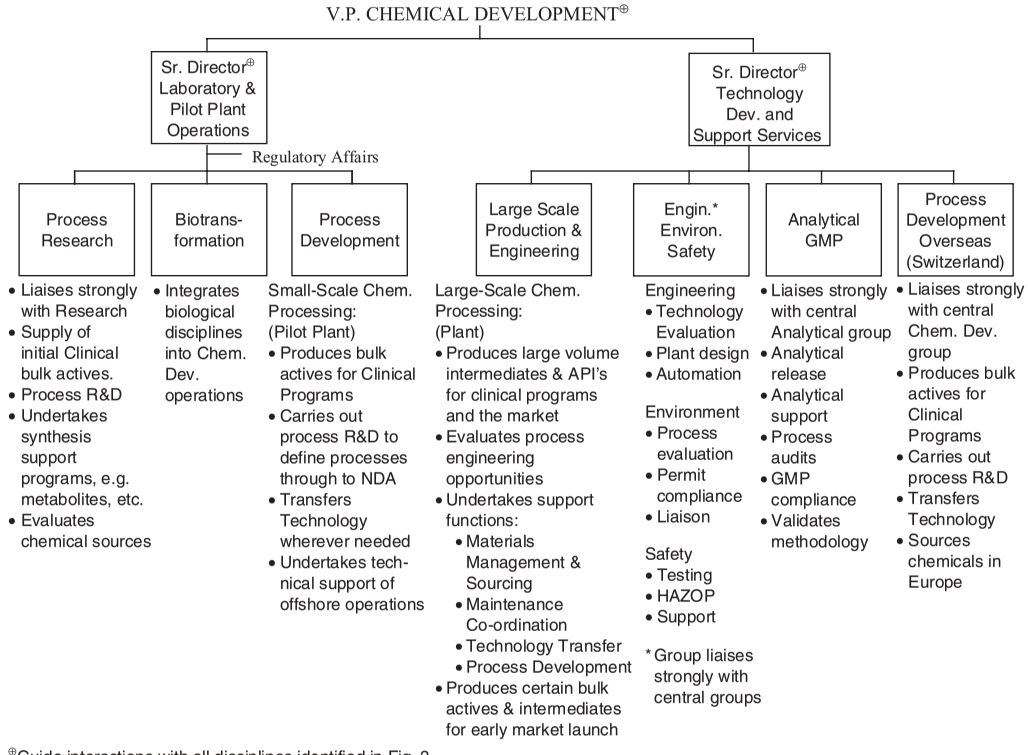


FIGURE 4. Chemical development organization and principal functions.

held off-shore at a manufacturing facility. In pursuing the manufacturing aspects of our mission, we also often held symposia on particular manufacturing issues on the manufacturing site in need.

The symposium agendas assigned individuals to prepare and speak on given subjects. The symposium agendas were issued weeks before the meeting such that speakers always came prepared to speak knowledgably about their projects. Minutes (mostly agreed action plans and assignments of responsibility) were published to ensure that all knew where they stood. International Development Symposia were usually held twice a year. Regular technical meetings were set up on a more frequent (as needed) basis to enable us to power projects along as efficiently as possible.

The composition of the teams that were forming and dissolving along with the projects, as well as the leadership of these teams, usually depended on the stage of the project. Chemists involved from the inception of a project frequently stayed with the project throughout its "life" in Chemical Process Development, though leadership could change depending on the aptitude and interest of the chemist.

Some experienced chemists could lead a project from the beginning to its implementation in a production plant. Frequently, chemical engineers took over at some stage in the development. Management generally had a strong input into such decisions.

As in any organization within a larger organization, governing day-to-day activities was an important function. To this end, having set up the organization's structure provided the human and physical resources, and having defined the organization's mission, constant attention was paid to its operation. This was done by developing a portfolio of standard operating procedures (SOPs) and codes of practice. The corporate SOP portfolio provided an umbrella of guidance documents that were developed, as one goes down the organization, into a cascade of more specific umbrellas governing, eventually, the operation of each subordinate organization or department. Each subordinate organization, such as Chemical Process Development, essentially put together its own portfolio of SOPs under the guidance and tutelage of an overall administrative (Regulatory) mogul within the organization. These SOPs, which were common-sense summaries of a logical system for running our technical operation, were important documents for everyone. In particular, they served as training documents for employees and were invaluable in demonstrating to outside regulators and auditors just how the organization ran.

In broad general outline the SOP manuals governing the Chemical Process Development organization, assigning duties, and ensuring the correct discharge of responsibilities were collected under the main categories of Administration, Documentation, and Operations. Each department within the Chemical Process Development organization was responsible for creating and working to its own specific SOP portfolio. The following is a partial list of SOP's governing pilot plant operations:

Administrative Procedures	Including an SOP Numbering System/SOP Distribution and Review/Master Batch Records/ Implementation of New Batches/and so on.

Documentation Procedures	Including Personnel Signature and Initialing lists/ Equipment Status Labeling/Sample Labeling/and so on.
Operational Procedures	Including Dress Codes for Various Rooms/ Instrument Calibration/Weighing Procedures/ Operating Instructions for Equipment/and so on. CLEANING PROCEDURES – Including Equipment Cleaning, Use and Maintenance/Specific Equipment Cleaning Procedures/Storage of Clean Equipment/and so on.

We tried to design the SOP's structures and train all staff in their implementation so that they would become second nature.

Organization Development

Organisations are concerned with the development of people as well as the development of products and processes. Human Resources (HR) is the company organization responsible for undertaking the work needed to meet the diverse people requirements of the company. In this endeavor, HR works with the leaders of all the disciplines needed for the company to succeed. HR aids in the identification and hiring of the best people they can attract to the company often with the help of their contacts, specialist personnel recruiters, and through recruiting visits to universities. HR also aids in setting up the mechanisms to follow the progress of people in the organization. Performance reviews provide one such mechanism. These evaluate the work of individuals and are often linked with salary awards. They also identify strengths and weaknesses and provide pointers for further development and improvement. In my experience, most scientists, analysts, and engineers prefer to grow within their professional discipline—though many like to be challenged by exposure to other areas. Thus another function of HR is to follow the development of a person by identifying his/her abilities, character, aptitudes for types of work, and so on. Over the longer term, performance reviews provide the basis for career progression, for promotions, further training and succession planning, inter alia. Occasionally, performance reviews identify people who are incompatible with the organization and its mission. Such revelations need to be shared with the person concerned, leading to programs to help the person become compatible or to find a suitable role elsewhere in the organization. It is very important for reviewers to listen carefully to possible misfits since they may be saying something the organization really needs to know. Should no progress be made, over say a several-month period, termination may be the only way to help an incompatible person move into more suitable employment. Such cases are relatively rare but, when identified, need to be documented every step of the way.

Organizations are also governed by budgets based on goals, manpower deployment, and time frames—with reports required at reasonable intervals, reviewing

progress. In these areas, technical assistance, especially in finance, was provided by the overall Research Administration's Planning, Finance, and Accounting departments. All the uncertainties in R&D projects led to lively interactions on money, manpower, and time. Changes and new agreements were facts of life, and often difficult to deal with. However, like all organizations, ours developed and changed with the continuum that is the world of Research and Development.

CONCLUSION

Organizations are fluid "living" mechanisms for implementing visions and achieving advantage. The more responsible ones change continuously to deal with those consequences of the activities which adversely affect the social system as a whole. In pharmaceutical research and development the success of matrix organizations in progressing drug discovery and development demonstrates the importance of integrating all the disciplines needed to discover and develop new drugs and illustrates the importance of conflict resolution in moving forward. The constant foment in discovery/development organizations requires that individuals and teams of individuals become aware of what is going on around them, enabling them to ensure that their position in the overall scheme of things is compatible with the overall objectives. The operation of an R&D matrix organization is quite different from the operation of the more complex company organization (especially marketing) at the public interface. The creative component in drug discovery is the R&D wild card. However, unlike the wild cards at the public interface, creativity is relatively sheltered from public scrutiny (excepting where it involves animal testing!). R&D organizations work in a more science-based, fact-driven framework than public interface organizations. Scientists live more by their brains than by their wits. In such as marketing, wits are more important. Of course both are vital to success. Public interface components create a marketing program based on drug facts and marketing "wild cards"—open-ended imaginations on what is needed to maximize public demand for the drug at a price they think they can get! Therein lies the major basis for the public perception of pharmaceutical organizations.

In the more down-to-earth chemical process development organization, embedded in a Research organization, the role that the chemists, chemical engineers, and analysts play is dependent on the openness and vision of the Research leadership. In the Schering–Plough Research organization there was agreement, before I joined, that the Chemical Process Development organization would take on a small manufacturing role, despite the possible downsides of a dual function. There was concern that a manufacturing involvement would divert resources from our API supply and new process development mission. For its part, Manufacturing also needed assurance that their budget contribution to the added staff, facilities, and functions (outlined earlier) was being used to meet their needs. The key was not to overpromise to either party. I regarded staffing for both roles as a boon—in all my previous appointments (with Arapahoe Chemicals/Syntex, Glaxo, and Bristol–Myers), manufacturing had been a considerable component of our activities. Involvement with the day-to-day

operations of Manufacturing sharpened attention to production detail, to all the Regulatory disciplines (Safety, Environment, and FDA Regulatory Affairs), to the importance of all our people (including people at the working level—for example, process operators), to diligent record-keeping, to disciplined warehousing, to consistent plant maintenance, and so on. These activities and collaboration with the Manufacturing sites generated invaluable feedback that contributed to the creation of more rounded processes, better meeting both FDA and Manufacturing needs. Both our chemist and chemical engineering staff were particular beneficiaries, especially in terms of training and exposure to the real world of manufacturing during their plant visits. As a result of this experience, all our personnel became more powerful contributors to the organization. Our Research colleagues, in seeing us (as many of them did) take their bench chemistry, with some modifications (especially for safety), into a pilot plant scale-up appreciated the attention to detail and the practical decision-making involved in selecting process parameters—solvents, reaction conditions, crystallization techniques, and so on. The success of this rigorous approach helped to foster the vital mutual respect that existed between the Research and Development organizations as well as between Development and Manufacturing.

Communication with all interacting parties is a core activity in running a successful organization. In addition to written reports, along with technical meetings on a regular basis, one of the most important activities in promoting the enthusiasm, sense of involvement, and passion for the work was to organize technical symposia to review broad progress on projects with a wide range of project participants. The personal interactions that grew from these meetings did much to move projects along.

Operating the Chemical Process Development organization was formally documented via manuals of Standard Operating Procedures (SOPs) governing all critical operations. We worked to train people to work to these SOPs, often finding that feedback from the training process caused SOPs to be changed. We tried to make them "applied common sense" such that time would not be wasted by continually having to refer to them.

Engaging and organizing the right people was the most important activity in the organization. In this we needed the close involvement of company Human Resources people, not only in the hiring process but, subsequently, to ensure that those engaged were the right people, that they were satisfied with their jobs, and that we set up the mechanisms to recognize their achievements, to deal with their (and the organization's) failings, to provide development opportunities, and to identify and groom the next generation of leaders.

As previously stated, there is no more important function than engaging and organizing the right people and creating the professional environment in which they can grow. The success of all organizations depends on it.

Also as stated, organizations are living entities created to deal with an infinite variety of unique missions. Looking back at the organizations I had a hand in creating, even my last one at Schering–Plough, they were not perfect. We could have done some things better. Thus this review of my last organization may contain much of interest to organizations elsewhere, but it is already passé and not intended as a blueprint for other organizations.

4

PROCESS SAFETY

The safety of the republic is the supreme law.

—— Ancient Latin Watchword

INTRODUCTION

Throughout history, the chemical and pharmaceutical industries have gained mind-boggling unexpected experience in the hazards of working with chemicals. The safety literature provides a sobering and dark commentary with regard to explosions, runaway reactions, fires, toxic emissions, asphyxiations, spills, and so on, and their consequences. Consequences are seen in the injuries and deaths of people and in physical, social, and environmental damage around the world.

Industry has learned greatly from these experiences but has also had to accept outside analysis and governance in the safety field. As a result, many government agencies have grown to provide guidance, oversight, and regulation for all who handle chemicals. Notably, in the United States, the main agency is the Occupational Safety and Health Administration (OSHA).[1] The National Institute of Safety and Health (NIOSH),[2] part of the Center for Disease Control and Prevention (CDC), conducts research and makes recommendations for the prevention of work-related injuries and illnesses. OSHA's mission is to protect workers from hazards, which in part includes setting limits for exposure to chemicals. Other safety organizations have developed,

[1]http://www.osha.gov
[2]http://www.cdc.gov.niosh

The Management of Chemical Process Development in the Pharmaceutical Industry by Derek Walker
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such as the Chemical Safety and Hazard Investigation Board (CSB),[3] which may be described as a hybrid of OSHA and the Environmental Protection Agency (EPA), various Manufacturers Associations, and the Laboratory Safety Institute.[4] Fittingly, the American Chemical Society's Division of Chemical Health and Safety (CHAS)[5] does much to help educate people at the student level regarding the nature of chemical hazards. The American Institute of Chemical Engineers' Center for Chemical Process Safety also provides invaluable Safety information.[6] Similar organizations have been established around the world.

Numerous books on the hazards and safety aspects of handling chemicals have been published. Two of the now standard works to be found in most technical libraries are under the original authorship of Sax[7] and of Bretherick.[8] Those engaged in assessing health risks can gain further insight into the variability of human response to chemical exposure from the book by Neumann and Kimmel.[9]

The EPA is also building a Risk Management Program (RMP) database from five-year reports required from those manufacturing facilities covered by the RMP rule (see the Compendial Federal Register 40CFR 68). It is expected that the collected five-year histories, disclosing broad accident information, will allow a more proactive approach to predicting future safety performance, avoiding accidents and improving safety management.

However, despite the initiatives of governments, outside agencies, and internal company safety organizations, more needs to be done by the individual. Specific problems require that every scientist and engineer has to be his/her own safety officer in working with chemicals in laboratory and pilot plant situations. Every scientist and engineer also has to be aware of health issues that can arise in handling chemicals. The chemist's earliest introduction is often through reading Material Safety Data Sheets (MSDSs) that he/she puts into the perspectives of his/her experience in handling chemicals.

This chapter provides an introduction, which, hopefully, will enable chemists and engineers to appreciate the major Safety/Health issues faced by people working with chemicals. The most immediately devastating are obviously explosion and fire. Adverse health effects resulting from the exposure of people to certain chemicals can also be immediate (e.g., exposure to methyl isocyanate in Bhopal), but health effects can also take time to manifest themselves. In view of the unknowns, it is best to maintain caution in all situations even though, putting matters into perspective, exposure to many chemicals (solvent vapors are the most common) can be tolerated

[3] www.chemsafety.gov/circ—this site provides often detailed reports on incidents and accidents.
[4] www.labsafety.org
[5] http://chas.cehs.siu.edu
[6] www.aiche.org/ccps
[7] *Sax's Dangerous Properties of Industrial Materials*, Lewis, J. R., Ed., Van Nostrand Reinhold, New York, 1992.
[8] *Bretherick's Handbook of Reactive Chemical Hazards*, Urben P., Ed., Academic Press, Oxford, 2006.
[9] Neumann, D. A. and Kimmel, C. A. *Human Variability in Response to Chemical Exposures: Measures, Modeling and Risk Assessment*, CRC Press, Boca Raton, FL, 1998.

provided that they are below published time-weighted averages.[10] Notwithstanding all of the above, safety infractions still occur for many reasons, the most common often being at the extremes of a lack of knowledge and comprehension on the one hand and too much familiarity with a given safety risk (especially if it is reinforced by a long record of no incidents or near misses) on the other. Such conditions can lead to complacency and erosion of vigilance.

Inadequate knowledge and comprehension are best overcome by gathering experimental information, including calorimetric data, on the chemical reactions being undertaken. Gathering calorimetric information is useful not only in identifying immediate dangers, but also in gaining a wealth of invaluable data on such as heats of reaction and crystallization, polymorphic form evaluation, and thermal stability, inter alia. Examples of the use of the differential scanning calorimeter (DSC) and the accelerated rate calorimeter (ARC) in evaluating potentially explosive situations are provided in this chapter. The use of the reactive system screening tool (RSST) and the Radex safety calorimeter in evaluating reactions for runaway potential is also described. In addition, a short account of the use of a reaction calorimeter (RC1) in gaining thermal information on a chemical process, as an aid to process development, is provided.

An outline of the main functions of the above five instruments follows:

Differential Scanning Calorimeter (DSC). A DSC is a versatile instrument allowing the chemist and engineer to screen for thermal hazards and also to determine the heat capacity and purity of a chemical. Another area of significant use is in the determination of polymorphism in crystals of a given chemical. One of the main advantages of a DSC is that it enables the user to gain a great deal of information from a small sample size (1–5 mg). The instrument is robust and easy to use, enabling the user to rapidly obtain and quantify results. The DSC provides information concerning the onset of thermal events including exothermic/endothermic decompositions without jeopardizing the instrument or user. It helps by providing data for a "go" or "no-go" process decision and indicates whether additional testing is needed with larger samples in other calorimeters.

Accelerating Rate Calorimeter (ARC). The ARC is sturdily constructed for the main purpose of simulating runaway reaction conditions on a small scale, typically using a 2 to 5 g sample. The sample is heated to a predetermined starting temperature in a spherical metal bomb. The sample is allowed to incubate at this temperature while the instrument control system scans for initiation of an exotherm. If no exothermic activity is found, the sample temperature is raised, and the "wait-exotherm search" routine is

[10](a) *NIOSH Pocket Guide to Chemical Hazards*, U.S. Department of Health and Human Services, Public Health Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, June 1997, published by the U.S. Government Printing Office, Superintendent of Documents, Washington, D.C. 20402. (b) *Handbook of Chemistry and Physics*, 78th edition, Lide, D. R., Ed., 1997–1998, Section 16–20. The time-weighted average on a given chemical is the limit a worker can be exposed to in an 8-hour working day and a 40-hour working week. It is recognized there may be individual exceptions.

continued until either an exotherm is found or a temperature limit of the system is reached. When an exotherm is detected, the controller maintains the temperature of the calorimeter wall at the same value as the spherical bomb. Time, temperature, and pressure data are recorded while the sample self-heats under adiabatic conditions. The heat evolved in the exothermic process is moderated by the bomb and its contents. This moderating effect is taken into account when the data are analyzed by using a thermal inertia factor to adjust both the self-heating rate and the observed adiabatic temperature rise.

The ARC provides accurate temperature, pressure, and time data to enable a protocol to be devised which avoids operating problems when reactions are scaled up.

Reactive System Screening Tool (RSST). The RSST is a thermal screening instrument. The sample to be tested is placed in a 10 ml insulated spherical glass test cell that in turn is placed in a 0.5 liter pressure vessel equipped with a simple heating system. A thermocouple is placed in the sample to be tested; the thermocouple provides feedback control to the pressure vessel heater, enabling heat losses to be overcome, thereby ensuring a linear sample temperature ramp from 0.25°C/min to 2°C/min. The whole system can be pressured up to 800 psi in part to suppress the boiling of light solvents that could mask an exothermic onset. The addition of reagents to the test sample can also be arranged through a valve and syringe directly to the sample (to estimate heat of reaction). The system carries provision for accumulating temperature, time, and pressure data via a dedicated microprocessor. The accumulated data can be plotted for the interpretation of test results.

Radex Safety Calorimeter. The Radex calorimeter is a modular instrument that can simultaneously evaluate six different samples (size range 0.5 to 5 ml), or one substance under a variety of conditions. Each module is a separate entity with its own calibrated oven capable of being operated under an open, closed, or pressurized condition, with all temperature differences between the sample and the oven being stored in a microprocessor for further analysis. The Radex calorimeter is very versatile; samples can be tested in either an isothermal or ramp mode. In the isothermal mode, each oven is heated to a preset temperature and held at that temperature throughout the experiment. In the ramp mode of operation, the oven is heated linearly to a preset temperature, or can be maintained at a given temperature for a predetermined time. The flexibility of oven function in the Radex calorimeter enables the user to determine the intrinsic stability of a chemical and to also compare the impact of such parameters as temperature, atmosphere, and impurities on the stability of a given substance.

Reaction Calorimeter (RC 1). This calorimeter has grown in popularity as a practical process development tool. Its value is based on the precise measurement of thermal events occurring at each step of carrying out a chemical transformation. The reaction calorimeter enables the chemist to gain a realistic insight into heating and cooling a reaction on a large scale. In running an exothermic reaction in a small reaction flask in the laboratory, the chemist generally relies on a large cooling bath with a very

large temperature differential, versus the reaction mixture, to maintain a reaction at a desired temperature. In this situation, the chemist essentially conceals the importance of the ratio of cooling/heating surface area to reaction volume. In using a reaction calorimeter, wherein the reaction vessel is cooled and heated via an external jacket, much like a pilot plant vessel, the chemist acquires a better appreciation of the limitations of a jacketed vessel—in short, the effects of a smaller surface-area-to-volume ratio. A reaction run in a reaction calorimeter allows the chemist to determine the importance of heat transfer, and the need to address it, in developing a chemical process. In another sense, the process development chemist can often save many hours of operation by obtaining heat of reaction data from a reaction calorimeter to determine when a reaction is complete, thereby often avoiding the convenient practice of "stirring a reaction mixture overnight to complete the reaction."

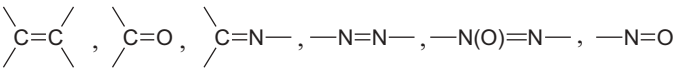
Application of the above instruments in identifying the potential hazards associated with any process or chemical enables the chemist and the engineer to make recommendations for the safest possible operation of that process and the best way of handling a particular chemical, or, indeed, whether to do so at all.

EXPLOSION (CHEMICAL, DUST, AND VAPOR) AND RUNAWAY REACTIONS

Chemical Explosion. Efforts to avoid explosion and fire have the highest priority in creating a safe operation. In the laboratory, the trained chemist and engineer usually recognize the dangers in working with particular chemical structures. The most important structures with intrinsic explosion potential are listed in Table 1.

Most of the groups in Table 1 may be regarded as metastable intermediates which are on their way to carbon monoxide, carbon dioxide, nitrogen, or another more thermodynamically stable structure.

A simplistic way of classifying these structures is through comparison with the dyestuff industry, where groups are assigned chromophore or auxochrome status. A chromophore is a chemical group that gives rise to color when allied in a suitable manner and in sufficient number with hydrocarbon moieties—for example,



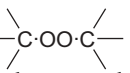
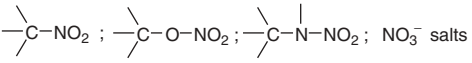
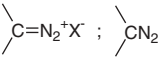
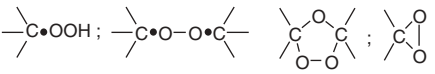
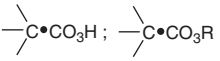
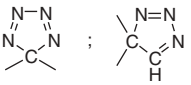
By analogy, —NO_2,  ,  , —N_3, ClO_4, and —C≡C— groups, which can produce explosion, may be named plosophores. Plosophores are defined as chemical structures which are predisposed to cause molecules containing them to decompose violently when they absorb energy (e.g., shock or heat). This intrinsic explosivity characteristic is reduced when the oxygen balance with carbon declines (e.g., trinitrobenzene versus nitrobenzene) or when the plosophore content is diluted (e.g., diazomethane versus diphenyldiazomethane) or by dissolving (diluting) the compound in a compatible solvent.

TABLE 1. Chemical Structures with Intrinsic Explosion Potential

Group	Structures
Nitrates and nitro compounds	
Diazo compounds and diazoalkanes	
Peroxides and ozonides	
Peracids and peresters	
Tetrazoles and triazoles	
Hydrazoic acids and azides	HN_3 , $M^x(N_3)_x$ e.g. $Pb(N_3)_2$
Acetylenes, especially polyacetylenes	
Chlorates and perchlorates, especially in the presence of organic matter	$HClO_3$, $M^x(ClO_3)_x$, $HClO_4$, $M^x(ClO_4)_x$

Continuing with this theme, an auxochrome is a group that can deepen or intensify color—for example, NH_2 or OH. By analogy, these same groups can be regarded as auxoploses, since combination with a plosophore will enhance the potential for explosion (see Table 1 for auxoplose–plosophore combinations).

Application of Differential Scanning Calorimetry (DSC) in Dealing with a Potentially Explosive Situation.[11] Everyone working with chemicals containing plosophoric groups needs to address the hazards long before scale-up is contemplated. Information gained from calorimetry studies enables those responsible for scale-up to specify conditions that will prevent explosion. However, as an illustration of how potential problems can creep up on the unwary, it is pertinent to describe a situation occurring in Schering–Plough's process for manufacturing Nitro-dur skin patches (prescribed for the treatment of angina). The patches comprise nitroglycerine incorporated into a polymer matrix via an aqueous emulsion process. During the drying operation, water is removed which passes through a charcoal scrubbing unit.

During an intersite meeting involving chemical development, the manager of our Chemical Development Safety Group, Joe Buckley, asked for samples of charcoal from the Nitro-dur scrubbing unit to ascertain whether any nitroglycerine vapor had condensed and accumulated on the charcoal. Differential scanning calorimetry (DSC) analyses were carried out on the charcoal versus fresh unused carbon. Each sample

[11] Buckley, J. T., Marino, J. P., Emery, R. L. Process Hazard Identification in the Pharmaceutical Industry, ACS 1991 Spring National Meeting, April 19, 1991.

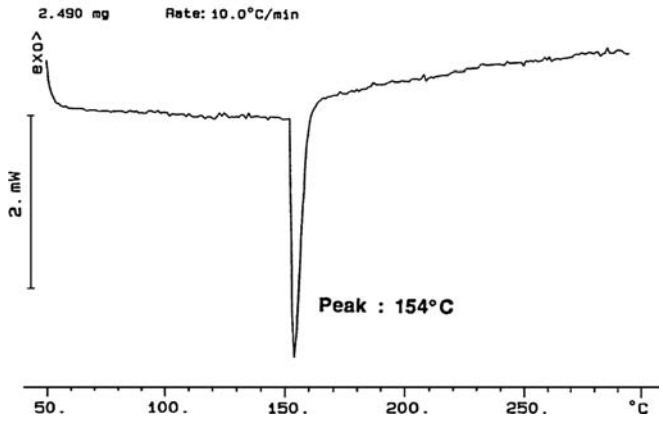


FIGURE 1. DSC of unused charcoal heated at 10°C/min from 50°C to 300°C in a hermetically sealed aluminum pan.

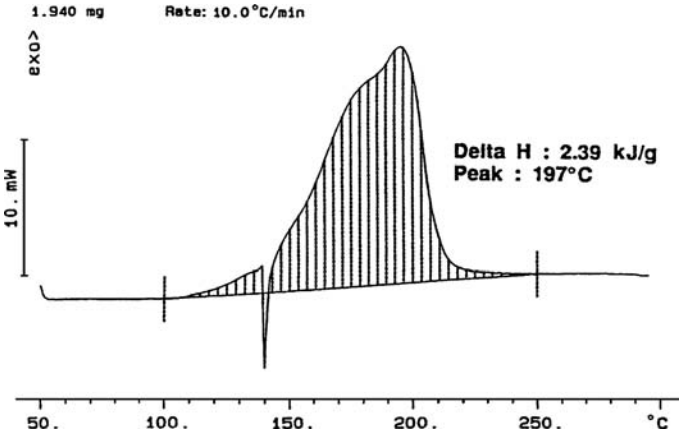


FIGURE 2. DSC of scrubber charcoal heated at 10°C/min from 50°C to 300°C in a hermetically sealed aluminum pan.

was heated at 10°C/min from 50°C to 300°C in a hermetically sealed pan. The unused charcoal exhibited a rapid endotherm at 154°C as water desorbed (Figure 1). DSC scans of all scrubber charcoal samples (Figure 2 is representative) showed a small water endotherm at 140°C superimposed on a highly energetic exotherm that began at approximately 100°C, peaking at 197°C and generating 2.3 kJ/g of energy per sample. This information, indicating that substantial nitroglycerine was absorbed on the charcoal, led us to undertake an impact sensitivity test to gain insight into whether or not the scrubber charcoal might be detonated by an impact or friction shock, or by a spark. A JANAF drop weight test was carried out by specialists in explosives.[12]

[12]Hazards Research Corporation, 200 Valley Rd., Mt. Arlington, NJ 07856.

TABLE 2. Comparison of Explosivity of Nitro-dur Scrubber Charcoal with Known Explosives Using the JANAF Drop Weight Test

Substance	Height of Drop Weight Causing Initiation of Explosion (Inches)
Nitroglycerine (neat)	0.39
Benzoyl peroxide	5.20
RDX[a]	8.00
Scrubber charcoal sample	12.50
Picric acid crystals	13.00
TNT	15.00
Ammonium perchlorate	21.60

[a] *Sym*-trimethylenetrinitramine.

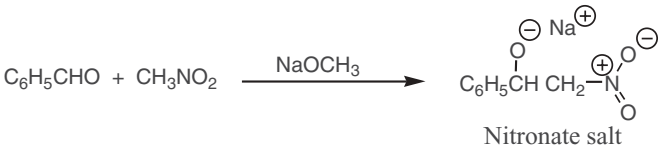
This test utilizes a known weight—2 kg in our case—that is dropped from a series of increasing heights up to 36 in. onto a sample in a specially designed cup. A loud report, flame or other indication of combustion indicates a positive test. The test result is regarded as the height which indicates a 50% probability of initiation of an explosion. The JANAF test was carried out 20 times on scrubber charcoal samples and indicated a 50% probability of initiation at a 12.5-in. drop height. This sensitivity result was consistent with results on other known explosives. The results are summarized in Table 2.

Given the results in Table 2, indicating that scrubber charcoal had an impact sensitivity between picric acid and the commercial explosive, RDX, new procedures were adopted for the use and storage of scrubber charcoal:

- The charcoal in the scrubber unit was replaced more frequently to minimize nitroglycerine accumulation.
- Contaminated charcoal was stored in a segregated area and mixed with an inert material (vermiculite) prior to being sent out for disposal.
- The company undertaking the disposal (incineration) was advised of the new composition of scrubber material.

Application of Accelerating Rate Calorimetry (ARC) in Evaluating a Reaction with a Potentially Explosive Nitro Compound. One of our process development projects required the preparation of 2-hydroxy-1-nitro-2-phenylethane via the addition of sodium methoxide to a mixture of one mole of benzaldehyde and one mole of nitromethane in methanol (Scheme 1).

The nitronate salt precipitated as a thick slurry, posing heat transfer and stirring problems. Before taking the process into the pilot plant, we needed information on the thermal stability of the nitronate in order to provide operating guidelines to eliminate the risk of explosive decomposition. Our accelerating rate calorimeter was selected for the test since it afforded great sensitivity and the best user protection for the technician running the test in the event of a detonation.



SCHEME 1. Preparation of 2-hydroxy-1-nitro-2-phenylethane.

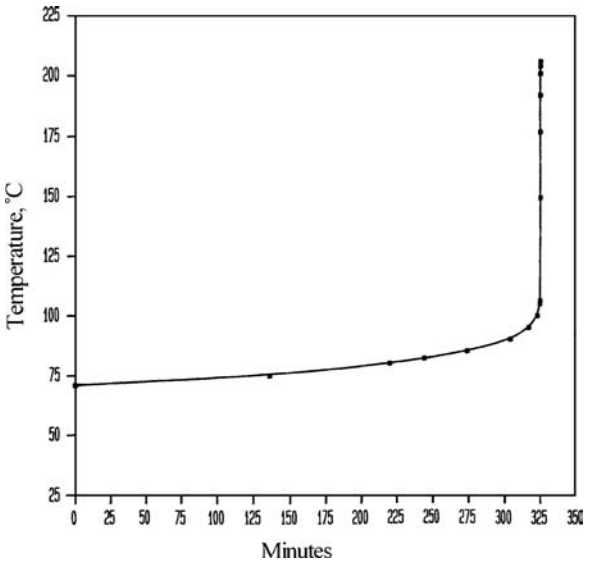
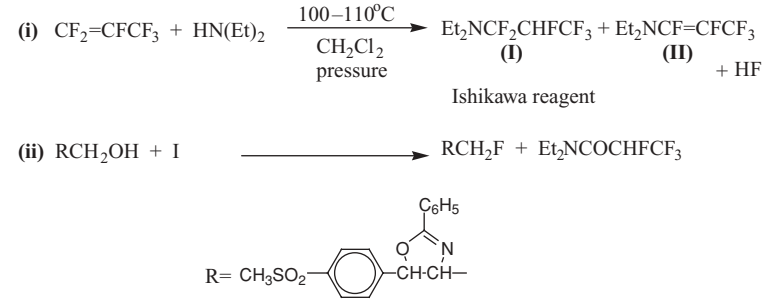


FIGURE 3. Temperature versus time. Nitronate heated in the ARC under adiabatic conditions.

A sample of nitronate (0.8 g) was heated in a titanium "bomb" in 10°C increments from ambient temperature. Under adiabatic conditions the nitronate began to self-heat at 70°C and violently deflagrated at 106°C (Figure 3). The deflagration produced temperature rates of 700°C/min, pressure rates of 6000 psi/min, and nitrogen oxide off gases.

The ARC test enabled us to set up guidelines for the preparation and use of the nitronate salt on a pilot plant scale:

- The reaction temperature was held at no more than 30°C during formation of the nitronate.
- The solvent quantity used in the reaction was increased in order to efficiently stir and cool the nitronate.
- The nitronate salt was not isolated or dried. Instead, acidification of the salt was carried out to produce the more stable nitro alcohol.



SCHEME 2. Conversion of CH_2OH to CH_2F with Ishikawa reagent.

Runaway Reactions. Such reactions may not have the catastrophic severity of an explosion, but thermal runaway reactions can also be extremely destructive. The thermal runaway may not be in a reaction solution itself, but may occur as a result of say a condenser failing, leading to loss of solvent from the reactor such that the residue of reagents alone is now being subjected to heat.

Application of the Reactive System Screening Tool (RSST) in Examining the Potential for a Runaway Reaction Associated with Plant Failure. A "what-if" scenario was examined by Schering–Plough in the in situ manufacture of Ishikawa reagent for a subsequent reaction with a primary alcohol group to produce an intermediate for manufacture of the antibiotic Florfenicol (Scheme 2). We asked the question, What if a leak developed in the pressure reactor used for the preparation and use of the Ishikawa reagent such that all the methylene chloride solvent distilled out and the residual reagents were now being heated on their own?

The stability of the Ishikawa reagent itself [**(I)** in Scheme 2] was examined in our reactive system screening tool (RSST); this equipment was used, since, by design, it allowed us to test the effects of heat in a pressure vessel. The reactor and contents were heated at a rate of 1°C/min under a pressure of 200 psi.

As seen in Figure 4, a small exotherm occurred over the temperature range 65–100°C, possibly coinciding with Ishikawa reagent **(I)** converting to the enamine **(II)** and HF.

A maximum self-heating rate of 2.2°C/minute was reached at 91°C in 16 min. The system stabilized and no further exotherm activity occurred until the temperature reached 136°C. At this temperature a violent exotherm ensued reaching 495°C, with a maximum self-heating rate of 2000°C/min being reached at 340°C within 23 min. In regard to pressure, other measurements showed that the violent exotherm produced a pressure of 387 psi/min at 405°C and a maximum pressure of 1600 psi at 307°C. Venting of the RSST at room temperature released large amounts of HF. The contents of the RSST cell were a polymerized mass. It was reasoned that HF was causing an acid-catalyzed polymerization of the enamine, but we have no absolute proof of this. Nevertheless, the RSST test enabled us to impose the following safeguards for reagent preparation **(i)** and reaction with the alcohol **(ii)**:

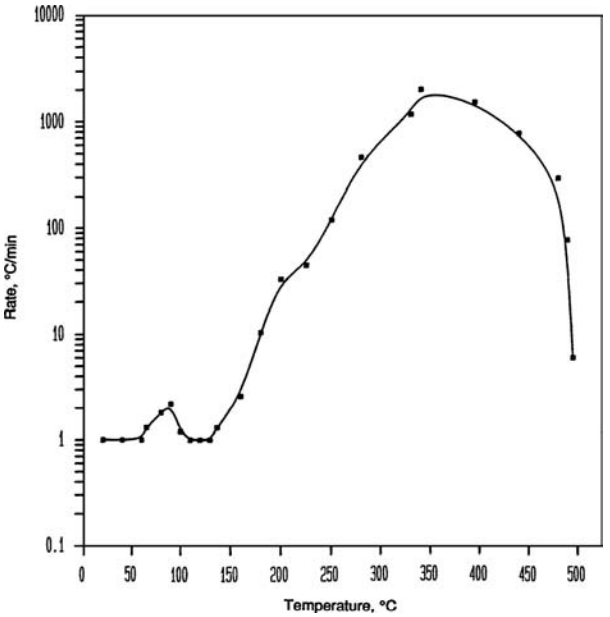
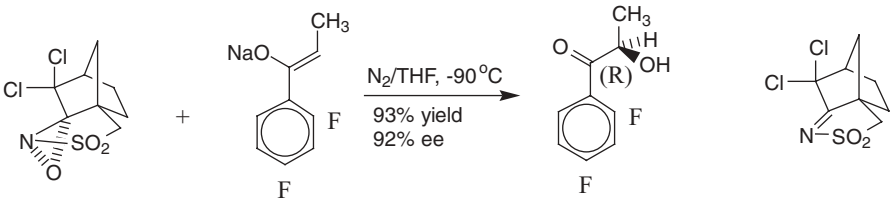


FIGURE 4. Temperature rate versus temperature. Ishikawa reagent heated in the RSST at 1°C/min with a 200 psia nitrogen atmosphere.

- During the reagent preparation step, process temperature limits were set at ambient temperature to reduce enamine formation.
- A Hazard and Operability Study (HAZOP) of the proposed operating procedure in the plant was undertaken to ensure that the "fluorination reaction" heat exchange system could not exceed 100°C.
- The batch sheet for operation of the process was written to ensure that the correct amount of the alcohol intermediate (RCH_2OH) was added to consume the Ishikawa reagent produced.

Guarding against runaway reactions has become one of the more important activities resulting from HAZOP studies now undertaken more or less routinely before running a process in the pilot plant. In more cavalier times past, most readers can probably recall bursting discs failing and the contents of their reactors spewing over the rooftops of their pilot plants. I can personally recall a runaway decomposition of a hot solid on the M6 motorway in England in 1970. A pilot plant peracetic acid oxidation of potassium penicillin G had been carried out in water at our Ulverston plant and the penicillin G sulfoxide (25% water content) had been taken by car to the Midlands of England for drying tests using a fluid bed dryer (previously a vacuum tray drier had been used at 40–45°C without incident). After the fluid bed drying was complete (to approximately 0.5% moisture level), the hot solid (later estimated at >50°C) was packed into a plastic lined fiber drum and loaded into the back of the car



SCHEME 3. Chiral hydroxylation of a sodium enolate.

(a station wagon estate car). Everyone wanted to get back north as rapidly as possible and could not wait for the solid to cool. Some 30 miles north, the fiber drum lid blew off with a gentle pop and the car occupants witnessed the decomposing product fizzing slowly to the front of the car, causing them to abandon the vehicle. This traumatic experience led us to investigate the decomposition (probably acid-catalyzed by traces of sulfuric acid—the peracetic acid contained small amounts of sulfuric acid). Rather than relying only on improving the washing step before drying, we created a process for producing a sugar-like crystal of the sulfoxide as an acetone solvate that was free of acid contaminants and dried without incident.[13]

Application of the Radex Calorimeter in Examining the Effects of Iron Contaminants on the Stability of a Potentially Labile Reagent. The synthesis of chiral compounds is now a de rigueur activity in the search for active pharmaceutical ingredients (APIs). Frequently chiral chemical reagents are employed for the introduction of chemical groups in a chirally specific manner. One such reagent, employed for the introduction of a chiral hydroxy group onto a prochiral carbon atom in a *Z*-enolate, is (−)-(2*S*,8*aR*)-[(8,8-dichlorocamphoryl)sulfonyl] oxaziridine[14,15] (Scheme 3).

The chiral oxaziridine is very reactive, even at low temperature, leading us to query its stability. Since we were proposing to carry out the preparation of the oxaziridine in a steel vessel, we investigated the thermal stability of the chiral oxaziridine on its own, in the presence of stainless steel and in the presence of ferric ion. The stability test was carried out in a RADEX safety calorimeter. The results are summarized in Figure 5.

As can be seen, the neat sample (Trace C) began to decompose at approximately 165°C. Decomposition occurred much earlier, at approximately 84°C, in the presence of ferric ions (Trace A) whereas stainless steel, in the form of filings, caused decomposition to commence at 148°C (Trace B). In all cases, once decomposition started, it became self-propagating within 15 min—a 1-g sample underwent a 40–50°C temperature rise within seconds and violently frothed out of the sample tube.

The effect of ferric ion content on the temperature at which decomposition started was studied, with the results summarized in Table 3.

[13]Wilson, E. M., and Taylor, A. B. U.S. Patent 3,853,850, 1974 (to Glaxo).

[14]Mergelsberg, I., Gala, D., Scherer, D., DiBenedetto, D., and Tanner, M. *Tetrahedron Lett*., 1992, **33**, 161.

[15]Gala, D., DiBenedetto, D., Mergelsberg, I., and Kugelman, M. *Tetrahedron Lett*., 1996, **37**, 8117.

TABLE 3. Effect of Fe^{3+} on the Onset of Decomposition of (−)-(2*S*,8*aR*)-[(8,8-Dichlorocamphoryl)sulfonyl]oxaziridine

Sample	Onset of Decomposition (°C)
Neat	165
0.04% Fe^{3+}	120
0.09% Fe^{3+}	112
0.60% Fe^{3+}	84

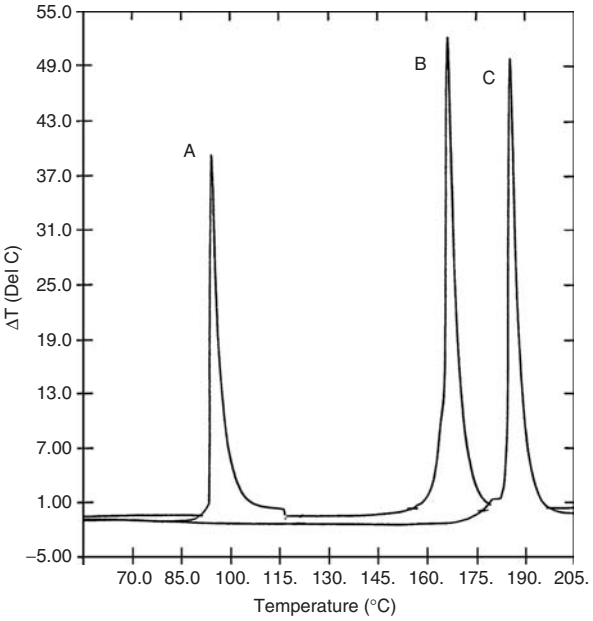
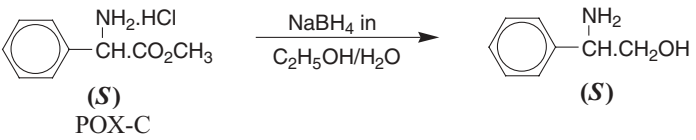


FIGURE 5. Thermal stability of (−)-(2*S*,8*aR*)-[(8,8-dichlorocamphoryl)sulfonyl] oxaziridine.

As a result of this work, the following recommendations were adopted to avoid possible runaway decomposition:

- The temperature limit in the preparation of the oxaziridine was set at 50°C.
- All solvents were tested to ensure that they were free of ionic transition metals before use.
- Only deionized water was used in processing the oxaziridine.
- Glass-lined vessels, passivated with dilute nitric acid or alcoholic EDTA, were used in reactions with the oxaziridine.
- No metallic tools (scoops, etc.) were used in working with the oxaziridine.



SCHEME 4. Sodium borohydride reduction of methyl (*S*)-phenylglycinate hydrochloride.

Application of the Mettler RC 1 Reaction Calorimeter in Optimizing a Process for the Reduction of Methyl (S)-Phenylglycinate. The sodium borohydride reduction of methyl (*S*)-phenylglycinate (hydrochloride salt) to the corresponding primary amino alcohol (Scheme 4) had been worked out in the laboratory and taken to a pilot plant scale where an unexpected exotherm was observed.

In outline the procedure was as follows:

Methyl (*S*)-phenylglycinate hydrochloride (POX-C, 10 kg, 49 moles) in 50% aqueous ethanol (20 liters) was added over approximately 2 hr to a solution of sodium borohydride (7.5 kg, 198 moles) in 50% aqueous ethanol (30 liters—previously adjusted to pH 9.5 with aqueous 2 N sodium hydroxide and cooled to 0–5°C). The operating procedure for the reduction step called for the reaction solution to be held at 5–10°C during POX-C addition. In the actual pilot plant run, the temperature was held in the range –2.5°C to 9°C during the addition (in fact, the temperature was difficult to control because the cooling circuit to the pilot plant reactor was at −40°C). The addition of the ester (POX-C) was also prolonged and intermittent because each addition caused a rapid temperature increase requiring time to drop to approximately 0°C before the next aliquot was added. At the end of the ester addition (batch temperature 1.2°C), the batch was warmed slowly. At approximately 10°C a rapid temperature increase to 56°C occurred, coinciding with a vigorous evolution of hydrogen, in spite of maximizing flow of the cooling circuit.

This event, which caused no personnel injuries nor equipment or batch loss, was unexpected—there had been no indications of unexpected exotherms in the laboratory process development work.

In continuing the pilot plant reaction, once the temperature had subsided to 25°C, the solution was stirred for 2 hr to ensure that the reduction was complete (HPLC). The excess sodium borohydride was consumed by the addition of acetone (20 liters) over approximately 90 min. The exothermic reaction was readily controlled in the temperature range 30–35°C. To recover the product, salts were filtered and the acetone distilled out. The desired product was extracted with *n*-butanol and the extract was washed with water. The *n*-butanol layer was stripped and the residue was dissolved in toluene. Further salts were filtered, the toluene was stripped out, and the (*S*)-2-amino-2-phenylethanol product was distilled under vacuum; the yield was 81%.

In order to understand, and avoid, the exotherm observed in the reduction reaction, the following process steps were examined using the Mettler RC-1 reaction calorimeter:

Step 1: Cooling the $NaBH_4$/ethanol/water solution from 2°C to 7°C.

Step 2: Warming the mixture obtained after adding the methyl (*S*)-phenylglycinate to the $NaBH_4$/ethanol/water from 7°C to 25°C.

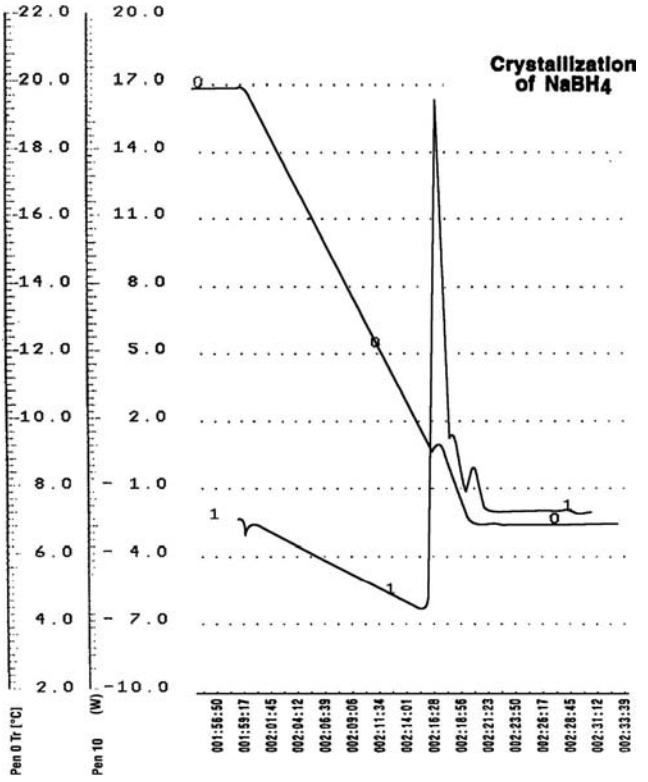


FIGURE 6. POX-C/EtOH/water/$NaBH_4$. Temperature ramp from 20°C to 7°C of $NaBH_4$/EtOH/water; $Q_{rxn} = -0.7$ kcal/mole of $NaBH_4$; adiabatic temperature rise is 4.33°C.

As can be seen from Figure 6, a small exotherm (adiabatic temperature rise of 4.33°C) is apparent, corresponding with the heat of crystallization of some of the sodium borohydride.

Figure 7 shows the result of warming the reaction mixture. At approximately 10°C a rapid heat evolution occurs (adiabatic temperature rise of 44.33°C). It was reasoned that this exotherm was a composite of an endotherm resulting from dissolution of the crystallized sodium borohydride and a larger exotherm corresponding to the reduction of the ester, POX-C.

As a result of these observations, the following action steps were taken and reinvestigated using the RC-1 reaction calorimeter:

1. The volumes of 50% aqueous ethanol used for dissolving the sodium borohydride and POX-C were increased by 233% and 75%, respectively.
2. The sodium borohydride solution was cooled to approximately 10°C (instead of the original 0–5°C) prior to adding the POX-C.
3. The addition of POX-C was carried out at 10–15°C instead of 5–10°C.

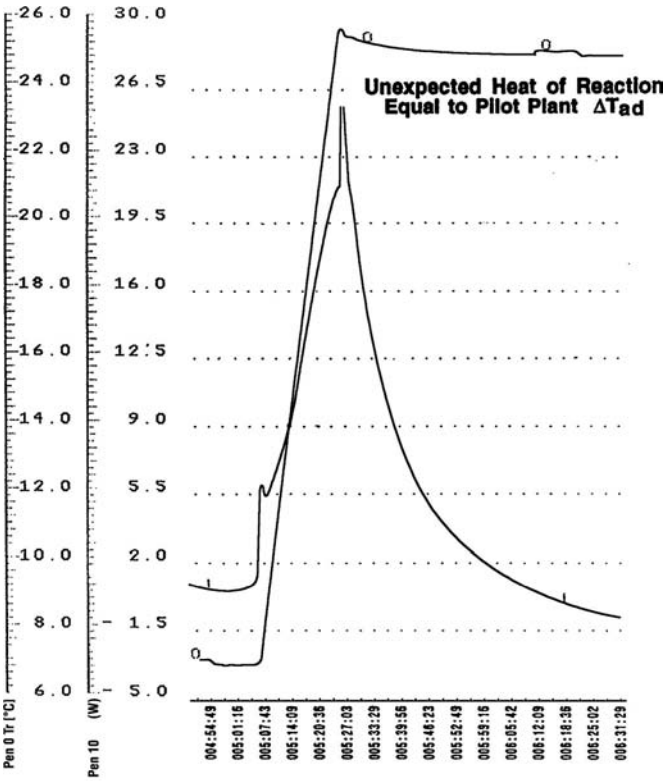


FIGURE 7. POX-C/EtOH/water/$NaBH_4$. Temperature ramp from 7°C to 25°C in 20 min; $Q_{rxn} = -41.8$ kcal/mole of phenylglycine Me ester HCl; adiabatic temperature rise is 44.33°C.

The RC-1 results indicated that no unexpected exotherm would occur. This was confirmed on the pilot plant scale.

The RC-1 work was extended to a study of the exotherm resulting from the acetone addition step (to consume the excess sodium borohydride). The data obtained from RC-1 work was invaluable in calculating the cooling requirements needed for larger-scale work and for further optimization of the process.

As an important aside, the reader will have gathered from the foregoing examples that uncontrolled foaming and violent gas release are fairly common outcomes of runaway reactions. Such events have resulted in the need for emergency venting to prevent or minimize catastrophic damage. This is usually done via a properly sized vent line fitted with a bursting disc rated at less than the pressure rating of the vessel.

Dust Explosion. Dusts, like solvent vapors, when in the presence of oxygen concentrations that will support combustion, represent potentially dangerous situations. Explosion and/or fire can be triggered by a spark, derived from an impact or friction or an electrostatic discharge or from hot spots (e.g., overheated motor bearings)

that expose flammable chemicals to temperatures above the flash point. The thermal degradation of materials may produce flammable gases amplifying the destructive power.

Dusts are most often encountered in milling operations and drying operations, with dust explosions being mostly associated with organic compounds. The need for caution is often the greatest for final APIs since a fine particle size, particularly a form suitable for preparation of the marketed dosage form, is frequently a requirement for bioavailability. The problem of potential explosivity of dusts can be an even greater factor in the preparation of drug products since formulations frequently contain sugars as a major ingredient; sugar dusts can be particularly hazardous in situations where there is a risk of such as an electrostatic discharge.

The potential risk of initiating a dust explosion is best determined by contracting specialists to carry out explosivity tests on dusts.[16,17] Such testing provides better understanding of the explosion, fire, and thermal properties of the powders being processed. In this way, measures to deal with the potential hazards can be selected to greatly reduce or eliminate the risk. General measures include a HAZOP study to identify and exclude potential ignition sources, backed up by inert gas blanketing. Grounding of equipment is a first line of defense against electrostatic ignition of an explosion. Large vents are also usually provided for explosion relief.

Vapor Explosion. Vapor explosions occur when an ignition source causes a flammable organic vapor and oxygen to burn at an increasingly very fast rate to create a high pressure shock wave. This becomes a detonation when the front velocity of the shock wave exceeds the speed of sound. Chemical plants have the potential to bring all three elements (ignition source, fuel, and oxygen) together. Elimination of any one of these three elements creates a safe condition.

Elimination of possible sources of ignition is addressed by building plants with explosion-proof equipment (motors, light switches, etc.), by equipping operators with clothing that will not build up an electrostatic charge, by providing them with conducting safety shoes, and by using only nonsparking tools. Plants also use inert gas blanketing in operations where there is a potential to generate sparks. Maintenance programs need to be such that there is no chance of hot spots developing in any of the equipment, and they also need to ensure that equipment is properly grounded.

One operation requiring especially high vigilance is the use of a centrifuge. The bowl of a centrifuge spins at a high speed, and any mechanical failure of a moving part (such as a bearing) might generate frictional sparks or a hot spot. The centrifuge's own switches and drive motor are also potential sources of electrical sparks. The possibility of electrostatic discharges from ungrounded metal parts, operators' clothing, or old safety shoes offer additional concerns. Footwear and flooring need to be inspected regularly to ensure that their anti-static properties are maintained:

[16]The Health & Safety Laboratory, Broad Lane, Sheffield S37HQ, Yorkshire, England. e-mail: info@hsl.gov.uk

[17]Factory Mutual Research Corporation, 1151 Boston-Providence Turnpike, P.O. Box 9102, Norwood, MA 02062. Tel: 617-762-4300.

TABLE 4. Flammability Characteristics of Heptane[18]

Item	Result	Notes
Flash point	−4°C	Temperatures above -4°C produce a vapor concentration above the liquid which can be ignited.
Flammability limit	1–7%	Concentrations between 1% and 7% heptane in air are flammable. Above and below these concentrations, combustion cannot be supported.
Auto-ignition temperature	204°C	Heptane spontaneously combusts above 204°C.
Minimum ignition energy[19]	0.24 mJ@ 3.4%	At this concentration it takes a spark of only 0.24 mJ to ignite the vapor. Higher-energy sparks are needed when the vapor concentration becomes more or less than 3.4%.

Resistance between a person and the ground should not exceed 10^8 ohms. Operations employing insulating liquids of low flash point need special attention. The use of inert gas blanketing is standard practice in operating a centrifuge; this is usually supplemented by installing oxygen meters that shut off the equipment when oxygen levels rise into the explosibility limits zone for the solvent being used; this zone varies from solvent to solvent.[18]

The use of flammable solvents always touches off a "spark" of concern! I recall one serious incident occurring in the drying of a penicillin wet with heptane. After filtration the heptane wet product was loaded into plastic lined fiber board drums and moved to the drying area. During the process of digging out the wet product and spreading it on trays for drying, an explosion occurred that severely burned the two operators involved. The subsequent investigation led to the conclusion that an electrostatic charge generated by the use of plastic scoops had created a spark which set off the explosion.

The potential dangers of working with heptane can be seen by reference to its flammability characteristics (Table 4).

THE PRACTICE OF SAFETY IN THE WORKPLACE

A short account of the major considerations for the assurance of a safe working environment follows. This account provides perspective on the culture of safety needed in a chemical process development organization.

[18] *Handbook of Chemistry and Physics*, 78th edition, Lide, D. R., Ed., Chemical Rubber Company, Boca Raton, FL, 1997–1998, Section 15, pp. 14–18.
[19] *Plant/Operation Progress*, 1992, **11**, No. 2.

TABLE 5. Major plant service Functions of In-House safety organisation

Item	Service
Safety training	Documented in-house induction and safety reinforcement. OSHA mandated requirements including evacuation, emergency response, fork-lift, fire extinguisher, respiratory, eye and hearing protection, HAZCOM, vessel entry, hotwork, lock-out/tag-out, laboratory safety and documentation
Safety inspections	• Plant inspection with team of rotating membership • Local housekeeping with team of rotating membership • Follow-up meetings • Incident review (including outside incidents for information) • Audits with company Safety/Health organisation • Action plans and compliance reviews
Supplies & MSDSs	• Ensuring the availability of protective equipment [head (eyes & ears), hands and feet] • Ensuring on-site limits on dangerous chemicals are being observed (quantity, warehousing and conditions) • Update MSDS logs

The Chemical Safety Organization. Every company has its own umbrella Safety/Health organization to promote its particular safety culture, to provide the leadership for the creation of safe operating conditions, and to ensure that such conditions are adopted. Those departments, or divisions, wherein safety requires far more emphasis than in such as office areas, create their own in-house "mini-Safety/Health" organizations with dotted line relationships to the company-wide (umbrella) Safety/Health organization. In short, the chemical process development in-house organization, which faces many unknowns in its day-to-day work with new chemical syntheses, has to have all the capabilities needed to ensure that both laboratory and pilot plant operations are intrinsically safe. The in-house organization is also accorded the power to enforce safe operations. To ensure that priority is given to chemical development needs, the in-house Safety/Health organization has the laboratories, the instrumentation (notably calorimetric), and the staff to undertake the evaluations needed in the timeframe needed to meet the urgent requirements of clinical supply programs. This in-house organization also works closely with the umbrella Safety/Health organization in implementing a variety of functions needed to ensure safe operation and worker health, and to provide the data needed to assure safety compliance. These areas are listed in Table 5.

The in-house Safety/Health organization works with the umbrella organization in liaison activities with outside groups, including manufacturing, maintenance, environmental, and others, as needed.

Beyond the above framework (focusing on training, follow-up, attention to detail, and vigilance in the pursuit of safety), companies endeavor to continuously improve their safety performance. One popular approach has developed from a critical evaluation of behavior and an in-depth examination of the "why's and wherefore's" of the

choices people make in adjusting their actions to meet both relatively routine and also sometimes unpredictable situations on their work site. Adoption of behavior-based safety programs[20] appears to be a promising addition to the armory of approaches for improving safety.

The mechanisms of protecting people from exposure to unsafe situations are too numerous to summarize here, but one preemptive action that stood out for me was practiced by the physician in the Glaxo, Ulverston penicillin/cephalosporin factory in the 1960s. He looked askance at ginger-haired, blond, and generally fair-skinned people when they interviewed for employment in areas where they may be exposed to the potentially allergenic compounds being produced, purely on the grounds that the record showed that they were much more likely to suffer allergenic reactions than dark-haired or darker-skinned people!!

Operating Procedures. After having gained a great deal of information regarding the potential hazards of a chemical reaction, the chemist intent on scaling the chemistry up to a pilot plant scale needs to work with chemical engineers, process operators, and Safety/Health, environmental, and regulatory people in the creation of an operating procedure, often referred to as a Standard Operating Procedure (SOP). All involved in creating SOPs work under the guidelines set by the various government agencies charged with oversight in these areas: OSHA, EPA, FDA.

The Safety Section of the SOP is the most vital component, since it deals with the education and protection of those who will run the process. However, it covers more than the dangers addressed in the hazard evaluation phase. It requires the creation of Material Safety Data Sheets (MSDSs) for all the chemicals needed in operating the process. It provides overall guidance on the safe operation of the process and identifies what protective gear to wear and what precautions are needed in the operation. These efforts are also inextricably linked with what needs to be done regarding process emissions and wastes.

Generally, in the early phases of an API synthesis project, many new chemicals are prepared and used for which there is no or very little safety information or industrial hygiene data. However, rather than delay the project by waiting to gather *all* the safety data (calorimetric data are always gathered to determine whether there are any major risks), a judgment call is usually made to go ahead using the best safety protection available, and with the most appropriate plant systems, to deal with the eventualities that can be perceived. This judgment call usually follows a meeting to evaluate line-by-line detail of the new process, and also the detail of how the plant equipment will be used—a form of the hazard operability study. Emissions and wastes are captured or contained using the best available technology and are usually sent away to approved disposal experts. In general, a conservative stance is adopted in all first-time activities.

Eventually, as a project matures to become a candidate for development to a manufacturing scale, it becomes necessary to gather a great deal of additional data,

[20]Behavioral Science Technology, Inc., 417 Bryant Circle, Ojai, CA 93023. E-mail:bstojai@bstsolutions.com

both to create comprehensive MSDSs on all the chemicals involved and to deal with the testing requirements for storage of the chemical and for its shipment between locations. Particular concerns are the stability of materials and dealing with spills. Happily, the approach to dealing with spills has improved dramatically over the last four decades. I recall as a young chemist in the 1960s being the sole technical person in the office area of Arapahoe Chemicals in Boulder, Colorado, when a frantic call came in from a man on the dock in New Orleans. One of his men had punctured a drum of 3 M ethylmagnesium chloride in diethyl ether with his forklift truck and was urgently seeking information on how to deal with it. I ran across the office for a disposal procedure manual, but in the 30 seconds taken to get back to the telephone, a calmer voice at the other end said "it's OK buddy, somebody kicked the drum into the harbor and it's buzzing around putting on quite a show." Today the procedures for dealing with such eventualities are an essential part of the package of documents sent out with the chemicals being shipped.

Material Safety Data Sheets. MSDSs should be available for all chemicals sold in the chemical marketplace. No transportation of any chemical should be undertaken without an MSDS. In building an MSDS for a new chemical to be shipped, the following information needs to be provided:

1. Chemical product and company identification
2. Composition/Information on ingredients (formula and CAS number)
3. Hazards identification
4. First aid measures
5. Fire-fighting measures
6. Accidental release measures
7. Handling and storage
8. Exposure controls/personal protection
9. Physical and chemical properties
10. Stability and reactivity
11. Toxicological information
12. Ecological information
13. Disposal considerations
14. Transport information
15. Regulatory information
16. Other information

Provision of all of the above information is primarily for the shipment of larger quantities of materials. The reality is that gram quantities of laboratory samples, especially research samples, are shipped with whatever data can be quickly mustered. The shipper of laboratory samples is responsible for ensuring that proper precautions are taken in the shipment of potentially hazardous small samples.

Safety Award Programs. Although organizations do much to make people more conscious of safety—for example, through doormats displaying safety messages at the building entries, through safety posters on the wall, or through case studies in safety meetings—my experience with safety awards suggests that, if they are adopted at all, they are devised to avoid fudging and cover-ups. I have known injured employees (notably with back problems resulting from poor lifting practices or bad lacerations) to take vacation days rather than spoil their department's safety record!

CONCLUSION

Although this presentation has provided little more than an introduction to the Safety field, I have tried to promote an awareness of the need to work respectfully with chemicals for the good of all those involved in a project.

Safety is the most important of the prominent regulated activities (Safety, Environmental, and FDA Regulatory Affairs) encountered in progressing chemical process development projects. Death, serious injury, and property damage still result far more often from events occurring in the manufacture of a drug than from environmental excursions or during the process of developing the drug efficacy and adverse reaction information for a new drug application (NDA).

Safety/Health and Environmental Affairs are often interwoven in practice, especially where process emissions, chemical exposure, and waste disposal can impact on public health. Many, if not most, companies with chemical synthesis plants in populated areas work with local communities to foster good relations sometimes via open house days or in the creation of action plans to deal with adverse events which may occur in plant operation. The presentation on Environment (Chapter 5) addresses the canon that has developed to deal with exposure to chemicals, with the impact of spills and emissions on all life forms and with waste recycle, treatment, and disposal.

As will be seen in the presentation on FDA Regulatory Affairs (Chapter 6), human safety issues are an integral part of the development of the API through the FDA.

In closing, it is worth pointing out that the controls, discipline, and documentation built into chemical processes for the manufacture of APIs, to satisfy FDA requirements, has also greatly improved approaches and attitudes to safety and environmental affairs.

5

THE ENVIRONMENT

> Where there are threats of serious or irreversible damage, scientific uncertainty shall not be used to postpone cost-effective measures to prevent environmental degradation.
>
> ——1992 Rio Declaration on Environment and Development

INTRODUCTION

Environmental issues continue to occupy a prominent, real and emotive place in world thinking as populations increase and the earth's declining resources are developed to meet a variety of "needs," from growth and employment to survival and creation of a steady state, and much in between. As a result, the world's thinkers have become polarized, with developers and conservationists trying to agree on the best ways of moving "civilization" into the future.

The effect on industries, which generally try but are also obliged to be "wise" in the development of anything, has been equivocal, with one good result being that they have joined, to one degree or another, the movement to build a world public conscience on the environment. Governments, aware that conscience was not enough, have worked to overcome egregious environmental exploitation, while still encouraging development. As a result, as in other fields subject to government oversight (including Safety and FDA control over pharmaceutical development), environmental guidance has been established with the Environmental Protection Agency (EPA) taking a leading role in providing regulatory oversight. Apart from government activities, Chemical Societies everywhere are promoting environmentally friendly chemistry. The American Chemical Society's Green Chemistry Institute, for example, provides

The Management of Chemical Process Development in the Pharmaceutical Industry by Derek Walker
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information and encouragement worldwide in a drive for everyone to create processes that minimize the release of chemicals into the environment.

Although pharmaceutical companies are small players with respect to the volume of chemicals prepared and used, they subscribe to the high standards of the chemical industry, generally with special operations for dealing with the new, exotic and hazardous chemicals frequently encountered in synthesizing APIs. Chemical Process development chemists and engineers, because of their bridging role in developing the processes to be used in the eventual manufacture of an API, need to be fully aware of the hazards associated with exposure to chemicals and wherever possible to avoid the use of dangerous chemicals. In this area, safety and environmental protection are closely integrated, and process chemists and engineers share a common interest in knowing what to avoid and what laws apply to the use of new chemicals as well as toxic chemicals and what limits need to be observed with respect to personnel exposure.

An outline of the major environmental laws in the United States follows. These laws provide a framework for the basic standards used in the governance of environmental matters. The most important laws are the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA—now more often referred to as Superfund, a name derived from the passage of a later supplement to CERCLA), the Resource Conservation and Recovery Act (RCRA), the Clean Water Act (CWA), the Clean Air Act (CAA), the Safe Drinking Water Act (SDWA), the Emergency Planning and Community Right-to-Know Act (EPCRA), and the Toxic Substances Control Act (TSCA). A brief description of these acts follows:

Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). The original Act (1980) was amended in 1986 by passage of the Superfund Amendment and Reauthorization Act (SARA). The law governs sites that have been contaminated by hazardous substances or could become contaminated (e.g., by leaks developing in corroded drums of hazardous materials held on a site). The law imposes liabilities on all those with any connection to the site at the time the hazardous substance was left there. This includes the generator of the hazard as well as the transporter; it also includes the owner or operator of the site, as well as any future acquirer (say, through a merger). Liabilities include investigation of the site and cleanup charges. The only defenses against liability are (a) Act of God, (b) Act of War, and (c) Act of Omission (such as an innocent purchaser of the site, proving that tests of the site had been undertaken and no environmental concerns found).

Another requirement of Superfund is that notification of a hazardous substance release (in reportable quantities) must be made at the time of the release – failure to report is treated as a felony.

The Oil Pollution Act is roughly similar to Superfund but is specifically applied to releases of oil and petroleum products.

Resource Conservation and Recovery Act (RCRA). This law governs the "cradle to grave" tracking of hazardous wastes all the way from generation through treatment, recycling, storage, shipping, and disposal. A permit system governs the entire

tracking process through to approved destruction in a licensed, permitted facility. As in other regulated disciplines, documentation tracking every phase of hazardous waste movement is required.

The law allows a generator of hazardous waste to undertake treatment, storage, and disposal, provided that these steps are properly documented; in the early days of governing RCRA, the steps of treatment, storage, and disposal led to much confusion (see later).

Amendments to RCRA were introduced in 1984, notably governing the use of underground storage tanks, many of which were found to be leaking. This amendment essentially led to underground storage becoming a less favorable and expensive option – today, all storage tanks need to be in bunded containment areas, with above ground storage being preferred.

Clean Water Act (CWA). The discharge of wastewater from industrial facilities in the United States is controlled by a permit system (National Pollution Discharge Elimination System). The limits of pollutants allowed by the permit depends on both the nature of the pollutants present and also the situation prevailing in the receiving body of water, whether this be a river, estuary, lake, publicly owned treatment works (POTW), wetland, or any other. Effluent limitations are set by the EPA, but individual states may require stricter limits to ensure that the receiving body of water can absorb the discharge volumes and pollutant levels proposed. The company discharging the waste is required to monitor discharge composition and periodically provide a report, available to the public, logging the levels of pollutants discharged.

The discharge of wastewater to a POTW is usually strictly controlled since the POTW itself is a permitted facility. Wastewater such as process wastewater, received from industrial facilities, must meet pretreatment standards so as not to compromise the treatment undertaken by the POTW. Usually, industrial wastewater is subjected to pH adjustment and has to meet carbon oxygen demand (COD), biological oxygen demand (BOD), and particulate content standards set in collaboration with the POTW.

The discharge of all wastewater from a given industrial site is controlled, including storm water collected from company land, roads, rooftops, and car parks.

Discharges in excess of permits can exact considerable financial penalties, and even prison sentences.

Clean Air Act (CAA). In the United States the CAA enjoins the EPA to set ambient air quality standards and emission limitations that have been adopted by the states under federally approved plans. The CAA standards and limitations apply to all sources that might pollute the air including power stations, automobiles, and industrial sources. Operating permits require emissions monitoring to show compliance with the standards. As with the CWA, periodic reports on emissions are required which, again, are available to the public. The public can use reports, showing noncompliance, in citizen suits against an infringer.

There have been several amendments to the original act including the highly publicized permit requirements for volatile organic compounds (VOCs) that cause ozone

depletion; some VOCs such as the chlorofluorocarbons are in the process of being completely replaced by compounds found to be less damaging to the environment.

Safe Drinking Water Act (SDWA). This act regulates suppliers of drinking water to the public and also those companies that supply their own water (e.g., on-site well water) to their employees. Maximum contaminant levels and maximum contaminant level goals have been developed to try to ensure that the risks in deaths from diseases such as cancer are controlled to a low range [e.g., for cancer, one excess death (over average) in 10^6]. Standards are continually improving; for example, the maximum allowed level of lead in drinking water has been reduced from 50 parts per billion to 5 parts per billion.

The standards developed under the SDWA are often used in setting the standards for clean up under RCRA and CERCLA.

Emergency Planning and Community Right-to-Know (EPCRA). This 1986 act was a component of the (SARA), and it mandates that the use of hazardous materials in a manufacturing operation is preceded by the provision of information on the "intent-to-use" to regulatory authorities and the local community. This information is usually supplemented with a response plan addressing the actions that would be taken in the event of a spill or other release.

EPCRA also requires that companies compile a hazardous chemical inventory record and report releases. The EPA has used this information to create a nationwide record on the usage and release of hazardous materials.[1] The dialogue resulting from the availability of such information to the public led most companies to subscribe to voluntary hazardous emission reduction programs.

The Pollution Prevention Act of 1990 essentially formalized a movement that now requires that industrial companies report their progress in toxic chemical source reduction and recycling for each toxic chemical during the prior calendar year. The information collected is available to the public.

The Toxic Substances Control Act (TSCA). One of the most important aspects of TSCA lies in the power given to the EPA to regulate the use, storage, disposal, and clean-up of hazardous substances. The most publicized example of this power is the case of the enforced clean-up of polychlorinated biphenyls (PCBs) from the Hudson River in New York. After years of legal wrangling, General Electric was ordered (in 2001—24 years after production stopped) to dredge the river to remove PCBs. Another high-profile PCB case, concerning dumping in landfills and local waterways near Anniston, Alabama, is being defended by Solutia, Inc., a spin-off from Monsanto.

TSCA has given the EPA broad control over the production and importation of new chemical compounds. Before production of a new chemical can commence, the EPA can require that the substance be tested. In essence, this situation is little different

[1]For example, Consolidated List of Chemicals Subject to the EPCRA and Section 112(r) of the CAA. Title III Lists of Lists EPA 550-B-01-003, October 2001. www.epa.gov/ceppo

from the long-standing practice in Europe, embodied in their efforts to register all chemical substances, both old and new. The drive for this came in part from releases of chemicals (some accidental, some unauthorized) and the exposure of untrained people during the transportation of chemicals. The European Dangerous Substances Directive of June 27, 1967 is the European equivalent of TSCA. This directive led to the compilation of a list of all known chemical substances made and used in commerce between January 1, 1971 and September 18, 1981, and it was formally published on June 15, 1990 under the title "European Inventory of Existing Chemical Substances" (EINECS). All known chemical substances appearing in this list were essentially "grandfathered" on the assumption that they had been shipped and used previously such that the hazards associated with them were presumably known and methods of dealing with spills and emissions were already available. However, in cases where the quantities marketed have grown substantially, further testing may be required. APIs (active pharmaceutical ingredients) are themselves exempt from TSCA since they are the subject of comprehensive toxicity testing prior to FDA approval.

New chemicals produced after the EINECS list was closed were required to be the subject of a battery of tests, depending on the quantity, before they could be registered for use and shipment. The ever-growing list of new substances was first published under the title "European List of Notified Chemicals Substances" (ELINCS) on May 29, 1991 and is updated periodically. A brief outline of the major tests required before a new substance can be registered is provided later.

The framework of basic environmental standards is governed by a quality system that companies set up to oversee all activities. One such quality system, set up in Europe by the International Organization for Standardization (ISO), requires that a quality management and registration operation is built into a process plant and that manufacturers govern themselves through policy and procedure manuals, training operations, and audit programs to ensure that their activities are properly validated, documented, and continually comply. The European System covering environmental standards is often referred to as ISO 14000. ISO qualification generally results from passing a one-time inspection with the applicants being left with the responsibility of ensuring that their approved validated control systems are a starting point for long-term improvement and that renewal audits show they continually comply.

PRACTICAL OPERATIONS

In practice, responsible companies processing chemicals operate under an ISO 14000 framework or an equivalent. Their policy and procedure manuals detail the control of activities all the way from receiving and storing chemicals to moving and processing them and, finally, dealing with wastes. They cover worker protection (often with Safety), equipment requirements and setup, chemical and solvent dispensation, processing operations, emissions capture, intermediate and product isolations, and wastewater/waste solvent treatment and disposal.

It is pertinent to provide an overview of the environmental concerns associated with the major aspects of chemical processing in large-scale operations, particularly

pilot plants. These are process emissions to the air, chemicals' handling, organic process wastes, and wastewater.

Process Emissions to the Air

The final regulation covering hazardous air pollutants was published in the *Federal Register* on September 21, 1998.[2] At the time the laws were set up in the State of New Jersey, I failed in efforts to gain an exemption for R&D pilot plant operations, up to the final stage of defining a process that would be taken into large-scale manufacture. My grounds were that in the early stages of development we needed to delay work on environmental monitoring, data collection, and control issues until we had determined the best chemistry to use and that, anyway, pilot plants work with only small quantities and create little pollution. To capture this little pollution, I proposed that we should set up a low-temperature system for trapping all emissions (i.e., an overkill chiller system backed by scrubbers and/or carbon absorption), protect operators in the most practical and aggressive way (in collaboration with Safety), and drum waste solvent streams for incineration – I agreed that process wastewater should meet the standards needed for discharge to the local Publicly Owned Treatment Works (POTW). In this way I hoped to (a) delay the considerable data collection and paperwork associated with reportable operations until the final process selection had been made and (b) use the time and scientist/engineer/operator expertise we would free up to responsibly and diligently speed process selection, including factoring in related environmental issues into the equation. Unfortunately, this did not happen because no one saw an easy way of separating out R&D from our small-scale manufacturing activity. In short, we fell afoul of a strict interpretation of the regulation (reference 2, p. 50294). Therefore, before every pilot plant run we made, we were obliged to carry out "pre-" and "post-emissions" calculations. This involved calculating the vapor emissions from the chemical reactions being undertaken over the time of an operation, at all temperatures and accounting for all gas blanketing. The "post-emission" calculations were done to account for any deviations in the operating procedure during the actual running of the process. The objective of carrying out emissions calculations in the first place was to ensure that emissions did not exceed the capabilities of our scrubbing systems. I eventually only succeeded in eliminating the "post-emission" calculations when no significant process deviation occurred.

The control of emissions to the air both protects process operators and preserves the quality of the air for local communities. In addition, control minimizes any impact that volatile organic compounds (VOCs) may have on the larger environmental picture (including ozone layer depletion and global warming). The New Jersey State and Federal environmental control programs also require control over so-called fugitive emissions (leaks from piping flanges and valves for example).

[2] 40 CFR Parts 9 and 63, pp. 50279–50386.

The protection of workers has been well dealt with by OSHA. Limits on worker exposures allowed have been published[3] in the form of threshold limit values (TLVs) and time-weighted averages (TWAs), the latter being the amount of substance a person can be exposed to in a normal 8-hr day in a 40-hr work week. In both production plants and pilot plants, emissions' capture is most usually achieved by coupling reaction vessels to a scrubbing system, a carbon bed absorption system, a low-temperature condensing system, or a combination of these. Incineration and catalytic oxidation are also used to destroy emissions. In opening reactors, companies frequently employ "elephants' trunking" exhaust for emissions' capture at the open manhole, but worker protection can extend all the way to the use of "breathing-air" suits when particularly noxious materials are being used. In manufacturing practice, programs are set up to obtain emissions data for all chemical process operations to ensure that the plant is operating within its permit. This is often a one-time operation with occasional audits of routine production to assure compliance. Frequently, purpose-built emissions control units are installed to capture process emissions.[4]

Manufacturing processes generally meet environmental requirements, but a restless search is always going on to improve them (e.g., reducing solvent usages and waste volumes). I recall one such effort in the manufacture of albuterol (salbutamol), wherein work to introduce a simpler, environmentally beneficial and lower-cost process led to air emissions problems which spurred further beneficial changes.

The old process for the manufacture of albuterol[5] requires the use of a number of chemicals, particularly formaldehyde and bromine, which are classified as extremely hazardous substances (and subject to reporting requirements under EPCRA and CAA—see later). Clearly, we preferred not to handle these. At the time, albuterol manufacture, because of its small volume, was being carried out in Chemical Development plants. Because we were enjoined to reduce wastes as part of our RCRA and EPCRA commitments, we initiated a search for a better and simpler process. Such a process evolved from our work on the manufacturing process for dilevalol hydrochloride (q.v.). Scheme 1 summarizes our first new process starting with low-cost methyl salicylate.[6]

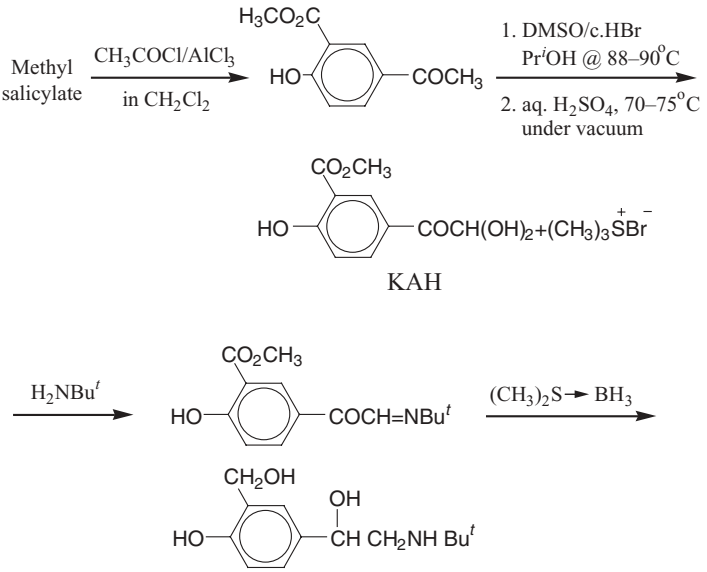
High-quality albuterol was obtained in good yield from this process. However, several environmental disadvantages were identified. The preparation of the keto aldehyde hydrate (KAH) generated dimethyl sulfide, methyl bromide, and trimethylsulfonium bromide (this compound sublimed in the condenser). In addition, reduction of the Schiff base with dimethylsulfide borane, although very attractive in simplifying

[3]*Handbook of Chemistry and Physics*, 78th edition, Lide, D. R., Ed., Chemical Rubber Company, Boca Raton, FL,1997–1998, Section 16, pp. 32–28.

[4]The Robinson Brothers Ltd. Manufacturing Plant in West Bromwich, England, has a ring main emissions control system around its plant for capturing odorous sulfur compounds from its processes, for central treatment and/or incineration. Robinson works on the principle that a good environmental standing in the local community is easily lost and hard to regain.

[5]Kleeman, A., Engel, J., Kutscher, B., and Reichert, D. *Pharmaceutical Substances, Syntheses, Patents, Applications*, 4th edition, Georg Thieme Verlag, Stuttgart, 2001, p. 1849.

[6]Tann, C. H., Thiruvengadam, T. K., Chiu, J., Green, M., McAllister, T. L., Colon, C., and Lee, J. U.S. Patent 5,283,359, 1994 (to Schering Corp.).



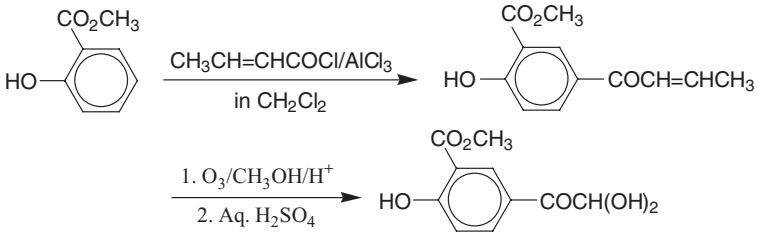
SCHEME 1. Process for the preparation of albuterol from methyl salicylate.

the process by achieving three reduction steps in the one pot, gave odorous dimethyl sulfide as a byproduct. Our proposal was to source KAH from a third-party supplier (instead of the 5-bromoacetyl methyl salicylate produced for the old process). However, scale-up of the Scheme 1 process to KAH revealed considerable difficulties in dealing with the sublimed trimethylsulfonium bromide and in accommodating the high costs for the pollution control equipment required to remove the unreacted dimethyl sulfide and methyl bromide. In addition, traces of 3-bromo KAH were found in the KAH produced by the Scheme 1 process. The third-party's price idea for KAH, from initially appearing attractive, escalated considerably because of the added charges calculated as needed to depreciate the cost of emissions control equipment. In spite of this, the Scheme 1 process provided a foundation for Sepracor, Inc., to build a chiral process route to synthesize the allegedly more active (*S*)-albuterol.[7]

As far as the conversion of KAH to albuterol was concerned, our production colleagues in Ireland (Drs. Brian Brady and Maurice Fitzgerald) were able to find practical process conditions under which sodium borohydride replaced dimethylsulfide borane, with the same quality and yield result.

Nevertheless, the setback on the cost of KAH coupled with the relatively low kilo requirements for albuterol and plans to move production off shore quenched interest in the Scheme 1 process despite my rearguard laboratory efforts (with our Dr. C. H. Tann and Dr. Beat Zehnder, Fachhochschule Nordwest Schweiz) to identify the basis of an alternative much cleaner route into KAH (Scheme 2).

[7]Gao, Y., Hong, Y., and Zepp, C. M. U.S. Patent 5,442,118, 1995 (to Sepracor Inc.).



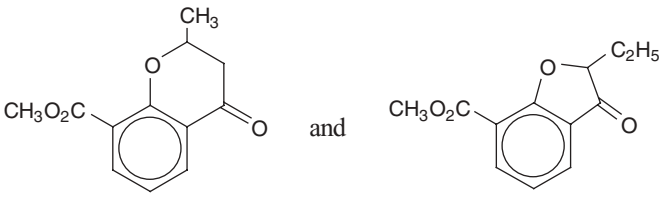
SCHEME 2. Proposed new synthesis of ketoaldehyde hydrate for albuterol.

The principal raw materials were low in cost: Methyl salicylate was $5.50/kg and crotonic acid was $3.85/kg in 1996.

Although there was useful literature precedent for crotonoyl chloride acylation[8] of bromo methyl salicylate, there was none for the ozonolysis reaction. There was speculation that ozone would open the phenol ring, but for my part I argued that the carbonyl groups would inhibit this. Based on my oft-stated homily that one should "never allow theory to abort an experiment," our Dr. Tann showed that the crotonoylation reaction in Scheme 2 could be carried out directly in apparently high yield with aluminum chloride in methylene chloride and that ozone did not open the phenol ring.

The ozonolysis step was studied in Switzerland using methanol-methylene chloride as the solvent at $-15°C$ to $-70°C$. The starting methyl 5-crotonylsalicylate was fully consumed in less than 30 min. The presence of KAH was determined by thin-layer chromatography (Figure 1).

The two ozone-resistant impurities in the starting methyl 5-crotonoylsalicylate were speculated[9] to be



The principal low-level impurity was later identified to be the keto acid produced by oxidation of the ketoaldehyde. A very small amount of the benzoic acid resulting from hydrolysis of the methyl ester could also be detected.

It appeared to us that given a successful development effort, the methyl 5-crotonoylsalicylate route to KAH would eliminate all the air emission problems associated with the original manufacturing process for albuterol intermediates as

[8](a) Kawano, S., Komaki, T., and Watanabe, H. Japanese Patent 44077571, 1969 (to Eisai Co. Ltd.). (b) Kono, S., Komaki, T., and Watanabe, H. Japanese Patent 43013619, 1968 (to Eisai Co. Ltd.).

[9]Suggestion of Dr. J. Gosteli, Cerecon AG, CH-4416 Bubendorf, Switzerland. Dr. Gosteli also reasoned that the stability of methyl salicylate in the Friedel–Crafts reaction may be understood by regarding it as a vinylogous carbonate, noting that anthranalate esters are also slow to hydrolyze.

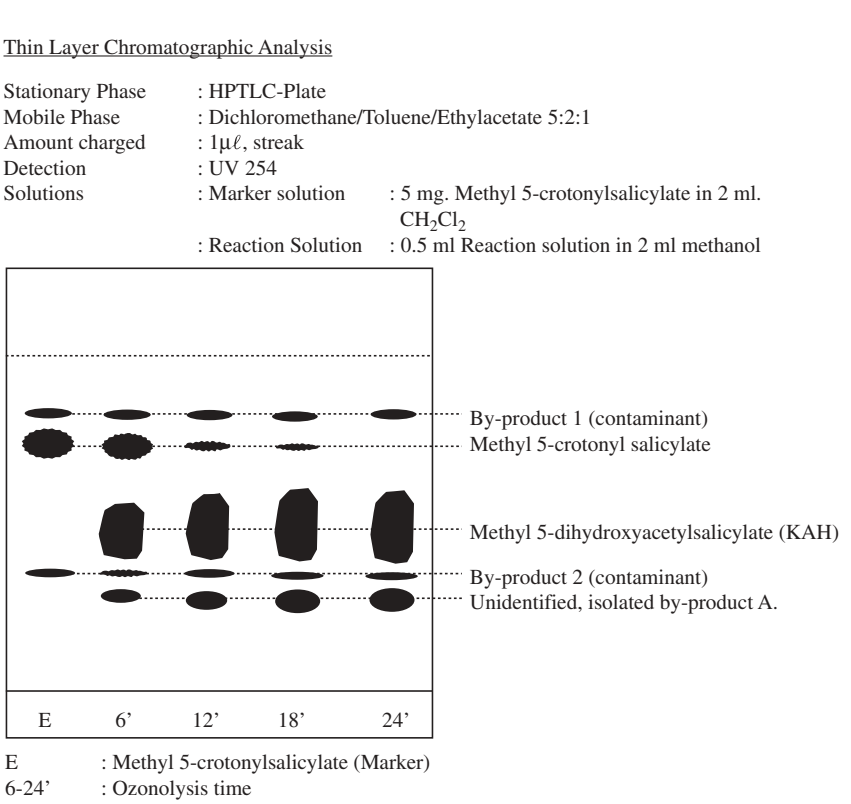


FIGURE 1. Thin-layer chromatogram of the solution obtained by the ozonolysis of methyl 5-crotonoylsalicylate.

well as those described above for the Scheme 1 process. However, because of other priorities/plans and the relatively low return on investment, support for exploring the new process lead withered away.

In the broader scheme of things, air emissions issues and especially setting limits on the amounts released, continue to spur debate. For the chemist and engineer developing a process in a responsible company, emissions need to be taken into account. As seen in the foregoing albuterol process example, air emissions can sometimes govern selection of the process to be developed for larger-scale use. Alternatively, one can work hand in hand with a third party who has the demonstrated capability to deal with specific emissions. In transferring technology to third parties, emissions calculations are always very helpful, even early in the life of a project, in establishing a good rapport with the third party.

Chemicals Handling and Organic Process Wastes

Chemicals Handling. The chemicals of most concern to all workers (including those who might become exposed—e.g., transporters via a spill) and to the EPA are

categorized in published lists. Thirteen chemicals with proven carcinogenic properties are regulated by OSHA. These are:

α-Naphthylamine
β-Naphthylamine
Methyl chloromethyl ether
Bischloromethyl ether
Benzidine
3,3'-Dichlorobenzidine and its salts
4'-Aminobiphenyl
4-Nitrobiphenyl
2-Acetylaminofluorene
4-Dimethylaminoazobenzene
N-Nitrosodimethylamine
β-Propiolactone
Ethyleneimine

Further additions to this list can be envisaged by structural implication—for example, tolidines, propyleneimine, nitrosoethylmethylamine, and so on. In practice, every effort is generally made by companies to avoid using these compounds.

Beyond the list of 13 substances, a larger list of chemicals has been consolidated and is subject to reporting requirements under EPCRA and CAA (see footnote 1). Most are classified as extremely hazardous substances (EHSs) and are subject to limits on the quantities allowed on site (threshold planning quantities—TPQs). The use of EHSs requires that documentation, training, surveillance, and emergency planning protocols are created for dealing with everyday use and inadvertent release.

Hazardous wastes containing listed toxic substances and wastes that are reactive, ignitable, corrosive, or toxic are covered under RCRA.

New chemical substances have to be qualified for use and transport by building a database that becomes more comprehensive as the quantities handled grow. In the United States, the shipment of small quantities (e.g., analytical samples) can be done with a very limited MSDS (especially if the sample is judged to pose little risk). Substances thought to be very toxic or carcinogenic need more testing, including an Ames test and an acute toxicity test (e.g., LD_{50}—lethal dose at which 50% of the rats/mice used in the test die). TSCA requirements for the shipment of larger quantities are similar to those used in Europe. An outline of European testing requirements for the Notification of New Substances (NONS) up to the level of one tonne/annum (or five tonnes, cumulative) is given in Table 1.

Increased production levels require additional toxicology and ecotoxicology data to ensure that prolonged exposure effects are understood.[10] Today, the ELINCS system is being progressed under European proposals labeled REACH—Registration, Evaluation and Authorization of Chemicals.

The above indicates that as a result of the increased knowledge base on chemical substances, chemicals handling has become more formalized. Gone are the times, as in my school days, when one could go down to a local chemicals supplier to buy small volumes of chemicals such as mineral acids and chemicals beyond the usual commercial chemistry set—for example, ammonium dichromate for the "Green Tea"

[10]It is appropriate to add that there is a growing effort to minimize the use of animals in all chemical testing programs.

TABLE 1. Outline of Testing Requirements to Qualify a New Substance for Inclusion in the European List of Notified Chemical Substances (ELINCS)

Kilo Threshold	Physicochemical	Toxicology	Ecotoxicology
Up to 10 kg	• Chemical identity (Spectra/HPLC) • Physical state	• Acute toxicity (1 route)	—
10–100 kg	As above, plus: • Flash point • Flammability	• Additional acute toxicity	• Acute toxicity to Daphnia • Ease of biodegradability
100–1000 kg	As above, plus: • Melting point • Boiling point • Water solubility • Partition coefficient (octanol–water) • Vapor pressure	As above, plus: • Skin irritation • Skin sensitization • Eye irritation • Bacterial cell mutagenicity	As above
1000 kg to cumulative level of 5000 kg/manufacturer	As above, plus: • Relative density • Surface tension • Explosivity • Auto-flammability • Oxidizing properties • Granulometry	As above, plus: • Acute oral toxicity • Acute dermal toxicity • Acute inhalation toxicity • Subacute (28-day) toxicity • Bacterial cell mutagenicity	As above, plus: • Acute toxicity to fish • Algal growth inhibition test • Bacterial respiration inhibition assay • Hydrolysis screening • Soil absorption/desorption screening

experiment, poisonous mercuric thiocyanate for creating "Pharaoh's Serpent," or magnesium ribbon, aluminum powder, and ferric oxide to demonstrate the "Thermit Reaction" in your back garden.[11] Sadly, even the spectacular Lassaigne nitrogen test, once used in college chemistry courses as a test for determining whether your unknown organic substance contained nitrogen, has also been consigned to chemical history; there was always an excitement to fusing your organic unknown in a Bunsen burner flame with a small "pea" of sodium, quenching the red hot fusion tube in water(!), and then adding a ruby red sodium nitroprusside solution and watching it turn Prussian blue if cyanide had been produced from nitrogen in your unknown! As an aside, one wonders whether loss of some of this old magic of chemistry has unwittingly dulled curiosity and enthusiasm for chemistry; however, given the insurance costs to cover legal liability, and probably a declining market for Bunsen burners, it had to be.

Although the professional chemist can still go to the company or university store or the Catalogue Supply houses for laboratory chemicals, control over the purchasing and storage of chemicals for pilot plant and plant use has become a highly organized and paper (or electronic)-intensive operation.[12] In regular commerce, warehouses are built for chemicals storage and divided into separate areas [receiving, in-process intermediates, APIs, quarantined chemicals, hazardous chemicals, and chemicals (wastes) for disposal]. The warehouse is governed by operating procedure manuals with particular attention being paid to the analytical status of every chemical.

The removal of chemicals from the warehouse and their processing in pilot plants and plants is controlled through Standard Operating Procedures (SOPs) protecting both the operators and the environment. SOPs are also developed for dealing with spills.

The major initial concerns of process development chemists lie in the selection of the process chemistry to be used, with safety, product quality, cost-of-goods, raw material/intermediate sourcing, process equipment requirements, and speed of implementation being the primary driving forces early in process selection. Environmental issues are an early consideration in process selection only when the use of environmentally noxious chemicals is proposed. Such chemicals are those that are acutely toxic (e.g., methyl isocyanate and phosgene), those affecting operator/community health (carcinogens, vesicants and lachrymators), those that may seriously compromise air quality (odorous chemicals, NO_x, SO_x, and ozone depleters), and those posing wastewater disposal problems (bactericides, heavy metals, ammonia, and phosphates). Some can be readily scrubbed (NO_x, SO_x). The use of noxious chemicals especially on a larger scale is often best left to third parties with facilities for handling them (e.g., phosgene).

[11] A large crystal of $(NH_4)_2Cr_2O_7$, when ignited, burns spectacularly to produce a green volcano of Cr_2O_3. The ignition of a trail of $Hg(SCN)_2$ causes decomposition with astonishing swelling. Iron objects are welded together by the intense heat generated when Mg ribbon in a mixture of Al and Fe_2O_3 is ignited.

[12] Unfortunately, the systems are not yet good enough to stop the acquisition of raw materials for making explosives by terrorists and chemicals for illegal drug manufacture.

Many hazardous and environmentally undesirable chemicals are in use in commerce and are appropriately controlled until another generation of chemical processes evolves (often in cost reduction exercises, or in securing a desirable patent position) to displace the original. The manufacture of 7(*R*)-amino-3-methylceph-3-em-4-carboxylic acid (often referred to as 7-ADCA) is a case in point where the original carboxyl protecting group, *p*-nitrobenzyl(using a vesicant, *p*-nitrobenzyl bromide, for esterification), was superseded by diphenylmethyl (using in situ diphenyldiazomethane for esterification), which in turn was superseded by the trimethylsilyl group (see Chapters 7 and 9).

Organic Process Wastes. Pollution from all industries, including that from chemical and pharmaceutical manufacturing plants, has over the years raised an enormous public outcry. Long ago, even in the so-called "developed world," industry was primarily concerned with the chemicals they could sell and paid relatively little attention to the wastes they produced. In my time, I can recall the Grand Canal on fire in Mexico City, resulting from dumped, organic-solvent-contaminated waste being set alight, and I remember the local "fallout" when irresponsible waste haulers in England illegally dumped spent fermentation waste in country woods. All of us are aware of acid rain, toxic sites, and their clean-up and have read of rapacious manufacturers around the world with little concern for anything other than maximizing their "bottom lines," dumping their wastes wantonly or illegally in landfills, in rivers and in the sea, or wherever they could. Rightly, such environmental atrocities, often compromising public health, led to government controls, massive fines, and even jail time for perpetrators in those countries that have enforceable environmental laws.

Today, most manufacturers are responsible and have been "ahead of the curve" for many years in waste recycling, treatment, and disposal. A waste-avoidance culture is also emerging in the selection of processes to be developed for use on a manufacturing scale. The aforementioned albuterol process work at least testifies that environmental issues are being raised and, in the 7-ADCA case, that dirty processes (the use of *p*-nitrobenzyl protection) are being replaced by cleaner ones (trimethylsilyl protection).

The reality in developing and operating chemical processes on a pilot plant scale is that waste treatment goes on continuously as part of the process, particularly to render wastes safe for disposal. Thus activated carbon cakes (say, from a decolorizing step), or a spent hydrogenation catalyst, often need to be washed to remove flammable solvent and treated with water to render them safe for disposal. Organic process wastes are frequently disposed of by incineration, often after a simple solvent stripping operation is used to recover a volatile solvent for recycle. Solvent recycle, which helps to meet environmental goals to reduce chemical usage, needs to be done with an eye to quality. This is particularly important in the last steps of a process—the recovered solvent needs to be subjected to careful analytical screening to ensure that the quality of the API, and even late intermediates, is the same as when fresh solvent is used.

There are other ways of reducing solvent (chemical) usage such as:

- Increasing reaction concentration (and with it plant productivity). An ultimate, if rarely achievable, goal would be to run the reaction without solvents.
- Harmonizing solvent usage within a plant by switching the solvent used in a process to one already established (and recovered) in the manufacturing plant receiving the technology.
- Redesigning the process to reduce the number of steps and solvent usage. An ultimate achievement in redesign would be to use water as the solvent and enzymes to carry out desired transformations.[13]

In a process development/improvement setting in the pharmaceutical industry, the process changes identified above are all likely to require regulatory approval before adoption, especially for late stages in the synthesis of an API (see Chapter 6).

There has been considerable growth of interest in so-called "Green Chemistry" or "Sustainable Chemistry" over the last quarter century. The terms "Green" and "Sustainable" have given new prominence to fermentation and enzyme-mediated processes and to systems that operate in water. Such processes build on the already major contribution that fermentation processes make to the pharmaceutical industry. As an aside, several important classes of API owe their commercial success to the fermentation of microorganisms:

Antibiotics:	Penicillins and cephalosporins
	Aminoglycosides
	Tetracyclines
	Macrolides
	Antifungals
	Nucleosides
	Avermectins
Anticancer agents:	Nucleosides (e.g., Bleomycins)
Cholesterol biosynthesis inhibitors:	Statins (e.g., Lovastatin)
Some vitamins	B_{12}, Riboflavin (some synthesized)

Fermentation is also the basis for the manufacture of biomass foodstuffs (primarily protein for animal and human consumption), amino acids (especially monosodium glutamate and L-lysine), and the major industrial feedstock and gasoline additive, ethanol.

More specific and growing uses of microorganisms are in the areas of finding enzymes for specific tasks, especially if one can integrate with established biological transformations. Thus, the Antibioticos success in harnessing an amino acid oxidase to convert the aminoadipic acid side chain of cephalosporin C into a glutaroyl side

[13]More speculatively, "cascade chemistry" has been proposed as an environmentally friendly approach to chemical synthesis. Process design mirrors nature in that the process of producing an intermediate leads to an active product that progresses to a further activated intermediate and so on down the cascade to a needed product; see Hall, N. *Science*, 1994, **266**, 32.

chain enabled them to tap into established amidase process systems to create an all-aqueous process for the manufacture of 7-ACA[14] (see Chapter 9).

There is little doubt that microbiological approaches to chemical transformations, and not only chiral transformations, are likely to grow substantially as the waste-avoidance culture becomes more established, and the laws are fully addressed.

In the early days of companies coming to terms with environmental laws, especially laws concerning process wastes, there was considerable overreaction by all parties involved—that is, internal company lawyers, waste haulers, and government inspectors charged with ensuring compliance. A pair of cautionary tales illustrate the disconnects that can occur in setting up new systems.

Case 1: Incident in the Early Days of Dealing with Process "Wastes". We in Chemical Development always felt that because of our knowledge base we were the right people to determine the best way of treating organic process wastes before disposal, regarding such work as part of any program to develop a process for use in a manufacturing plant. We felt even more strongly about this when it was decided that five drums of six-year-old lithium hexamethyldisilazane (prepared by us and erroneously labeled "Hazardous Waste") should be disposed of (a waste hauler quoted $100,000 for taking it away!). We relabeled the drums and neutralized the contents by adding them to cooled dilute sulfuric acid, disposing of the aqueous salts to the sewer and drumming the resultant relatively innocuous hexamethyl disiloxane for regular disposal. The Legal Department took us to task for relabeling the drums and for treating the waste without a permit. The Legal Department conducted an investigation; and based on their interpretation of the guidelines being adopted by the State of New Jersey and the self-reporting philosophy they had embraced, they sent a full report to the New Jersey State's Department of Environmental Protection confessing to a perceived illegality. The DEP made no issue about the case and it was dropped. Clearly, the Legal Department's interpretation of the embryo regulations was in error.

Case 2: Another Over-Strict Interpretation of the Wording of the Laws by a Government Inspector. I heard of this case on the radio in England during "Gardeners Question Time" one Sunday afternoon in June 1988. In creating the waste disposal laws, Parliament allowed that agricultural waste such as cow manure from farms could be spread on fields as a fertilizer, recognizing that this was, anyway, a long-standing practice. However, possibly useful industrial waste such as water waste from scrubbing ammonia could not. A large amateur gardener's allotment operation for growing vegetables and flowers had for years been taking deliveries of horse manure from a local racing stable. After auditing the racing stables, an officious environmental inspector came to the allotment and issued a court summons on the grounds that they were illegally disposing of *industrial* waste. It transpired that the stables had registered themselves as being in the horse racing *industry* and that race horse manure had been reclassified as an *industrial waste!* After the initial shock, the dilemma was resolved by allowing that the stable manure could be disposed of to the allotment if

[14]Cambiaghi, S., Tomaselli, S., and Verga, R. U.S. Patent, 5,424,196, 1995 (to Antibioticos, S.p.A.).

the allotment operators took charge of horse manure pick-up rather than continuing the previous practice wherein deliveries were initiated by the stables![15]

As the waste-avoidance culture develops, it is expected that other environmentally friendly technologies will emerge to, directly or indirectly, aid in finding better chemistry or avoid or reduce process wastes. Several of these technologies are outlined in the presentation on the future, including the use of polymer supports, electrochemistry, chemistry in greenhouse gases, and process hydration. Since waste reduction is a contributor to cost reduction, it is already in the mainstream of chemical process development activities for large-scale operation. It can thus be seen that, as well as being a socially responsible activity, waste reduction is a contributor to cost reduction, bringing it into the mainstream of chemical process development considerations.

Wastewater. Most pilot plants have a permit to treat (commonly by adjusting pH and removing volatile solvents) and discharge their waste water directly to a publicly owned treatment works (POTW) or, if the pilot plant is on a chemical manufacturing site, to an internal waste water treatment facility prior to discharge, under strict permit control, to a POTW or a natural body of water. As chemical process development work progresses to the stage where a process becomes a candidate for transfer to a manufacturing site, wastewater issues need to be addressed at the pilot plant level and with the manufacturing site taking over the project. Few of the large number of organic chemicals in use for API manufacture are the subject of guidelines on permissible levels that can be discharged in wastewater in the United States. Those that have been listed[16] are summarized in Table 2.

Frequently the manufacturing site will evaluate the waste water stream for compatibility with their existing waste water treatment/disposal systems and particularly to determine that the microbes used in COD/BOD reduction can accommodate the new wastewater when diluted in their existing wastewater feed. The most important parameters to control for wastewater disposal are pH, the volatile organic compound content, certain soluble salts and suspended solids, carbon oxygen demand (COD), and biological oxygen demand (BOD). Of these, pH is usually the easiest to maintain in the generally required range of 6–9 as it leaves the plant.

When the solvent content of the wastewater is high, incineration may be the lowest cost option for disposal. However, VOCs are often stripped for reuse or separate incineration. Soluble salts such as of widely used metals (iron, aluminum, and chromium) and of commonly used anions (cyanide and fluoride) can pose waste disposal problems. Excessive levels of such algal bloom promoters as ammonia and phosphate introduce effluent problems on a large scale.

[15]The story on the disposal of manure took another turn when the EU decreed restrictions in the amount of manure from pig, dairy, and poultry farms which could be spread over fields in "nitrate-vulnerable zones"—ostensibly to protect drinking water, rivers, streams, and coastal estuaries. Greater restrictions have been applied to farm waste disposal over sandy and shallow soils in Denmark and Holland in that disposal is banned over the period August to November. The smell accompanying the resumption of disposal in Holland can be detected on the east coast of England! Uhlig, R. *The Daily Telegraph*, March 12, 2002.

[16]*Federal Register*, **63**, No. 182, Sept. 21, 1998, 50434.

TABLE 2. Guidelines on Permissible Levels of Common Organic Contaminants in Wastewater.

Compound	Pretreatment Standards[a] Max. Daily Discharge	Pretreatment Standards[a] Avg. Monthly Discharge Must Not Exceed	Compound	Pretreatment Standards[a] Max. Daily Discharge	Pretreatment Standards[a] Avg. Monthly Discharge Must Not Exceed
Ammonia (as N[b])	84.1	29.4	Benzene	3.0	0.7
Acetone	20.7	8.2	Toluene	0.3	0.1
Methyl Isobutylketone	20.7	8.2	Xylenes	3.0	0.7
Isobutyraldehyde	20.7	8.2	*n*-Hexane	3.0	0.7
n-Amyl acetate	20.7	8.2	*n*-Heptane	3.0	0.7
n-Butyl acetate	20.7	8.2	Methylene chloride	3.0	0.7
Ethyl acetate	20.7	8.2	Chloroform	0.1	0.03
Isopropyl acetate	20.7	8.2	1,2-Dichloroethane	20.7	8.2
Methyl formate	20.7	8.2	Chlorobenzene	3.0	0.7
Methyl Cellosolve®	275.0	54.7	*o*-Dichlorobenzene	20.7	8.2
Isopropyl ether	20.7	8.2	Diethylamine	255.0	100.0
Tetrahydrofuran	9.2	3.4	Triethylamine	255.0	100.0

[a] Mg/liter (ppm).
[b] Not applicable to sources that discharge to a POTW with nitrification capability.

The pharmaceutical industry, because of the enormous diversity of chemistry used in the synthesis of APIs and their intermediates, probably carries more wastewater treatment/disposal problems than any other industry. Fortunately, the relatively small scale of production and the economic well-being of the industry has allowed all kinds of accommodations that would be major problems on a very large scale. Thus, gelatinous hydroxides of chromium and aluminum are frequently precipitated in small lagoons or basins and dug out for landfill disposal. Where this is not possible, imaginative alternatives are devised (e.g., Shionogi's disposal of waste from its aluminum chloride–anisole cleavage of cephalosporin esters is done via malic acid chelation and the solution shipped to a licensed processor). Cyanide in aqueous waste is usually oxidized to relatively harmless cyanate (by hydrogen peroxide, alkaline chlorination, or ozone), and fluoride ion is generally precipitated as calcium fluoride to reduce the fluoride concentration to a desired level (frequently <5–6 ppm). Where water waste streams contain large-molecular-weight organic compounds, membrane filtration technology (particularly ultrafiltration and reverse osmosis) offers a useful technology for concentrating the waste stream to recover water and an aqueous organic waste for incineration. This approach has been successfully applied to the disposal of a polyol waste stream in a petrochemical plant.[17]

The primary means of reducing COD/BOD in industrial wastewater is via settling basins and aeration in lagoons, biotowers, or large tanks. Tanks are frequently lidded and equipped with a scrubber if noxious off gases are present. A cascade of lagoons is often necessary to bring COD/BOD levels down to compliance levels for discharge to a POTW or a natural body of water. At Bristol–Myers' plant in Latina, Italy, the last lagoon is covered in water hyacinth, which absorbs "nutrients" and, through harbored aerobic and anaerobic microorganisms, also metabolizes polluting chemicals and absorbs metals (particularly lead and zinc). In addition, the visual effect of a field of water hyacinth at work, often with fish swimming about, is quite pleasing.[18] Related to this, treatment of industrial wastewater via manmade reed beds is now being practiced on a very large scale using macroscopic plant life (including bulrushes and reeds), often to valuable effect (e.g., the dechlorination of chlorophenols).[19]

Another illustration of the potential in harnessing plant life for soil remediation is the finding[20] that the fern, *Pteris vittata*, when grown in soil containing 6 ppm arsenic, hyper-accumulated 755 ppm of this metalloid in its fronds in only two weeks. When *Pteris vittata* was grown in artificially contaminated soil (1500 ppm As), the fronds took in 15,861 ppm As in the same two-week time frame. Similarly, research in both the United States and the United Kingdom has demonstrated the potential of using plants from the family Brassicacae in the remediation of soils heavily contaminated with zinc, cadmium, nickel, lead, and selenium.[21]

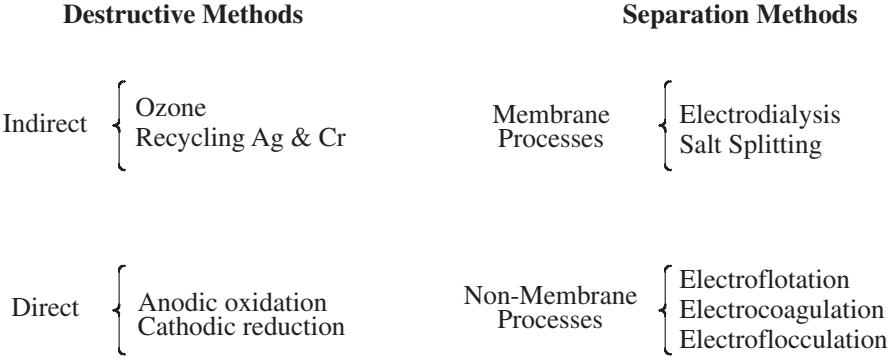
[17] Pearson, D. *Chemical Processing*, January 2002, 24. Website: www.chemicalprocessing.com

[18] However, it should be noted that the above-described Latina wastewater treatment system has now been replaced by an activated sludge treatment system.

[19] Cobban, R., Gregson, D., Phillips, P. *Chemistry in Britain*, 1998, **40**.

[20] Ma, L.Q., Komar, K. M., Tu, C., Zhang, W., Cai, Y., and Kennelley, E. D. *Nature*, 2001, **409**, 579.

[21] Rouhi, A. M. *Chemical and Engineering News*, 1997, Jan. 13, 21.



SCHEME 3. Outline of major electrochemical wastewater treatment options.

More recently, growing awareness of the presence of APIs in wastewater has drawn the attention of Environmental Protection Agencies in both the United States and Europe, and it has also drawn the attention of the U.S. Geological Survey (USGS). This has resulted from increased recognition that the following have come together to reveal new issues: (a) wastewater from feeding large quantities of antibiotics to livestock, (b) the common practice of flushing unused, outdated (and excreted) medications down the toilet, and (c) the development of exquisite analytical methodology to detect extremely low levels of APIs in water. For instance, the USGS has detected (at the part per billion level) almost all of 95 selected APIs (mostly antibiotics, antidepressants, anti-inflammatories, analgesics, antacids, and cardiovascular drugs) in streams across the United States.[22] In the United Kingdom, the Environmental Agency (EA) has gone even further in one case. Thus the EA has called for water companies in England and Wales to investigate sewage treatment technologies to effectively remove estrogenic steroids from rivers. Work at Brunel and Exeter Universities has indicated that 17α-ethinyl-estradiol (component of contraceptive pills) is having an adverse effect on the reproductive ability of male fish, even at concentrations lower than 1 ng/liter.[23]

A few other waste treatment technologies are outlined below.

Low-cost sources of electrical power have stimulated the widespread application of a number of electrochemically based technologies in wastewater treatment (Scheme 3).

The electrical generation of ozone is used in municipal water treatment. Ozone is a very powerful oxidizing agent (its oxidation potential being exceeded only by fluorine) and has the advantage of being about 12 times more soluble in water than oxygen. Ozone also has the advantage over chlorine (still the most favored oxidant

[22]Hileman, B. *Chemical and Engineering News*, 2001, Dec. 3, 31. See also HTTP://PUBS.ACS.ORG/CEN

[23]*Chemistry in Britain*, May 13, 2002; and Burke, M. *Chemistry in Britain*, January 30, 2003. This work is extending to wastewater from agricultural operations and aquaculture where steroid hormones are in use; see Nicholls, H. *Chemistry World*, October 2004, 21.

for municipal water treatment, and itself generated by electrical means) in that its use avoids the formation of chlorinated hydrocarbons from any organic materials which may be present. As an aside, ozone is also used in destroying odorous gas emissions and in chemical ozonolysis.

The electrochemical oxidation of metal ions (e.g., $Ag^{+} \rightarrow Ag^{2+}$) for the catalytic oxidation of organic compounds has been practiced on a small scale.[24] The feasibility of recycling Cr^{3+} produced from Cr^{6+} in the Marker degradation of diosgenin acetate is outlined in Chapter 11.

The direct electrochemical oxidation (no cell divider membrane) of wastewater has been employed in the textile industry. Typically, this industry produces an organic-contaminated wastewater that also contains sodium chloride; sodium chloride is desirable in promoting anodic oxidation. The presence of sodium chloride is fortuitous for textile manufacturers since the hypochlorite byproduct produced in the electrochemical oxidation process is used for textile bleaching operations.[24]

Of the separation methods, electrodialysis is the most widely employed, especially in the removal of nitrates from water. The electrochemical splitting of sodium sulfate in industrial wastewater streams has been employed to regenerate sodium hydroxide (and hydrogen) at the cathode and sulfuric acid (and oxygen) at the anode, for use in other processes, thereby greatly reducing the burden of disposing of sodium sulfate waste. In a nonelectrochemical sense, membrane technology (particularly ultrafiltration and reverse osmosis) is now used on an enormous scale for the purification of brackish water. Membrane technologies will no doubt grow in importance as a means of producing high-quality water from wastewater streams and, as already described (see footnote 17) a low-cost way of concentrating wastewater in some situations.

It is worth mentioning the use of supercritical water oxidation as a means of destroying organic compounds in complex effluents produced by the pharmaceutical industry, since this technology has been evaluated for treating a variety of biotechnology and chemical process wastes.[25] When water is heated under pressure above its critical point (374°C and 218 atmospheres), its character changes significantly. Its dielectric constant and viscosity are greatly reduced, and it becomes an excellent solvent for organic substances and oxygen. The SmithKline and Johns Hopkins University workers[25]demonstrated that the technology, operated at 650°C and 252 atmospheres, essentially destroyed all organic compounds, including microorganisms and protein in recombinant fermentation broth.

CONCLUSION

As far as the environment is concerned, the pharmaceutical industry occupies a unique niche since process development chemists, chemical engineers, and manufacturing people generally deal with relatively small quantities of complex waste which, not

[24]Dr. Guillermo Zappi, private communication.

[25]Johnston, J. B., Hannah, R. E., Cunningham, V. L., Daggy, B. P., Sturm, F. J., and Kelly, R. M. *Bio/Technology*, 1988, **6**, 1423.

infrequently, contain quite hazardous chemicals. All involved in developing chemical processes for scale-up to a manufacturing operation need to increasingly embrace the air, chemicals' handling, organic waste, and water waste issues as an integral part of their thinking during the period of developing an API to the marketing stage. The search for the highest goal, namely to find the simplest, safest, most environmentally friendly, and lowest-cost process to produce a quality API, is frequently rendered extremely difficult given the prevailing climate calling for the fastest possible delivery of the needed material. Although the effort to meet all the regulatory requirements inhibits the will to seek potentially better process options, chemical process development workers need the towering strength of purpose, along with management support, to rise above the deadening weight of bureaucracy, as well as delivery and quality goals, to seek the highest goal—inadequate compromises are better than nothing at all, at least allowing a start to creating the next generation of processes. Outside efforts with universities and research contractors often provide a good start.

However, compliance with the legal requirements outlined in this presentation has to also be achieved. All changes in process chemistry, operating procedures, and equipment need to be supported by environmental calculations showing that comparison of emissions versus the original process are within the boundaries of the operating permit and that consistency has been achieved. The onus is on the manager to ensure that the calculations are without error and available on site for environmental auditors. The most important factor as far as regulators are concerned is that a written record has been kept documenting compliance with the laws.

Environmental matters need the same enthusiastic personal involvement as one gives to safety and regulatory affairs matters in order to reduce risks, protect people, and meet Food and Drug Administration requirements. When a major investment in a new process is being proposed, it is fairly common for the manufacturing plant management to initiate a dialogue with the local community by way of advice and to gain feedback. Such considerations are vital in an industry that needs to build and maintain a high standing in the local community.

6

REGULATORY AFFAIRS: MEETING THE U.S. FOOD AND DRUG ADMINISTRATION (FDA) REQUIREMENTS

Our objective is to have you build quality into your drugs, not test it in.
—Henry Avallone, FDA

INTRODUCTION

Regulations, whether in the process safety, environmental, or food and drug field, were originally introduced in response to significant events such as factory explosions or catastrophic releases of environmentally damaging chemicals, or to stop the promotion and sale of useless or potentially dangerous pseudo medicines. Once established, regulations and regulatory agencies gained a life of their own, providing a framework to accommodate refinements such as creating legislation in response to safety risks or for eliminating potential causes of environmental damage, or in the case of this presentation, for building quality into processes for producing APIs.

Henry Avallone's compelling statement, made during a pre-approval inspection (PAI) of a Schering–Plough Chemical Development manufacturing facility in the late 1980s, left us in no doubt that the FDA wanted us to create a comprehensive system to ensure that the manufacture of active pharmaceutical ingredients (APIs), as well as dosage forms, was being undertaken to guarantee the quality of our

The Management of Chemical Process Development in the Pharmaceutical Industry by Derek Walker
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products. Although we thought we had been doing a good job in ensuring that our APIs were of the highest quality, the first FDA inspection of one of our process development/production operations[1] made us aware of our inadequacies in light of the FDA's pursuit of quality[2] and how they were working in their role as the public's champion to promote drug safety, efficacy, and quality.

The Food, Drug and Cosmetic Act of 1938, requiring that new drugs be tested for safety, was quickly approved in response to a 1937 tragedy caused when the SE Massengill Company used diethylene glycol, without testing it for safety, in its syrup formulation of sulfanilamide – 108 people died, mostly children, from ingestion of the glycol. In 1962 the Act was overhauled. Safety testing was made more rigorous, and proof of a drug's efficacy was added. The reach of the FDA's mission was slowly extended to cover the quality of APIs, with their key precursors and the synthesis sequences perceived as having an effect on product quality (by introducing a liability to cause API contamination). In the 1960s the FDA began to promote the concept of Good Manufacturing Practice (GMP) as a foundation for ensuring API quality. GMP has become cGMP (current Good Manufacturing Practice) to reflect continuing evolution in quality assurance. The FDA also continues to refine its guidance role and is addressing the future through an ambitiously titled document[3] "Pharmaceutical cGMP's for the 21st Century: A Risk-Based Approach." One can sympathize with the process development chemist in the pharmaceutical industry who is still struggling to fully understand and implement the broader principles and interpretation of system needs for cGMP documentation, validation, and compliance, if he/she sometimes feels like the Red Queen in "Alice in Wonderland." Her observation "it takes all the running I can do to keep in the same place . . ." mirrors the seemingly endless effort needed to meet the high standards set by the FDA to protect public health. Few can even deal with her next sentence "If you want to get somewhere else, you must run twice as fast as that!"

Some, and especially those manufacturing APIs, argue that there have been relatively few adverse public health effects, and that the in-depth focus on quality and the excessive validation and documentation associated with conforming to the requirements of cGMP is not justified. However, there have long been concerns about contamination of APIs and drug products, whether these have been due, inter alia, to impurities generated in the synthesis of the API, or via cross-contamination from the air, or from the use of equipment also employed in producing other products. One of the earliest examples concerned potential allergenic reactions to penicillin contamination. This led to the complete segregation of penicillin (and later cephalosporin and other related β-lactams) production from other operations. It can also be seen from FDA Inspection Reports on Pharmaceutical Companies that sometimes serious "quality" excursions still occur, creating chronic problems and, rarely, serious events.

[1] For more detail see the case study on Dilevalol Hydrochloride: Development of a Commercial Process.

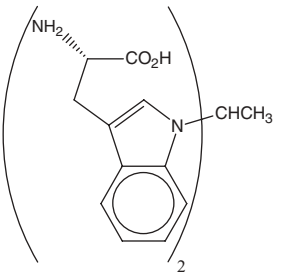
[2] The equivalent European, Japanese, and other agencies similarly strive, with leaner resources, to promote drug safety, efficacy, and quality. These agencies, although not as far-reaching or aggressive in their oversight as the FDA, contribute invaluable perspective—for example, through joint efforts to harmonize regulations. Such efforts ensure that industry and its regulators are all working with the same script.

[3] www.fda.gov/cder/gmp/gmp2004

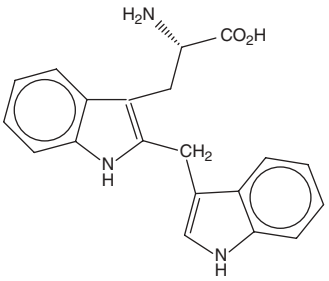
Examples from the drug product area and from the API production area illustrate the continuing need for vigilance.

The variable potency of one manufacturer's sodium levothyroxine tablets, prescribed for hyperthyroidism, led to numerous adverse reaction reports, starting in the 1980s. Some patients were getting too little drug and others too much. Underdosed patients exhibited a greater incidence of fatigue, depression, fuzzy-headedness and itching—some gained weight, others reported brittle hair! Overdosed patients reported more muscle tremors, insomnia, heart palpitations, and heart rhythm abnormalities. It took considerable time for the findings to play out to the point of linking patient symptoms with variability of tablet potency. Ultimately, after much dialogue with the mostly disbelieving manufacturer, efforts were initiated to qualify other suppliers and phase out the now wayward manufacturer.[4]

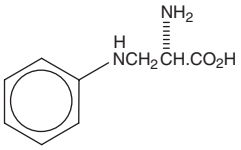
Another case, much more serious and also more pertinent to the chemical process development area, occurred in 1989 when over 1600 people became ill with eosinophilia–myalgia syndrome (EMS) and 38 died, worldwide, after taking L-tryptophan (Trp) manufactured by one producer in Japan. Prior to the outbreak, this producer whose Trp met the >98.5% purity specification had decided to employ a new genetically modified strain of the established *Bacillus amyloliquefaciens* and also to halve the amount of activated charcoal used in the purification step. These changes cause the Trp product to become contaminated with several new impurities, principally **I** to **III**, all associated to some extent (using a crude animal model) with EMS.[5]



I



II



III

The total impurity content of the Japanese Trp was also greater than in the product made by other producers. In order to be allowed back into production, draconian changes had to be made to the manufacturing process. In addition, a reverse-phase

[4]During this phase, the wayward manufacturer suppressed contradicting information and argued that its product was better than that of others. This led to a class action lawsuit against the wayward manufacturer which was settled in August 2000 with a $100 million payout to affected consumers. The wayward company was taken over by a large pharmaceutical company that resolved the problems and continues to market the drug.

[5](a) Simat, T. J., vanWickern, B., Eulitz, K. D., and Steinhart, H. *J. Chromatography, B: Biomedical Applications*, 1996, **685**, 41. (b) Simat, T. J., Eulitz, K. D., and Steinhart, H. GIT Fachzeitschrift fuer das Laboratorium, 1996, **40**(4), 339.

HPLC analytical specification for **I** (<8 ppm) was introduced. The sum of detectable contaminant peaks eluting prior to Trp was reduced to <100 ppm and the sum of those eluting after Trp was reduced to <300 ppm. This case, more than any other, has served to reinforce the FDA's position on the vital importance of building quality into process operations.

It seemed for the longest time that the chemist's search for high-yielding processes giving the highest-quality intermediates and APIs was dependent on no more than scientific common sense. The term scientific common sense is, however, too vague, open-ended, and subjective to be embraced as the sole foundation of quality. Even given that the instruments used by the scientist to determine API quality are rigorously maintained and calibrated and that the API analytical standard is impeccable, how many chemists have found (to their consternation) that an HPLC trace on their API, say when inadvertently run out over the lunch period, has revealed unsuspected peaks at unacceptable levels? How many have found that they not infrequently have needed to recrystallize an API more than once to achieve the desired purity and yet failed to seek the reasons why the level of causative impurity had risen to require multiple recrystallizations? How many have introduced a raw material from a new supplier, or tweaked a process step, or changed to a lower-cost source of solvent, or reduced the level of carbon used for color removal, or made some seemingly innocent change, often in the name of convenience or cost reduction, only to create some unanticipated problem? Again, how many chemical engineers have transferred a process from one vessel to another with, say, a different stirrer configuration, or a different temperature control capability, only to find an adverse effect on product quality? Such occurrences may not happen every day, but they happen frequently enough to make the concept of building quality into an API something of an imperative.

This presentation provides an outline of many facets of the work undertaken by chemists and engineers to produce an API of acceptable quality, in a way that satisfies regulatory requirements. It is not intended to be a guidance document outlining all the activities that must be undertaken to satisfy every detail of the requirements. In this sense it is incomplete. The purpose is to give the process development chemist/engineer an overview of the combination of science, technology, and quality, which is the basis of assuring that API production will meet FDA requirements. The science/technology/quality combination essentially provides the information for the Investigational New Drug (IND) and New Drug Application (NDA). The work needed to create these documents is summarized, leading to a Chemistry, Manufacturing, and Controls (CMC) document which is the foundation of the chemical process development contribution to the NDA. Before the NDA is approved, the company is subjected to a Pre-Approval Inspection (PAI). In order to initiate this, the chemical process development staff concerned with the project works with others as needed (particularly the company Regulatory Affairs, Manufacturing, and Quality Control groups) to provide additional information for the FDA to commence the PAI inspection. The principal document is the Development Report. The other major interests of the FDA are Technology Transfer and Validation.

The undertaking, from the beginning, needs to adapt to the continuum of change which is the reality in developing a process to manufacture an API. Initially, most

effort is devoted to modifying the usually raw research API synthesis scheme (*Recipe*) to eliminate the obvious safety hazards and thereby make it acceptable for scale-up to supply API for Toxicology and Pharmacology programs. These two most important disciplines essentially decide whether the subject API is sufficiently safe and effective to be considered a potential drug development candidate and to determine whether metabolites are factors and what program should be followed in further development. The initial quantities of API needed for the analytical and pharmaceutical dosage form disciplines are also produced by chemical development in this early phase of scale-up and process development, though scale-up difficulties often limit API supply.

The major governing factors in the process development program to produce quality APIs within cGMPs (and provide for regulatory submissions) are summarized under the following headings:

- Building a Quality System
- The Toxicology Batch
- Establishing the API Quality Specification and the Last Process Steps
- The R&D Work Needed to Define the Synthesis Methodology Before the IND Filing (including solvent, raw material and intermediate quality considerations)
- Creation of the CMC Section for the FDA
- The Pre-Approval Inspection (PAI)—The Development Report, Technology Transfer and Validation

THE CHEMICAL PROCESS DEVELOPMENT PROGRAM AND MEETING cGMPs

Building a Quality System

This starts with assembling an organization of people not only capable of meeting the technical needs in producing an API, but also educated and trained to provide the documented record that they have done so, with full attention paid to assuring the quality of the API and the quality of the data. This needs investments in analysts and analytical instrumentation, in laboratories, in a well-equipped pilot plant containing a controlled environment room, and in a comprehensive warehouse facility. It is also desirable, particularly in the preparation of parenteral or inhaled drugs, to invest in a water purification system if the API is to be prepared in water or in a water-containing medium [alternatively, capital investment can be avoided by the relatively expensive purchase of water-for-injection (WFI)].

As a general rule, the analysis of APIs is undertaken by an independent analytical research/quality control (QC) unit. Nevertheless, in my experience, the chemical development organization greatly benefits from having its own QC organization to provide analytical support on a fast-track basis. This organization, which maintains a documented profile on all of its instruments (including operating procedures and calibrations as well as files on all standards), undertakes the rapid well-documented

analysis and labeling of raw materials and intermediates and plays a vital role in the management of the chemical development warehouse. The warehouse should have areas for receiving and weighing chemicals, segregating them according to their status, and for the storage of final APIs—refrigerated if stability tests indicate a need to do so. The warehousing operation is governed by a manual of operating procedures. In a corresponding way, the chemical development organization benefits from assigning and training one of its employees to become a regulatory affairs "expert" working to represent the chemical development point of view with the central regulatory affairs organization (which interacts with the FDA). Both of these satellite QC and regulatory affairs operations have dotted line relationships with their respective central organizations. Although somewhat controversial, these organizational arrangements continue to work well in Schering–Plough (see Chapter 3).

All personnel, including pilot plant management and operating personnel, need to prepare and continually update curriculum vitae documenting their qualifications, experience, present job descriptions, and their training in cGMPs. This record shows that those producing APIs are qualified to do so. It also recognizes that pilot plant personnel contribute invaluable process observations and detail, and essential input in maintaining the documentation (batch records, standard operating and cleaning procedures, etc.), as well as equipment upkeep and equipment logs (history, operating instructions, maintenance, and calibration records).

The Toxicology Batch

The chemical development organization usually produces the proposed API for the animal toxicity tests to ensure that the API is both safe and can be safely administered to humans in the Phase I human safety study. Since toxicology tests are among the first activities undertaken in the drug development process, it follows that a great deal of attention is paid to the quality of the toxicology batch, including the impurity profile. Ideally, one would like to use the same quality API in the toxicology tests as would eventually be produced in the final manufacturing plant. However, since the final process and the API quality are usually unknown, all that can be done is to produce the API by the most practical process available at the time. The early focus on quality generally leads to a major effort being disposed to establishing the last process steps (and particularly the final step) first (see next section: "Establishing the API Quality Specification and the Last Process Step(s)").

In producing API by the most practical process available, one generally strives to achieve an API quality of $\geq$98% and to identify all the impurities present in $>$0.1% amount. In practice, especially if the anticipated dose is likely to be high (as say with an antibiotic) or an API is to be delivered to a sensitive organ (e.g., the lung by inhalation), we have generally identified all impurities $>$0.05% and in one case I recall, $>$0.02%. There is nothing sacrosanct about $\geq$98%. I recall that the purity specification on one of our antibiotics was set at $\geq$97%. In practice, the impurity levels in toxicology batches are usually higher than those in the final marketed product. This provides chemical process development with some flexibility since the FDA readily

accepts changes to lower levels of impurities. It is very difficult to gain approval for higher levels without further toxicology tests.

Usually, in progressing process development work, one eventually finds a better process (e.g., lower in cost and/or safer or more environmentally friendly) that creates a different profile of impurities. Since no company is likely to sanction delays in its drug development program by undertaking the added cost of further toxicology work, a better process is generally only acceptable if the new impurities in the API can be held to <0.1%. There is some flexibility. A few years ago, because of the urgent need to progress a chiral antifungal candidate, preliminary toxicology work was undertaken on a several-hundred-gram sample of the desired enantiomer (purity 100%) prepared by separation using chiral chromatography. Limited acute toxicology work was also carried out on the pure unwanted enantiomer. The agreement with Toxicology was that additional toxicology work would be undertaken on material produced later using a classical resolution process to qualify the API containing the unwanted enantiomer. In this case, the unwanted enantiomer content of the classically prepared product appeared likely to be at a level of about 1–2%. This dialogue with Toxicology indicated that impurities that are close in structure to the API are more likely to be similar to the API in toxicology profile, and therefore more acceptable as impurities, than those impurities that have large structural differences versus the API. However, the <0.1% new impurity limit is still generally preferred for progressing a new synthesis option to IND filing. In the above case we did not have the opportunity to establish the resolution process because the particular antifungal was dropped.

In practice, it is fair to say that chemical development organizations have coped fairly well with the inhibitions to change, which are the fallout of adopting the ad hoc "specification" set in using the toxicology batch. Nevertheless, because of such inhibitions, companies have undoubtedly restricted opportunities to find the best (and lowest cost) commercial process for manufacturing the API in the interest of the fastest possible rate of development of a drug to the marketplace. In my experience, the inhibition to change has adversely affected process research. There may be ways of changing this situation, which I will address in Chapter 11.

Establishing the API Quality Specification and the Last Process Step(s)

These are often very difficult tasks because chemical development is usually drawn into its API supply mission at a very early juncture. At the start of a program there are many uncertainties to resolve before identifying the most desirable API structure and scoping out the market opportunities. Is the desirable API one of several chiral options? Is the desired activity associated with the API as synthesized, or one of its metabolites? The corollary of this is, Will the API structure need to be modified to prevent an unwanted metabolic conversion—often by substitution of the metabolic site (e.g., an H atom may be replaced by F)? Will the API need to be delivered in an oral, topical, parenteral, or inhalation form, or more than one of these? Once selected, will the desired API be a salt or a pro-drug? Even then there will be questions as to which salt or what structure will be selected for the pro-drug moiety. Inevitably,

adding to the uncertainty, the question of establishing the polymorphic form will also surface.

It will be appreciated that some of the changes in direction that result from addressing these questions are often momentous enough that the toxicology program is extended or restarted, thereby giving chemical development more time to carry out experiments to help determine the best synthesis option to pursue. Frequently, however, chemical development effort has to be diverted into the synthesis of large quantities of one or more key intermediates to enable research to accelerate their programs to identify the desired API.

The chemical process development work to define the final process step and aid in setting the API specification is undertaken, as far as possible, outside the API supply program and is the initial component of the exploratory effort needed to determine the eventual industrial process.

API Quality Specification

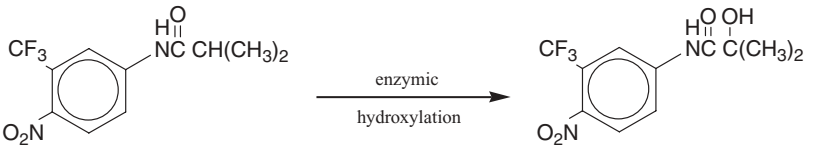
Setting the API specification is one of the prime tasks undertaken by the central independent analytical research and quality control unit using the data gathered over the course of early research studies and in preparing the toxicology batch. The process of setting the specification occurs over a period of time, evolving to accommodate the findings made as knowledge is gained, uncertainties are resolved, and the synthesis of the API develops.

Many factors are tracked in order to create the API specification, which is part of the Investigational New Drug (IND) and New Drug Application (NDA) filed with the FDA, or other regulatory agencies. The major factors are:

- The API structure itself [including identification of the active enantiomer, metabolite, salt, solvate (hydrate) or pro-drug as needed]
- The crystal form (in particular the polymorph) and particle size
- The API assay, the assay of impurities, and product stability

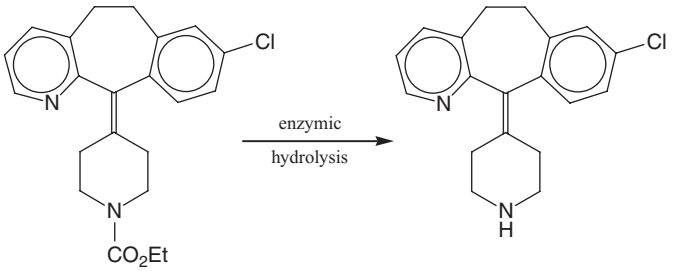
The API Structure. In searching for the most active API structure to develop, it is routine today to separate and test the enantiomers of a racemic molecule since desired biological activity generally resides mostly in one enantiomer. This point was appreciated long ago in the marketing of the oral β-lactam antibiotics ampicillin, cephalexin, amoxicillin, and cefadroxil, all carrying either the (*R*) phenylglycyl or (*R*) p-hydroxyphenylglycyl side chain. The potential for enhanced biological activity with single enantiomers has been realized in other therapeutic areas, though follow-up has not been universal (e.g., β-andrenergic blockers; see footnote 1).

More recently, partially as a result of increased research sophistication and observations made in ADME (Absorption, Distribution, Metabolism, and Excretion) studies, increased attention is being given to evaluating metabolites of APIs. An old example (not being pursued because of the lack of patent protection) is the metabolite



Flutamide (Eulexin) **Not marketed**

SCHEME 1. Metabolism of Flutamide.



Loratadine (Claritin) **"Desloratadine"(Clarinex)**

SCHEME 2. Metabolism of Loratadine.

of the antiandrogen, Flutamide (Eulexin). The metabolite was later shown to be the true API (see Scheme 1) .

A recent switch to a metabolite of a compound already in the marketplace is the move from the nonsedating antihistamine, loratadine (Claritin), to "desloratadine" (Clarinex) (Scheme 2).

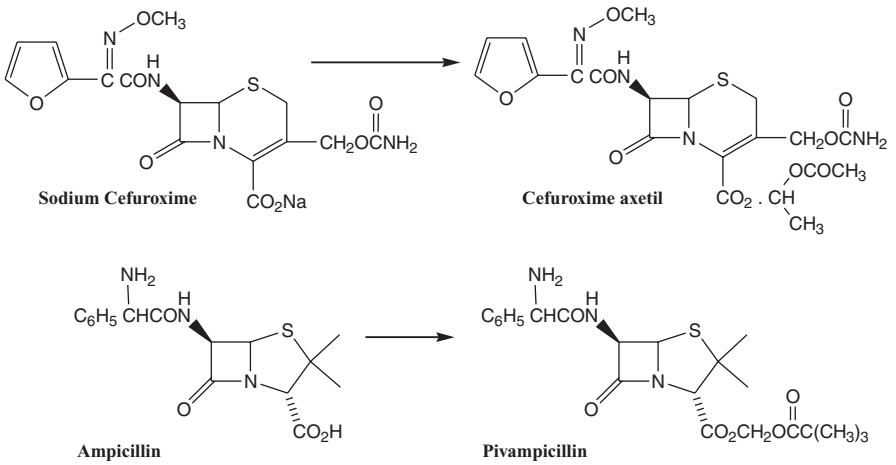
Desloratadine is the most abundant of the several compounds produced when loratadine is metabolized.

There are other considerations in searching for the most active API structure, creating the need for close collaboration with Pharmaceutical Development scientists.

Many APIs are marketed in a salt form. Salt formation can confer a variety of physical, chemical, and biological properties on the API without changing its basic chemical structure. A few of the important properties are water solubilization, modified dissolution rates, improved stability, and beneficial pharmacological effects.

Preferred cations in salt form with API acids are sodium, distantly followed by potassium and calcium. Organic cations [e.g., diethanolamine and *N*-methylglucamine (meglumine)] are used to a lesser extent. Preferred salts of basic APIs are the hydrochloride distantly followed by the sulfate, bromide, and phosphate. A large number of organic acids are also used (again to a lesser extent), notably tartaric, citric, maleic, methanesulfonic, and acetic acids. The reader is referred to a review article by Monkhouse and co-workers[6] for a comprehensive, if old, list of acids and bases employed in the pharmaceutical industry. This article also reviews the effects of salt formation on bioavailability and on physiochemical, pharmacological, and toxicological properties.

[6]Berge, S. M., Bighley, L. D., and Monkhouse, D. C. *J. Pharm. Sci*., 1977, **66**, 1.



SCHEME 3. Preparation of penicillin and cephalosporin pro-drugs.

Pro-drugs are precursors to the API itself, being metabolized to the API in the body. Essentially, both loratadine and flutamide above are pro-drugs. Pro-drugs are often created to improve the oral absorption of the API, thereby creating patentable advantage. Such initiatives have extended the original patent holders rights or enabled competitors to gain a market niche. Two examples are sodium cefuroxime, which became the pro-drug cefuroxime axetil,[7] and ampicillin, which became the pro-drug pivampicillin[8] (Scheme 3).

Various other acyloxyalkyl esters of penicillins and cephalosporins were patented, which gave the inventors positions in the penicillin/cephalosporin market. In short, the pro-drug concept affords many opportunities to impart desirable properties to APIs.

Although chemical development organizations are not directly involved in identifying the API structure to be developed, they are involved in providing research with the building blocks, in the form of large quantities of advanced key intermediates, to help speed their search. Chemical Development, especially during its emphasis on defining the last synthesis step and the purification process, can also contribute, peripherally, if its chemists or engineers identify stable salts, or solvates, or polymorphs that have desirable properties (especially if these properties create a patentable situation).

The reader will appreciate that the greater the complexity involved in identifying tomorrow's APIs, the more difficult will be the challenge of creating the ultimate manufacturing process in a timely manner.

[7](a) Cefuroxime: Cook, M. C., Gregory, G. I., and Bradshaw, J. U.S. Patent 3,974,153,1976 (to Glaxo); (b) Cefuroxime axetil: Gregson, M., and Sykes, R.B. U.S. Patent 4,267,320,1981 (to Glaxo).

[8](a) Ampicillin: Doyle, F. P., Nayler, J. H. C., and Smith, H. U.S. Patent 2,985,648,1961 (to Beecham). (b) Pivampicillin: Frederiksen, E. K., and Godtfredsen, W. O. U.S. Patent 3,660,575, 1972 (to Lovens Kemiske Fabrik).

The Crystal Form and Particle Size. Many APIs exist in more than one crystal or polymorphic form. Since different crystal forms can possess quite different properties—for example, melting point, solubility, and rate of dissolution—it is essential at the start of the API development program, to establish which crystal form (or reproducible mixture of crystal forms) of the API will be developed. As an illustration, riboflavin (vitamin B_2) can exist in three different crystal forms varying in solubility in water at 25°C from 60 mg/liter to 1200 mg/liter.[9] Generally speaking, the high-solubility form of an API is the metastable form, usually with the lowest melting point and also the fastest dissolution rate. Such a situation raises the concern that a fast dissolution rate will lead to a faster absorption rate such that the therapeutic efficacy of an API may vary depending on the polymorph administered. A similar consideration exists if the API is isolated in an amorphous form (as happens with many aminoglycosides). Amorphous materials are always more soluble than their crystalline counterparts simply because more energy is required for a molecule of a crystalline API to leave the crystal lattice than is the case with the amorphous form. The form of the API can have a major impact on therapeutic properties. The antibiotic novobiocin provides a dramatic example.[10] The crystalline form is very slow to dissolve and produces no detectable blood levels after oral administration. In contrast, administration of the amorphous form leads to measurable blood levels and significant biological activity. Amorphous forms of an API can be produced by freeze-drying or the spray-drying of aqueous solutions.

Utilizing an amorphous form of an API is not, however, universally desirable. Amorphous compounds are often metastable. As a result, there is a real risk that they will transform to crystalline materials in the final dosage form. Novobiocin again provides a case in point. The amorphous form, in aqueous suspension, will transform on standing into the inactive crystalline form.[10] Similarly, the highly soluble metastable crystals of riboflavin revert to less soluble forms if they are washed with water above 10°C.[9]

The amorphous and crystalline forms of chloramphenicol stearate provide a further example,[11] underlining the importance of establishing the form of the API at the start of the development program. Finding the precise conditions for routinely reproducing the needed form of an API (also meeting other analytical criteria—for example, purity and particle size range) frequently requires considerable work[12] and thorough documentation, especially through the critical scale-up process.

[9]Dale, J. K. U.S. Patent 2,603,633, 1952 (to Commercial Solvents Corporation).

[10]Mullins, J. D., and Macek, T. J. *J. Am. Pharm. Assoc. (Sci. Ed.)*, 1960, **49**, 245.

[11]Alimarante, L., DeCarneri, I., and Coppi, G. *Farmaco (Pavia) Ed. Prat.* 1960, **15**, 471; *Chem. Abstr.* 1961, 905.

[12]There is always the risk that work done to find the needed form of an API will not succeed in a given time frame and that only after some time in production will the thermodynamically most stable form emerge. This happened to Abbott Laboratories in 1998. They were obliged to withdraw the capsule form of their HIV drug Ritonavir, because of the appearance of a new crystal form that possessed different dissolution and absorption characteristics (see Pharm. J. 1998, **261**, 150). The crystalline form in capsules was later replaced by a gel capsule formulation that could not crystallize. We in Glaxo also encountered a disappearing polymorph in manufacturing an early intermediate for Cephalexin (Bywood, R., Gallagher, G., Sharma, G. K., and Walker, D. *J. Chem. Soc., Perkin I*, 1975, 2030). In this case, our first preparations

The particle size of a crystalline API is often an important factor in achieving desired physical properties, such as reasonable drying times (see Chapter 8) and desired pharmaceutical properties, such as dissolution rates and blood levels. The FDA, in addition to requiring data demonstrating that the particle size reduction process is consistently under control, is also likely to require proof that no thermal degradation has occurred outside acceptable limits (i.e., no new impurity exceeding the 0.1% level is produced during milling or micronization).

The API Assay, the Assay of Impurities and Product Stability. The central independent analytical research and quality control unit is responsible for the analytical release of both the API and the formulated drug product for the drug development programs. The central independent QC unit provides all the analytical data needed to build the analytical specification for the IND. It is recognized by those involved that the IND is a relatively raw document compared with the later NDA, which is built on data from a more developed process situation, using more refined analytical techniques.

The major concerns of the analyst in finding and developing API analytical procedures are to provide the methodology for quantifying API purity, to work with process chemists in identifying, preparing, and quantifying impurities, to work with pharmacists and chemists in establishing the polymorph requirement, to provide methodology for determining solvent and water content, and to ensure appropriate limits are set for heavy metal, particulate, and residue-on-ignition (ROI) content. A starting point for an API assay may look something like the following:

Assay	Usually >97% pure (dry basis). A range is often given—for example, 97.0–103.0%.
Chiral purity	>95% e.e.
Polymorph	Stable and reproducible
Impurities	Total, ideally, ≤2%* with no single impurity >0.5%
Solvents	Levels depend on solvent (see later)
Heavy metals	Generally <20 ppm
ROI	Usually <0.5%; later this parameter may be <0.1%
LOD	Mirrors solvent and water content (excepting specified solvate)

*Initially, the assumption (for HPLC assay) is that all substances have the same UV extinction coefficient as the API.

Microbial contamination counts are often determined. Sterility and pyrogen tests are needed for parenteral APIs.

The research analyst also undertakes a major program to determine the stability of the API, including determining degradation pathways occurring under various

of the crystalline diphenylmethyl ester of penicillin G sulfoxide possessed an m.p. of 127°C to 128°C. Later a new form emerged, m.p. 146°C. The new crystalline form posed no manufacturing problems. We never saw the low-melting form again! Further examples of disappearing polymorphs have been cited (Dunitz, J. D., and Bernstein, J. *Acc. Chem. Res.* 1995, **28**, 193).

storage conditions and when the API is blended with the excipients to be used in the dosage form.

A few comments on impurities and on stability are worth making.

The major impurities produced in the process to be scaled up are usually identified at the research stage or in the early phase of developing the process for scale-up. To aid the analyst, impurities are frequently recovered from mother liquors obtained from the final crystallization step—for example, by preparative HPLC. The major ones are synthesized and purified to provide the analytical "standards" needed to quantify the amounts produced in the API synthesis. Over the course of time, the obvious impurity collection is supplemented by those substances that *might* be produced in the process, including other enantiomers. These "theoretical" impurities help to provide answers to almost every query on the impurity profile of the API.

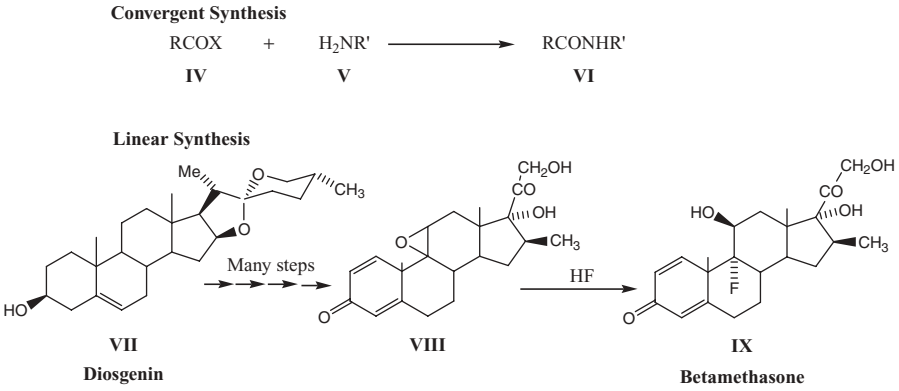
Levels of impurities found in the toxicology batch are usually accepted as the allowable upper limits for the IND/NDA. Levels can be as much as a percent or two, depending on the product and vagaries of the individual synthesis. High levels of impurities can be quite acceptable provided that the toxicology work to prove the safety of the API was carried out with API containing the same high level of impurities.

The starting materials in a synthesis are obvious potential impurities. More difficult to deal with are the impurities deriving from the impurities in the starting materials; situations developing from this often provide a good reason to set high quality standards for all the key starting raw materials.

The stability of the API (and also of chemical intermediates) is often a key factor in determining process requirements and API or chemical intermediate storage conditions. This is especially true for relatively unstable compounds such as the penicillin antibiotics. Stability testing can be important in evaluating variations in a process, especially in evaluating minor changes in a manufacturing process, or the impact of adverse shipping or storage conditions, or testing the compatibility of an API with various packaging materials. Differential Scanning Calorimetry (see Chapter 4) is often used to assess quality and gain information on the tendency of an API to degrade. It is also helpful in assessing the effect of impurities on stability. Frequently, simple heating of an API in an oven in an accelerated test at a given temperature for an appropriate time can give useful stability information, such as on potency loss or color generation, and can provide information on the impact of air versus nitrogen blanketing on the rate of degradation. However, the reader should be aware that accelerated tests (high temperatures for a short time) can exaggerate the actual results obtained by storing at room temperature for times up to the projected expiry date—usually a few years. Nevertheless, impurities produced in such as accelerated stability tests are often isolated and identified for use in assessing the effects of aging on the quality of APIs held to their expiry dates.

The most important objective of the above work on stability is to provide the data to qualify the sought-after expiration date of the drug product, and with it the API.

The independent research analysts and the chemical development QC analysts are vital players in the process development program. A strong interactive dialogue between them and the process chemist/engineer invariably pays enormous dividends. The research analyst generally has considerable sophistication in his/her armory of



SCHEME 4. Two simple last process steps.

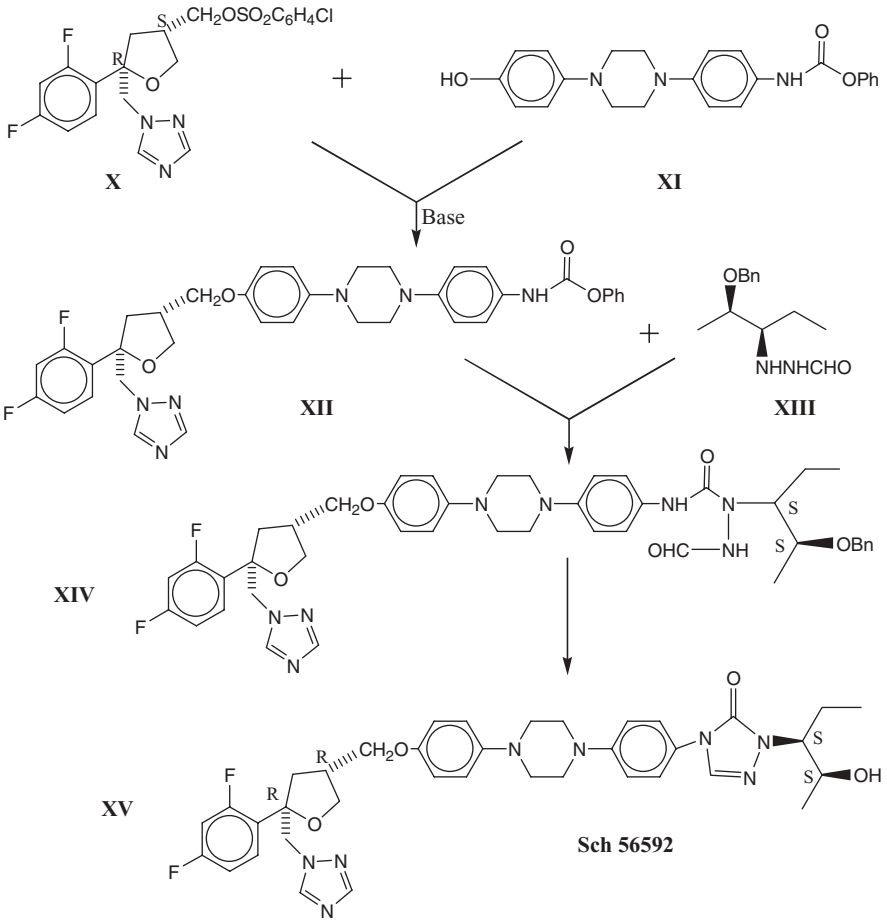
instruments (e.g., multinuclear and 2D-NMR, X-ray diffraction, FAB-MS, ICP-MS, GC-MS, and HPLC-MS) to aid in learning about chemical purity, the chemical transformations going on, the structure of impurities being produced, the polymorph profile, and the stability of materials at any stage of the process.

Establishing the Last Process Step

The work needed to define and establish the last process step is generally difficult inasmuch as it starts with the decisions to be made on what should be the final API structure. Initially, therefore, it embraces all the uncertainties associated with defining the API structure and establishing the crystal form and particle size.

The construction of the API molecule depends on the synthesis selected for assembling the molecule. Many APIs are, or can be, simple to put together—for example, in convergent syntheses such as when acylation of an amine is a logical last step, as in the synthesis of most β-lactam antibiotics and peptides, or in linear syntheses such as the manipulation of a steroid molecule produced from an earlier long sequence (Scheme 4). In these cases, simple synthesis strategies allow the major quality concerns to be focused on controlling the quality of the intermediates **IV**, **V**, and **VIII**, as well as the quality of reagents and solvents used to effect the conversions to **VI** and **IX**, including the subsequent recrystallization solvent(s), if needed.

The process development chemist faces a markedly more complex problem in quality control if the convergent synthesis is more open-ended as in Scheme 5. In addition to ensuring that process conditions do not cause racemization of the chiral centers, the number of key intermediates (**X** to **XIII**) being produced in such a convergent synthesis usually slows the selection of the best intermediate structure to use and may lead to variations in the impurity profile both of these intermediates and the final API **(XV)**. As an illustration, a change from the *p*-chlorobenzenesulfonyl leaving group in **X** could conceivably lead to **XI** being alkylated by the **X** fragment at sites other than the phenolic oxygen. Furthermore, the commercial availability of low-cost intermediates



SCHEME 5. More complex assembly in last process steps.

(building blocks) from other chemical intermediate manufacturers already producing building blocks for other companies may change the synthesis strategy. The availability of such building blocks may not be known at the start of a synthesis program but, when discovered, can lead to an outsourcing program to qualify the new supplier and often a new specification of impurities. The further back in the synthesis one goes to make a process change generally lessens the problems of qualifying new impurities (usually because the number of subsequent steps provides more opportunity to purge impurities—for example, in crystallization steps). Thus, changes in the impurity profile of **XI** in Scheme 5 might be expected to be easier to accommodate than changes in the impurity profile of **XIII**. For instance, if an impurity in **XIII** became combined with the large molecular fragment **XII**, the insolubility conferred by this fragment may make it difficult to separate two quite similar molecules carrying only minor structural differences.

Despite such considerations, economics generally favor adoption of a convergent synthesis over a linear synthesis. This is because outsourcing of building blocks minimizes capital investment in chemical production plants and, given detailed attention to the quality of outsourced building blocks, can minimize the steps subjected to regulatory scrutiny. The other side of the outsourcing strategy is, however, that companies investing in the plants to undertake a long synthesis themselves develop know-how and a position of controlling their destiny after patent expiration. Thus, they have a better chance of holding onto their market position long after their patents have expired. A good illustration of this is the steroid field—many of the same major manufacturers of steroids who were producers in the 1950s are still in production today. However, major steroid manufacturers are also leveraging their manufacturing capabilities for additional profit by offering late-stage building blocks, such as compound **VIII**, in the commercial marketplace. This is leading to consolidation in steroid manufacturing as less efficient manufacturers of steroids contract the most efficient to manufacture their late intermediates and even their APIs. The downside of such an outsourcing strategy is that the sourcing company does not always know whether a takeover of the efficient manufacturer by another company may change the operating plan to the exclusion of third-party manufacturing!

Nevertheless, third party manufacture of fine chemical intermediates has grown substantially in the last decade, primarily to reduce pharmaceutical companies' financial exposure and speed API development. Pharmaceutical companies are farming out their late-stage intermediates technology to third parties as the number of their API candidates increases, thereby avoiding investment in capital and human resources. Third-party manufacturers are building on their strengths—in particular, chemistry and technology (e.g., phosgene, explosives, handling odorous sulfur compounds, etc.)—and on their high-quality specialty operations to enable pharmaceutical companies to move more quickly in the development of APIs.

Returning to the main theme, one of the most important components in defining the last process step is to determine the purification scheme to be used for meeting quality and crystal form/particle size criteria for the API.

On the assumption that the synthesis steps for constructing the precise structural features of the API have been carried out from well-defined, good-quality building blocks, the main task of the process development chemist is to find a process for purifying the API to give the required physical form meeting the purity requirements. This is usually a crystallization process utilizing an acceptable solvent, or mixture of solvents, having low toxicity. Preferred solvents are listed in Table 1. Water was not included in the ICH list of preferred solvents, but where it can be used, most process chemists and engineers would regard it as the solvent of choice.

Less preferred solvents (Class 2) are listed in Table 2. As stated in the ICH document, these solvents need to be limited because they are suspected to be nongenotoxic animal carcinogens or possible causative agents of some irreversible toxicity such as neurotoxicity or teratogenicity. They may also cause other significant, frequently

TABLE 1. Preferred Solvents for Use in the Purification of APIs (Class 3)[13]

Acetic acid	Formic acid
Acetone	*n*-Heptane
Amyl alcohol	Isoamyl alcohol
Anisole	Isobutyl acetate
1-Butanol	Isobutyl alcohol
2-Butanol	Isopropyl acetate
Butyl acetate	Isopropyl alcohol
t-Butylmethyl ether	Methyl acetate
Cumene	Methyl ethyl ketone
Dimethyl sulfoxide	Methyl isobutyl ketone
Diethyl ether	*n*-Pentane
Ethanol	1-Propanol
Ethyl acetate	Propyl acetate
Ethyl formate	Tetrahydrofuran

TABLE 2. Less Preferred Solvents for Use in the Purification of APIs (Class 2)[13]

Acetonitrile	Methanol
Chlorobenzene	2-Methoxyethanol
Chloroform	Methyl *n*-butyl ketone
Cyclohexane	Methylcyclohexane
1,2-Dichloroethylene	*N*-Methylpyrrolidone
Dimethylacetamide	Methylene dichloride
Dimethyl formamide	Nitromethane
Dioxane	Pyridine
2-Ethoxyethanol (Cellosolve)	Sulfolane
Ethylene glycol	Tetralin
Ethylene glycol dimethyl ether	Toluene
Formamide	1,1,2-Trichloroethylene
Hexane	Xylene

reversible, toxicity. The ICH guideline[13] provides PDE data (mg/day) and concentration limits (ppm) for Class 2 solvents in drug products.

Although Class 3 solvents have no known human health hazards at levels normally found in drug products, generally corresponding with a level of <0.5% in the API, the solvents in Class 2 need to be controlled at levels which are less, sometimes substantially less, than those allowed for Class 3 solvents. The level of Class 2

[13]List taken from International Conference on Harmonization (ICH), harmonized tripartite (Europe, Japan, United States) guideline entitled Impurities Guideline for Residual Solvents. The above solvents are categorized as Class 3 solvents, with low toxic potential to man. Class 3 solvents have permitted daily exposures (PDEs) of 50 mg or more per day.

TABLE 3. Solvents to be Avoided in the Purification of API (Class I)[13]

Benzene	1,1-Dichloroethylene
Carbon tetrachloride	1,1,1-Trichloroethane
1,2-Dichloroethane	

Source: ICH Impurities Guideline for Residual Solvents.

solvents allowed in the API is generally determined by reference to the amount of the solvent calculated to be present in the drug product (i.e., after dilution with the excipients) and PDE data. Calculation methods are given in the ICH Impurities Guideline for Residual Solvents.[13]

Process development chemists make every effort to avoid using Class 1 solvents (Table 3) for the crystallization of APIs. The solvents in Table 3 pose carcinogenic, environmental, or other toxicity risks.

Solvents other than the above Class 3 or Class 2 solvents may be used, but doing so requires that the user provide information to assure regulatory agencies that there will be no untoward health consequences from the level of their presence in an API. Clearly, PDE information showing that the drug product containing the expected level of residual solvent was safe would be best.

In directing substantial effort into establishing the last process step, the development chemist must pay close attention to creating a written record that will not only provide others with precise detail on how to reproduce the process but what has been done to build quality into the process. The written record embraces the company cGMP policy and procedure manuals, chemists' notebooks, analytical control and product release data files, pilot plant SOPs, batch sheets and cleaning records, cGMP training manuals, and staff curriculum vitae. This documentation, initially in a relatively raw state, leads to the filing of the Investigational New Drug Application (IND) and eventually, in a refined state, to the New Drug Application (NDA). The company also prepares a dossier describing in detail the process for the manufacture of an API—referred to in the United States as the Drug Master File (DMF). Technology transfer, based on most of the above documentation, usually begins before the NDA is filed. The Development Report, summarizing the company's journey to the NDA process, is being built at the same time. Validation of the process and the manufacturing system follows. The validation record provides the written proof that you are doing what you say you are doing.

Establishing the last process step marks only the beginning of the effort to create a quality culture. The effort reaches both forward into ensuring that the pharmaceutical development regulatory needs are met and backwards into ensuring that the process steps leading to the molecular assembly of the API structure will guarantee the quality of the final API.

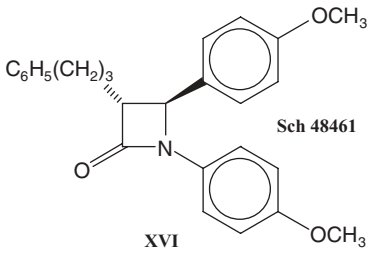
The iterative nature of the work to define the last process step also applies to the R&D work needed to define the synthesis methodology for the key steps leading to the last process step.

The R&D Work Needed to Define the Synthesis Methodology

The more uncertainty there is in identifying the synthesis to be developed for the early steps in the preparation of an API, the more difficult it is to define the last API step in a needed time frame. Experience in process chemistry and open-minded dialogue among proponents of the various synthesis strategies are essential components in the early selection of the best synthesis strategy. In my experience, exploration of more than one strategy is the norm with intense effort focused on trying to overcome the perceived weaknesses in each strategy—in short order! There is also the odd "bootlegger" who needs to get an idea out of his/her system—and who, maybe infrequently, wins the day.

Today, the real problem is time and setting a decision-making timetable. This has led to a sharper focus such that the research recipe for producing the API as quickly as possible for toxicology/pharmacology work is often driven into a larger-scale operation with no more than evolutionary changes to make the chemistry safer. The urgency generally causes effort that might otherwise be devoted to finding a better synthesis strategy to be diverted into improving the research recipe. One answer to this that has proved helpful is to establish a dialogue with research chemists to enable them to address development issues and specific concerns as soon as there is an indication that a particular API might become a development candidate. Another is to generate secrecy agreements with third parties, preferably those who might be expert in the technologies and the structural chemistry related to the API or its intermediates. However, identifying the right third party is not easy. One has the most control, including over costs, if you own (i.e., have patented) the intermediates being sought. This is usually a later consideration being helpful at the commercialization stage, enabling one to "shop around" to find the best supplier.

As far as research collaboration is concerned, the Schering–Plough manufacturing process for its cholesterol absorption inhibitor, Ezetimibe (Zetia), exemplifies the collaboration case. The close interaction between Research and Development, aided by the delay caused by the realization that the first API structure (**XVI**) had to be modified to overcome metabolism issues, provided the intellectual resource and the time for a fuller understanding of the chemistry needed to create the chiral β-lactam ring.



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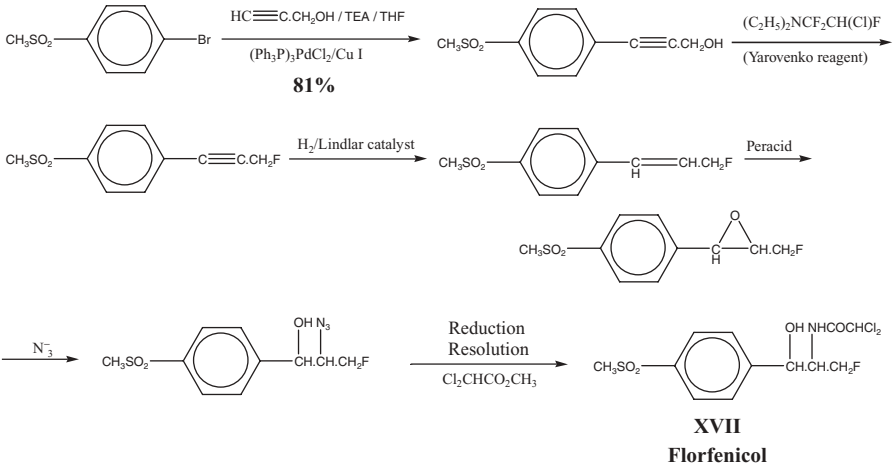
XVI

This led our Dr. T. K. Thiruvengadam to invent an exquisitely elegant synthesis of Ezetimibe—Scheme 13 in Chapter 9.

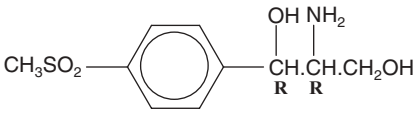


SCHEME 6. Florfenicol synthesis explored by a third party.

In regard to third-party collaboration in the manufacture of Schering–Plough's antibiotic, Florfenicol (**XVII**), the initial thrust by our Animal Health Division, developers of the molecule, was to involve a third party with an excellent track record in another project with them. The third party partially explored the synthesis outlined in Scheme 6.

Several problems with Scheme 6 were identified. The Yarovenko reagent led to several percent of an impurity containing $-C\equiv C\cdot CH_2Cl$, which proved difficult to remove, and the azide ring opening of the epoxide led to both possible hydroxyl azides. These problems and the need for a resolution step led to abandonment of Scheme 6.

A concurrent initiative with Zambon S.p.A. in Italy was much more successful since it was based on working with Zambon to utilize their commercially available thiamphenicol intermediate, **XVIII**, a molecule already possessing the structural requirements of Florfenicol, including chirality.



XVIII

Zambon succeeded in converting the terminal CH_2OH, in an N-protected derivative of **XVIII**, into CH_2 F confirming the viability of the option [see Chapter 7 for both the Zambon synthesis of Florfenicol (Scheme 9) and further ramifications of the project].

Every chemical process development organization will have its own experiences in the value of collaboration both with its own research organization and third parties.

Because of the structural novelty of new APIs, one rarely finds commercial sources of needed late intermediates such as in the Florfenicol case above. The problem then becomes either to produce the target intermediates yourself or to find and qualify one or more third parties, preferably experienced in the chemical technologies needed in the synthesis, to do so.

Qualifying a third party requires that detailed synthesis, analytical, and GMP information are provided to the third party. This is usually passed to the third party in a technology transfer package (see later). Eventually the third party is registered in the NDA as a supplier who has committed to meet an agreed analytical specification. For materials well back in the synthesis and for raw materials, including solvents, one may need no more than basic analytical release information—appearance, identity, purity (sometimes it may be necessary to set limits on specific impurities).

For late-stage intermediates, a very stringent set of additional criteria will usually be required. These will depend on many factors, but some of the major ones are:

- Impurities. Do some impurities persist through to the API or become converted to other undesirable impurities which are difficult to remove? If so, what levels should be set in the specification for the intermediate? Do transport or storage conditions affect impurity levels?
- Water/Solvents. Are the levels of water or solvent contaminants important, requiring a tight specification? If so, what levels should be set and what process (e.g., drying conditions) is needed to meet the specification?
- Optical Purity. Is optical purity crucial? Is optical purity changed by transport or storage conditions?

As the raw material/intermediate sourcing program develops, it is usual to qualify more than one supplier for "insurance" purposes, and to eventually encourage competitive pricing.

Establishing and reproducing quality is one of the most important objectives in developing a chemical process. Generally, the quality focus starts with the raw materials and, as indicated above, becomes a crucial factor in sourcing late stage intermediates. Today, in recognition of the importance of quality, most chemical raw material manufacturers in Europe and the United States have subscribed to a quality assurance standard initiated in the United Kingdom but developed, from 1987, by the International Organization for Standardization (ISO) in Geneva. Five quality assurance standards, applying to manufacturing quality in any business, are embraced under the logo ISO 9000.

ISO 9000. This standard, titled "Quality Management and Quality Assurance Standards: Guidelines for Selection and Use," is advisory describing the use of the standards in establishing supplier contracts as well as providing guidance on the use of the other four standards.

ISO 9001. This is a comprehensive standard that includes the requirements of both ISO 9002 and ISO 9003. It describes what is needed for quality assurance

in services and products all the way from design, development, and installation to production, servicing, and supply.

ISO 9002. This limited standard applies to quality assurance in installation and production.

ISO 9003. This standard only provides a guideline for the requirements of quality assurance in final inspections and testing.

ISO 9004. This standard, like ISO 9000, is advisory providing guidelines for the development and application of an internal quality management system.

ISO qualification is essentially a generic qualification specifying all the elements of a system that need to be in place in order to effectively control quality. It is flexible in that it is up to the user to determine how the elements are implemented. It does not tell users how to do their job. ISO qualification generally results from passing an audit which shows that you have the system in place to meet the requirements of the ISO standard. In regard to chemical manufacture, ISO qualification has been much sought after and recognized by those sourcing chemicals as a desirable requirement in a supplier of raw materials and intermediates.

It needs to be stressed that although raw materials, solvents, and intermediates made by ISO qualified producers are usually well regarded as inputs for the manufacture of APIs, the ISO system is not an alternative to cGMPs. One of my European colleagues has likened ISO qualification to passing the tests needed to obtain a driving license. Possessing a driving license does not say anything about how well you control your driving.

Returning to the theme of searching for the best synthesis methodology, the main driving force is usually provided by the imagination of chemists and collaboration with those expert in sourcing chemicals, with analysts, with chemical engineers, and frequently with their counterparts in the manufacturing division. Having identified a synthesis, it is relatively straightforward to make changes in the chemistry or introduce new chemistry before the IND is filed, although every change needs to be justified and proven using analytical findings to show that both process intermediates and API are within the quality parameters set in the toxicology batch and within those being developed for the IND. The pilot plant used in scale-up is generally qualified with records kept on all the equipment needed for all processes. This record shows that instruments are regularly checked and calibrated and that the process equipment can deliver what it is required to deliver—in terms of temperature control, rates of cooling and heating, stirring requirements, filtration, washing and drying characteristics, and so on. Company audits as well as calibration and maintenance records on equipment, especially equipment used for carrying out API production, are important in establishing a quality system. Quality risks, such as those evident when new suppliers of raw materials, intermediates, and solvents are being evaluated or when multiple recrystallizations are needed to meet quality criteria, have to be identified, the causes of potential problems understood, and steps taken to avoid compromising API quality. Activities to identify and resolve quality risks go on continuously. It is generally recognized that all quality risks and causes of potential

quality problems cannot be resolved by the time the IND is filed. Such work goes on into the pre-NDA phase. However, during the period between filing the IND and submitting the NDA, it is much more time-consuming to make changes. Small changes—for example, a switch to using sulfuric acid instead of hydrochloric acid (corrosion issue)—may be introduced on a well-documented basis, proving that the change has had no adverse effect on quality. Large changes can be made after the IND submission if rigorous analytical and process operating scrutiny is undertaken to ensure that the quality of key intermediates and particularly the API is maintained. However, the opposite of this is not uncommon wherein processes are "frozen" post the IND filing. After the NDA filing, it is considered unwise to make changes (see case study on "Dilevalol Hydrochloride: Development of a Commercial Process," —FDA Review and Compliance Activities, page 288) since they may delay FDA review of the NDA.

In cases where changes are being made between the IND and NDA, the API produced is generally put into a Restricted-Use category. Such materials may be used for work that does not find its way into any Regulatory submission. It may be used, for instance, in preliminary analytical, stability, and regulatory qualification work if it is agreed that there is overwhelming justification for the changed process, say on the grounds of significantly lower costs or considerable superiority from an API manufacturing standpoint. Restricted-Use API may also be valuable in evaluating API formulation ideas or for evaluating process conditions or alternative formulation machinery for producing the dosage form. Once this latter kind of work has been completed, the product from the work is usually destroyed.

Creation of the Chemistry, Manufacturing, and Controls (CMC) Document for the FDA

The CMC section of the NDA is a small component of the company's overall submission of data to the FDA seeking approval to market a new drug. The NDA submission is made to the Review Branch of the FDA in Washington. Final submission of the CMC section is usually preceded by a presentation of the proposed content to the Review Branch. Feedback from the ensuing discussion is incorporated into the final submission. Once a drug is approved, responsibility for FDA oversight in the implementation of manufacturing and marketing shifts to the Compliance Branch of the FDA, specifically to field offices close to the manufacturing sites.

As part of the preparation for creating the CMC document, the chemical development organization (or the manufacturing organization if technology transfer has already occurred) usually produces a minimum of three large-scale batches of the subject API using the procedure to be filed in the CMC documents. The results of this three-batch exercise demonstrate that the process operation and API quality are consistent with the criteria established for the CMC document.

The CMC section of the NDA is written by the company Regulatory Affairs organization in close collaboration with the Chemical, Pharmaceutical, and Analytical Development organizations. The CMC section contains the following information:

- A formula outline of the synthesis chemistry.
- A catalogue of solvents, raw materials, and sourced intermediates, vendor identification, and analytical release specifications for all these materials. (It is usually desirable to identify two or more vendors.)
- A journal-style description of the process used for API manufacture.
- A review of the critical parameters requiring specific control to secure quality.
- A summary of the analytical methodologies used to establish the quality of all chemicals used in the API manufacturing operation, as well as to ensure quality control throughout the process.
- A succinct description of the work done to establish the structure of the API and the crystal form.
- The API specification.
- Impurity identification and a specification for the level of impurities.
- API stability information.
- Corresponding information to the above on the formulation of the dosage form (drug product).

The pre-NDA meeting with the Review Branch of the FDA usually takes the form of a presentation much along the lines of a scientist presenting a paper at a scientific meeting. A pre-NDA meeting is invaluable in identifying and dealing with FDA concerns before the final NDA is submitted. The pre-NDA meeting also enables the company to gain approval, or other guidance, on its synthesis strategy in regard to the starting point of its API synthesis. Normally the FDA requires that the synthesis starting point should be a commercially available chemical. However, pharmaceutical companies, recognizing the uncertain nature of drug development and their financial exposure if they had to invest in all the manufacturing plant needed to produce the API, increasingly work with third parties enabling them to become suppliers of late-stage intermediates. Novel late-stage intermediates produced by third parties can sometimes qualify as being commercially available even if they are made exclusively for the contracting pharmaceutical company and are not offered for sale to others.[14] These circumstances require that the third party essentially create a Drug Master File, and thereby be subject to FDA inspection, to qualify themselves as a supplier of a specific late-stage intermediate in the NDA.

[14]There have been a few cases wherein the FDA has accepted that a late-stage new intermediate made exclusively under contract for one party can be classed as commercially available, not requiring FDA audit. These cases are notable in being more science-based and in exhibiting an extraordinarily high level of quality control throughout production. Tight quality control over the starting chemicals (including impurity levels), tight in-process controls in producing the late-stage intermediate, rigorous impurity mapping, and an exacting quality specification on the compound have been major factors enabling the FDA to approve the third-party supplier as a source of the late-stage new intermediate, without requiring DMF status. These few cases provide an indication that the FDA is beginning to apply the principles outlined in its document "Pharmaceutical cGMPs for the 21st Century: A Risk-Based Approach." However, it is clear that "risks" allowed by one Division of the FDA Review Branch may not be acceptable to another.

Analogous presentations to the Review Branch are made for the drug product. Both the chemical and pharmaceutical development presentations are supported by analytical development presentations providing the data to satisfy the FDA that all components of the API synthesis and dosage form preparation are well-controlled.

Before and following the NDA filing, many other activities are going on which are pertinent to regulatory matters and preparatory to the FDA Compliance Branch's Pre-Approval Inspection (PAI). The most important activities are the writing of the Development Report, Technology Transfer, and Validation of the operation.

The Pre-Approval Inspection (PAI)—The Development Report, Technology Transfer, and Validation

The filing of the NDA with the Review Branch of the FDA leads to the Compliance Branch being notified and given the CMC section. In turn, the Compliance Branch contacts the company, indicating its readiness to undertake a Pre-Approval Inspection of the facilities to be used for manufacturing the PAI. The company decides when it is ready for the PAI. Readiness is determined, inter alia, by the availability of the documentation needed to demonstrate that the systems for manufacturing the API are in place. This often starts with the Development Report, summarizing the genesis of the synthesis scheme and how this was developed to the NDA process. The process of Technology Transfer provides further insight. This embodies the mechanics of how the manufacturing technology was moved and controlled in scale-up to the production plant and demonstrates the discipline employed by the manufacturer in dealing with every component of the process, including plant equipment, operator training, and analytical oversight. Validation, which is not always completed by the time of the PAI, is an essential final component of the NDA approval process. The bottom line is, however, that APIs cannot be marketed without completed validations.

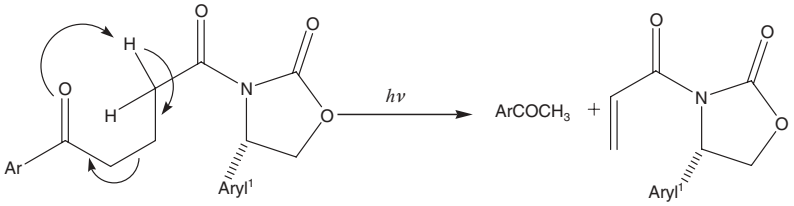
The Development Report

The Development Report is prepared via a succession of interim reports, usually over several years. When interim reports detail findings critical to the synthesis, they appear in an addendum form in the final report. The interim reports provide a journal-style write-up describing how the chemistry used for synthesizing the API was carried out. The identification of impurities and the determination of their level is a priority. Ways of maximizing the yield of the desired product, especially by overcoming side reactions (impurity formation), are described. Recrystallization and other purification methods (including chromatography) are detailed. The recovery and recycling of reagents and solvents is introduced as quality information on the acceptability of recycling becomes available. The Development Report also includes raw material specifications, analytical test methods, in-process control methods, and intermediate and API stability information.

The following gives an outline of the structure of a typical Development Report with some notes on the kind of information that can appear:

- Introduction. Provides a brief outline of the discovery of the API and the chemical process for its preparation.
- Process Flow Chart. Gives the sequence of reactions in chemical structure terms.
- Nomenclature. Provides an index linking the chemical structure of the intermediates and API with the shorthand designations used by the company and the Chemical Abstracts Name.
- Description of the Process. The typical large-scale batch operation (same size as in the NDA) is described in journal-style detail for each step.
  - Critical parameters are identified— that is, those which have a defined range. Range excursions may affect API quality. The consequences of range excursion are discussed.
  - Process control conditions are summarized. These may affect safety, yield, process consistency, or intermediate quality. Some of the common concerns are solvent hazards, moisture content of solvents or reagents, reaction temperatures and times, reagent addition rates, crystallization conditions, and drying temperatures.
  - In-process and final-test instruments are described along with analytical methods and reference charts (e.g., HPLC chromatograms) for assaying intermediates and final API. Typical analytical results profiling impurities, monitoring for reaction completion, and determining data such as the water and solvent content of products are provided.
  - Raw material specifications—lists of vendors and specifications for each material used in the step with particular attention to the impurity content of intermediates that contribute to the structure of the final API.
  - Stability of intermediates—provides data on the storage conditions (for solids, this is frequently polythene bags in fiber drums) that are desired for each intermediate. Such data are usually gathered to show that the intermediate is stable for *X* months (or years) under suggested (desired) storage conditions, alleviating concerns that out-of-specification materials might be used.
  - Yield data—the range of yield that is expected from the process is identified. Yields outside the range require investigations as to cause and what will be done to overcome the issues created.
  - Impurities—a list of impurities obtainable for each step is provided separately in the description of the process used for each step. The origin of each impurity, how each impurity is controlled, and each impurity's fate are described—typically most potential impurities are eliminated or reduced to acceptable (defined) levels during intermediate purification steps.
  - Process development—this section ends each step, providing a summary of factors involved in the selection of reagents, solvents, their amounts, process conditions, detail of critical parameters, efforts to streamline the process (e.g., increase concentrations and combine steps), and so on. When events occur that give special concern, these are detailed. One unexpected example in one project was the impact that light had on samples of an intermediate being

analyzed by HPLC. Light caused degradation of the molecule, leading to erroneous results. In broad terms, the reaction was



Preventing exposure to light avoided the problem.

- Ancillary formation. This can include, inter alia:
  - An outline of the NDA process
  - Detail of in-process and final test methods for raw materials, intermediates, and products
  - Description of special analytical method(s) for chiral assays
  - Preparation of chiral auxiliaries
  - HAZOP reports

In summary, the Development Report provides a comprehensive overview of the many factors addressed in creating and implementing the process for the manufacture of the API.

Technology Transfer

Technology transfer from a chemical development operation commences as soon as the decision is made to move any part of a process, say for preparation of an early intermediate, to a third party, or the company's own manufacturing division. Where third parties are involved, the transfer is usually undertaken after a confidentiality or secrecy agreement has been signed to ensure that no unwanted disclosures can occur—for example, to competitors. Early dialogue with potential manufacturers of intermediates is often informal and may comprise no more than the transfer of a laboratory procedure, analytical methodology, a sample of typical product, and the analytical "standard" existing at the time. Ideally, the third party will reproduce the chemistry exactly as provided, or agreed, and the analytical instruments, analytical methodology, and results will be compared to establish that the third party can reproduce the methods satisfactorily. Any changes in the procedure that may be necessary for scale-up have to be approved before implementation. As always, every step of the process is recorded to demonstrate that the operation is being properly controlled.

Transfer of the last process step for producing the API, generally to one's own manufacturing division, is a major endeavor. This often occurs between the IND and NDA filings. One of the desired objectives in doing this is to enable the company to carry out as much of the Phase III clinical and toxicology work as possible using

API produced by the commercial manufacturer. This timing, which helps to simplify the dialogue with the FDA, is not always achievable if the putative commercial site requires an investment in specialized equipment which takes a long time to deliver, install, and commission. It can be seen from this that investment in the manufacturing plant needs to be recognized and addressed early in the development of the final process step. Situations such as this demonstrate why great importance needs to be attached to developing the last process step as soon as possible.

In conducting technology transfer, most companies work to a "standard" operating procedure (SOP). The basic content of such an SOP may include some of the following:

Purpose:
- Establish the requirements for the orderly transfer of technology from one site to another in order to ensure equivalence of performance.

Responsibility:
- Outline those with the accountability.

Nomenclature:
- Define terms—for example, API, Analytical Comparison Report, ELINCS, Experimental Protocol, and so on.

Procedural Steps:
- Identify team members and their function on both sites.
- Create the technology package (process/analytical batch information, safety requirements, training/operating protocols, projected timelines, etc.).
- Establish plan to deal with deviations/variances.
- Coordinate efforts during preparation and analysis of demonstration batches.
- Review the results.
- Write and issue a Technology Transfer Summary Report.
- Create a Validation Readiness Checklist to document completion of the items that must be addressed prior to manufacture of the validation batches.

In technology transfer, it is necessary to establish that the plant equipment, instrumentation, and operating systems in the receiving plant will provide the conditions the process needs at every step and that the plant maintenance program is such as to assure continuity of these conditions. Plant cleaning is also a major consideration, especially if the plant is being used to produce several products. Procedures for the removal of solvents and process residues from previous batches are essential to the concept of "building in quality." This is particularly important in dryers, which are also used for several products. However, even dedicated dryers need to be cleaned using a validated procedure to prevent build-up of degradation residues. If the API is for parenteral or inhaler use—that is, produced in a clean environment room (see Chapter 8)—cleaning procedures become vitally important, not only for minimizing impurity contamination but for eliminating or greatly limiting pyrogen or bacterial contamination. In short, cleaning is a vital component of API manufacture.

Inevitably, as a process develops, improvements are made and changes are needed to accommodate them. Chemistry and operating changes, even seemingly very small ones, can adversely affect API quality, raising the need for all process changes to be

governed by a change control system. The system should be flexible. Process changes in producing raw materials and early intermediates generally need less attention than changes made in the last API step or in steps to produce key intermediates where quality changes can impact on the quality of the final API. Whereas a laboratory "use test" on a "new" raw material or early intermediate (i.e., using the "new" material to make the API and showing that API quality is unaffected)[15] might suffice for chemicals well back in the synthesis, a change in a process step late in the synthesis requires increasingly stringent scrutiny the closer to the API one gets. Change in the late steps of an API synthesis, or in the synthesis of the API itself, require a change control procedure monitoring every step of the improved process to ensure reproducibility and consistency with previous quality criteria and cGMPs—especially to ensure that the quality of the API is either improved or not adversely affected. The same diligence applies to the manufacturing plant operation.

Technology transfer is usually uneventful if it is carried out in a structured and disciplined way, with dedicated supervision, meticulous attention to detail, and constant vigilance.

Validation

This exacting discipline has come to the fore as API and drug product producers have been obliged to provide the proof that their process conditions, their instruments, and their plant equipment are verified, calibrated, and demonstrated to work as they say they work to consistently deliver API meeting the NDA specification.

The successful operation of a production chemical process to give a desired API depends on exactly reproducing the chosen chemistry, on the analytical instrumentation used to control the chemistry and determine the quality of the API, and on the equipment and services used to carry out the process steps as well as the cleaning procedures needed before equipment reuse. To ensure that these main components of the operating system are working optimally to deliver high-quality API, they all need to be validated. It is essential to start validation with a protocol detailing the work to be undertaken to prove that all components of the system set up for manufacture of the API consistently provide quality product. Implementation of the protocol work leads to the documentation establishing the proof.

The process chemistry chosen is defined in detail by determining the limits of process conditions (i.e., the operating ranges for temperature, time, pH, etc.) which consistently give API within the specification filed in the NDA. Really critical process parameters are flagged for particular vigilance—ideally the chemistry chosen will be robust enough to minimize the need for very tight control. Validation of analytical instrumentation through regular calibration using unimpeachable chemical standards provides the cornerstone of quality assurance. Plant equipment and instrumentation (i.e., measuring such as temperature ramps, pressure, pumping rates, pH, etc.) are correspondingly demonstrated to provide the expected services and correct read-outs

[15] It is always a good idea to monitor the quality of the "new" material for a time to provide assurance that its quality is being maintained.

in the ranges needed for controlling the chemical process. Protocols for cleaning validation are a vital component of the validation package. Cleaning validation comprises proving that the mechanics of cleaning, followed by the sampling of cleaned surfaces and analysis, together create assurance that the plant will not cause contamination of the API.

All validation activities associated with producing a minimum of three validation batches of the API are drawn together in the form of a Validation Report. This report essentially documents company compliance with the NDA process, making it a vital document in the effort to gain FDA approval of the NDA.

Although very considerable work is undertaken in validating an API manufacturing process, one should not overlook some of the benefits. The main ones are as follows:

- A fuller understanding of the process is gained during the exercise of determining the process conditions to be used in running the validation batches.
- Fuller understanding enables the plant to reach optimal process efficiency faster.
- Plant failures are minimized.
- In-process assays provide data for the statistical analysis of trends for yield/quality improvement or warnings of potential adverse events.

Validation is one of the most important exercises in completing the information requirements for NDA approval. As a result, considerable importance is attached to this discipline in pharmaceutical companies such that validation professionals have a place in all domestic and international Regulatory compliance organizations across the company.

The PAI carried out by the Compliance Branch of the FDA uses the NDA submitted by the company as the basis for the inspection. The inspection comprises an in-depth scrutiny of records and operations as well as a wide-ranging dialogue with the company, usually over several days. The inspectors, in looking for out-of-compliance situations, may focus on failed batches and their reprocessing or rework, or on the retesting of expired materials, or on the SOP for analytical instrument calibration, or on the conditions of storage for standard samples, or on process deviations and how they were addressed, or on cleaning procedures and the volumes of solvent used, or on warehousing and the label status of materials stored there, or . . . , the list could go on and on. In short, an inspection may take the FDA into any aspect of the manufacture of the API.

At the end of the inspection, a meeting is held at which the FDA summarizes its findings and outlines the deficiencies they found. Deficiencies are referred to as FDA 483's. Their findings are summarized in a written follow-up. The company then responds in writing, providing a program for overcoming the deficiencies. The dialogue continues until the FDA is satisfied that the company's manufacturing operation is in compliance and is properly documented and validated.

In order to prepare for a PAI, the company usually sets up an "independent" audit of the facilities well before the formal PAI. This audit, usually carried out by the company's own Quality Assurance/Regulatory Compliance groups, often assisted by

outside specialists, enables the company to address most of the items likely to be spotted by the FDA inspectors. Such audits serve as a form of training of the personnel in operations and enhance awareness of the Regulatory needs which should be being addressed as the development of information for the NDA is going on.

Irregular internal PAI-type audits of operations, like safety inspections, enable the company to maintain its vigilance and ensure that its operations are sustained at a high level of compliance with agency regulations.

CONCLUSION

The creation of a process to meet FDA requirements is a multidisciplinary activity. Although the Chemical Process Development organization generates the core process, its shaping and implementation to meet the needs of all other parties involved (particularly Regulatory, Manufacturing, Pharmaceutical Sciences, and Quality Assurance) requires an extraordinary level of collaboration. The principal objective is to produce, and to demonstrate that you have indeed produced, a high-quality API in a well-controlled system of operations.

Selection of the process is an iterative activity adapting to the changes occurring during the selection of the specific API and the definition of the last process step(s) to produce it. Most attention is devoted to producing a quality API for research and creating an efficient practical synthesis sequence for its preparation, in collaboration with analytical groups, chemical engineers, pharmaceutical scientists, and manufacturing operations. Outside vendors of raw materials and intermediates are "cultivated" and approved.

The relatively free-wheeling synthesis selection phase through the IND gives way to a much more controlled development phase, wherein the quality of the Toxicology Batch (and especially impurity levels) dictates the quality of the API batches to be produced, slowing process change. Analytical methodologies and specifications for the API, intermediates, and raw materials become more refined. Impurity and stability profiles are established. Process control mechanisms are developed and plant SOPs incorporate the better controls. The NDA process slowly takes shape.

The documentation package covering the operation also begins to emerge as the program moves toward NDA submission. The components of the Development Report and information leading to the CMC section are pulled together. Technology Transfer is formalized, and the time-consuming process of validation is begun. Preparation for the PAI is completed, and eventually NDA approval is gained. These activities, demonstrating that quality is being built in, also create the foundation for the system of governance needed for maintaining quality in ongoing operations.

The focus of the FDA continues to be guaranteeing that the drug products in the public domain have the reproducible purity and stability profile which they originally approved. Detail of the regulations continues to be debated and the FDA remains open to ideas for reducing the Regulatory burden carried by the pharmaceutical

companies.[16] The spirit of this dialogue is seen in the Pharmaceutical Research and Manufacturers Association (PhRMA) initiative to ensure quality while streamlining both regulatory and development operations.[17] A greater need, to enable process innovation to continue well into the NDA phase, is addressed later (see Chapter 11). Whatever changes are proposed, they all need to be based on scientific evidence that they are justified and that they do not jeopardize the FDA's main thrust, which is to ensure that the pharmaceutical companies produce the highest-quality APIs.

In this presentation, I have provided only a personal overview of how chemical process development scientists and engineers approach the task of creating a chemical process for the manufacture of an API and assembling the information and documentation needed for submission and approval of an NDA. Much detail is lacking. It is therefore important that all readers embarking on a chemical process development program work with their own regulatory specialists to ensure that they are accommodating the requirements of their own company's culture.

[16]Current FDA guidance documents can be accessed from the internet at http://www.fda.gov/cder/guidance/index.htm

[17]Cupps, T., Fritschel, B., Mavroudakis, W., Mitchell, M., Ridge, D., and Wyvratt, J. *Pharm. Technol.*, February 2003, 34.

7

PATENTS

> Inventions, protected for a single generation, promote the creation of new businesses, social prosperity, and better inventions.

There are many stories connected with every process discovery and development project. One of the least publicized is the patent story that usually unfolds in a well-orchestrated fashion through the dialogue of individual and company inventors with patent attorneys. Patent protection covering a given discovery lasts 20 years from the date of filing. In practice, this time is reduced by the several years taken to test and gain regulatory approval to market a drug product. Because of such delays, it is possible to gain additional years of patent protection in several countries to compensate for the time spent in the regulatory review process.[1] In the United States, the extension provided is for up to half the IND time and all the NDA time. However, the total extension time cannot exceed 5 years and the extended patent term cannot exceed 14 years from FDA approval.[2]

Patent exclusivity enables a company to recoup its research and development investment and make an appropriate profit. Once patents expire, generic competition greatly erodes sales, although generic competition is frequently delayed by the portfolio of patents usually created by a company. It will be apparent that because of the enormous costs of drug development and the need to recoup these costs, all drugs taken to the marketplace should have some form of patent protection, even if

[1] *Health News Daily*, October 1997.
[2] Associated Press, October 1997.

The Management of Chemical Process Development in the Pharmaceutical Industry by Derek Walker
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coverage only pertains to the use of an old (unpatentable) chemical structure for a specific hitherto unrecognized and therefore new medical indication.

One of the greatest satisfactions obtained by the chemist seeking a patent to protect his or her invention lies in meeting the intellectual challenge associated with analyzing the existing literature (art) and defining the invention. In competitive fields, the challenge is often to stake out a strategic position free of the impediment of third-party patent rights, while building a patent portfolio to protect one's own position. This may entail licensing third-party rights, or, where validity is in doubt, attacking the patent before the courts in proceedings, which can be complex and very costly. In this chapter, I will provide background and a few personal experiences to illustrate the great importance of protecting intellectual property through the patent system.

The worldwide patent system harmonized considerably during the 1980s and 1990s. It continues to harmonize as more countries sign the General Agreement on Trades and Tariffs (GATT) Treaty, requiring enhanced patent protection for pharmaceutical inventions over what many countries had previously provided. The subject matter of a patent filing not only may be the drug itself, as a novel chemical compound, but also may be later-found advantageous forms of a drug; these include polymorphs, salts, dosage formulations, and combinations of drugs. Most important, from the standpoint of Chemical Development, process features may be patented such as new synthetic methods and intermediates used for drug manufacture, unprecedented separation, and purification technologies and novel equipment applications.

A brief review of the following aspects of patent activity provides perspective:

1. Patent content
2. The driving forces leading individuals/companies to seek patents
3. Factors influencing the worth of a patent
4. Timeliness in seeking a patent
5. The defense of patent property
6. Designing around process patents
7. Patenting versus trade secrets
8. Patent aspects of the development of processes for Florfenicol manufacture
9. A lighter side of the patent literature

Several examples, most of which are based on the author's personal experience, are used to illustrate these areas.

PATENT CONTENT

To obtain grant of a patent, it is necessary to prepare and file a patent application describing the alleged invention and then legally defining what the inventor believes his invention to be in terms of a series of patent claims.

In writing a patent application, the inventors generally give a broad overview of the field (with references) and describe their invention in relation to the public disclosures. To support patentability, the inventors will often provide "surprising"

information showing why the invention would not be obvious to those "skilled in the art." It is incumbent on the inventor(s) to disclose in the patent application the best method known to them for carrying out the process claimed in the application. The claimed invention will identify the features responsible for the patentability of the process (e.g., temperature, pressure, pH, and other ranges) by a cascade of patent claims defining the invention from the broadest which can be justified down to the invention in its narrowest terms. The latter is essentially the very specific and preferred core process that the inventor actually carries out in practice. Where possible, compound claims will be included covering key useful intermediates.

The filed patent application will be examined by the receiving patent office to ensure that the claimed invention meets the statutory requirements for patentability. In order to be patentable, the claimed invention must meet three key requirements:

- It must be novel (i.e., be a novel compound/process/medical use not previously described or used anywhere).
- It must be nonobvious (i.e., it would not occur to one skilled in the art to arrive at the claimed invention).
- It must be useful (i.e., it must concern a composition, process, or novel device that is capable of commercial application).

Patent examiners, in examining a patent application, will search the literature to determine whether, in their view, the claimed invention is already described in the literature or "prior art" (i.e., the invention is not novel), or whether it can be said to be obvious in view of what is described in the literature. The findings of the examiner will be reported to the inventor in an Official Action or rejection notice, identifying what the examiner considers to be the closest "relevant art." For the purposes of illustration, a U.S. rejection on the grounds of obviousness will usually start:

The following is a quotation of 35 USC 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Invariably, the examiner will find what he or she considers to be "relevant art" even though in practice it may not be pertinent. It is the inventor's task to explain why the relevant art is not pertinent.

FORCES LEADING INDIVIDUALS/COMPANIES TO SEEK PATENTS

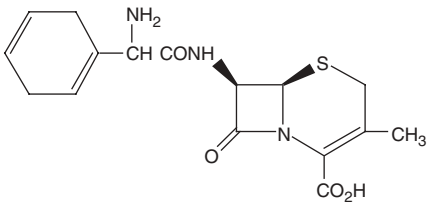
In process chemistry terms, change is a continuum. Discoveries and their development lead to processes that give higher yields, create cost reduction, introduce

environmentally cleaner and safer chemistry, provide a more stable product, and so on, all highly desirable and advantageous results. Where patentable inventions arise, individuals (in companies individuals generally assign their inventions to the company they work for) file patent applications directed to those inventions. In this way, companies create a portfolio of patents protecting the inventions and covering their drug substance or product, and processes thereto. This portfolio extends patent coverage, and with it company sales, often for years beyond expiration of the original patent granted by the patent office. It is important to reiterate that invention is generally not just an incremental improvement or evolution of a process. It must be a significant or even revolutionary change, a new and unprecedented step, which is commercially advantageous over the existing "art." New patents that cover a drug substance, such as a more stable form (e.g., a salt or a solvate) or novel and useful intermediates, represent the strongest patent protection; all of these have to show some unexpected advantage over the previous "art" to be patentable. "Use patents," covering a new therapeutic use of an old compound, may also provide effective protection. Patents that cover processes only are generally more easily circumvented (see section entitled "Designing Around Process Patents").

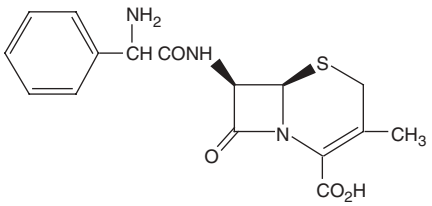
FACTORS INFLUENCING THE WORTH OF A PATENT

The cost of obtaining and maintaining a patent has to be justified by the potential value of the patent obtained. Clearly, a new drug substance patent provides a very broad scope of patent protection against copiers for the life of the patent. Then if later on a market switch from the original drug to a more pharmacologically advantageous form is found (say a salt, solvate, or pro-drug), this new form may itself be patentable. This situation would arise if the new form demonstrably enhances the drug product's performance (e.g., giving higher blood levels that increase therapeutic value). Such findings often extend the effective patent protection for a product and hence the associated market.

Sometimes patent protection may extend beyond the literal wording of what was initially protected. An example may illustrate this. In the 1970s, Eli Lilly's very successful antibiotic Cephalexin was the subject of a patent. Squibb then came onto the market with Cephradine. The Courts found that Squibb was infringing Lilly's patent on the basis that Squibb's Cephradine contained a few percent of Cephalexin. Reportedly, Squibb settled by agreeing to a royalty.



Cephradine



Cephalexin

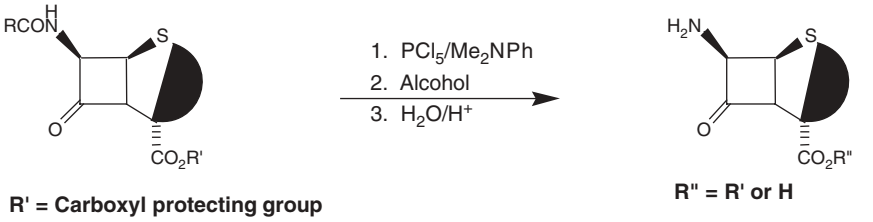
Patents, besides protecting a marketing position, may also act as a source of licensing income or as negotiating tools.

TIMELINESS IN SEEKING A PATENT

Diligence of pursuit is often critical in winning a patent race in a competitive market area. Where several parties are working in the same field and independently arrive at essentially the same invention, it is generally the first party to file an adequately supported patent application that achieves grant of a valid patent and hence is in a position to dominate (or roof) the other party (it should be noted that a patent gives a right to exclude others, rather than a positive right of use). This system of according priority to competing inventions is termed the "first to file" system. Critics say that it leads to a counterproductive "race to the patent office." It is, however, a simple system for according priority to inventions and is now universally adopted throughout the world, with the notable exception of the United States. In the United States the patent goes to the "first to invent" rather than the "first to file." I do not need to comment any further on the U.S. "first to invent" system because the examples on timeliness given below relate to activities judged primarily according to who was the first to file.

One example illustrating the importance of diligently pursuing an invention occurred in Glaxo in the late 1960s during a period when the PCl_5-cleavage process was being exploited for the conversion of the amide side chain of fermented or semisynthetic penicillins and cephalosporins to the corresponding 6-aminopenicillanates and 7-aminocephalosporanates (Scheme 1).

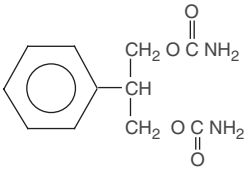
Temporary protecting groups [R' = residue of a carboxylic anhydride, trimethylsilyl (Beecham and Gist-brocades), chlorodimethylsilyl (Bristol–Myers)] were usually used for the production of 6-aminopenicillanic acid (6-APA) and 7-aminocephalosporanic acid (7-ACA). Labile carbon esters were often preferred where it proved preferential to leave the carboxylate protecting group intact while additional manipulations were carried out on the bicyclic β-lactam [e.g., *p*-nitrobenzyl (Lilly), diphenylmethyl (Glaxo), *p*-methoxybenzyl (Otsuka), 2,2,2-trichloroethyl (Ciba)]. Labile refers to the ready removal of the carbon ester—*p*-nitrobenzyl by hydrogenolysis, diphenylmethyl and *p*-methoxybenzyl by acids, and 2,2,2-trichloroethyl by zinc reduction.



SCHEME 1. The temporary protection of carboxyl using phosphorus trichloride.

In order to provide a protecting group of our own for 7-ACA manufacture, we in Glaxo evaluated many options for the temporary blockade of the carboxylic acid group of cephalosporin C and its derivatives. These included compounds such as BCl_3, $POCl_3$, $SOCl_2$, and PCl_3. Unfortunately the evaluation of too many compounds all at once delayed our realization that PCl_3 at low temperature (approximately $-20^{\circ}C$ to $-30^{\circ}C$) was a viable candidate. Although Glaxo's patent department filed our patent application within six weeks of realization of its superiority, we learned several months later that Professor Ishimaru of Osaka University had filed a patent some four months before us.[3(a)] Professor Ishimaru visited Glaxo. Negotiations took place, but no agreement could be reached. Although Glaxo allowed its patent to go through to publication,[3(b,c)] it dropped the development of PCl_3 as a temporary protecting group.

A happier result occurred a few years ago in our Chemical Development group in the Schering–Plough Research Institute. We sought a process for producing 2-phenyl-1,3-propanediol (PPD), an intermediate for the antiepileptic drug Felbamate, which Schering licensed from Carter–Wallace for marketing in Europe.



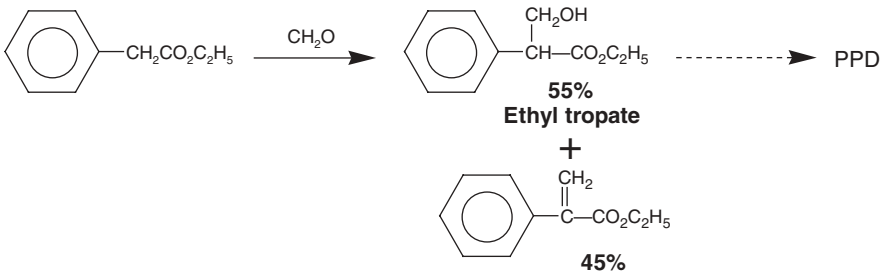
Felbamate

The then-commercial process required several steps, used relatively hazardous reagents, and employed a difficult hydrogenation step. We projected the cost-of-goods (COG) for PPD produced by the commercial process[4(a)] would lead to a COG for Felbamate that was more than double the figure desired by our marketing group, even allowing for the economies of large-scale operation. A low COG was considered essential because of the indicated high dosage (2 g/patient/day, with some groups of epileptics receiving a dosage of more than double this figure in early treatment).

We set ourselves the urgent objective of finding a shorter, simpler, safer process based on methyl phenyl acetate (cost for large tonnages: ~$5.50/kg in 1992). Based on our ideas for the conversion of methyl phenyl acetate to PPD, we calculated that the COG for PPD might be reduced to about a third of the COG projection for the commercial process. The marketing group agreed that in order to control our own destiny, we needed to be in charge of the technology and supported an urgent evaluation program. We proposed to prove and, if possible, patent our technology, and then take it to several potential partners with a view to identifying the one or two most suited to adopting the technology and meeting our COG target.

[3](a) Ishimaru, T., and Kodama, Y. U.S. Patent 3,896,118,1975 (priority date November 17, 1970, to Toyama). (b) Chapman, P. H., and Holligan, J. R. U.S. Patent 3,882,108,1975 (to Glaxo). (c) British Patent 1,391,437,1975 (priority date April 7, 1971, to Glaxo).

[4](a) Choi, Y. M. U.S. Patent 4,982,016,1991 (to Carter Wallace).



SCHEME 2. Possible ethyl tropate route to PPD.

Our task was complicated by the fact that we were aware, from our licenser, that others were working on the same problem, might be ahead of us, and may be developing patent positions that could potentially negate our efforts.

Work published in 1989[4(b,c)] showed that Choi (Carter–Wallace) had prepared PPD by the reduction of diethyl phenylmalonate using lithium aluminum hydride or lithium borohydride. This approach did not, however, appear to us likely to meet the requirement for a low COG.

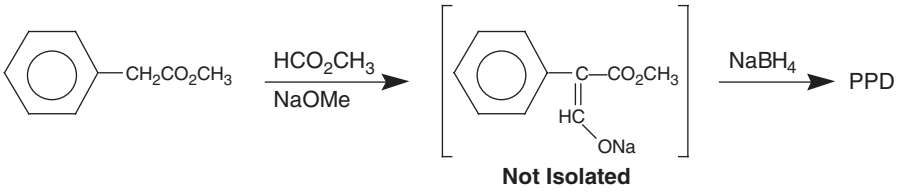
In June 1992, we reasoned that the preparation of methyl tropate via the reaction of formaldehyde with methyl phenyl acetate may provide a low-cost intermediate capable of being reduced to PPD. The preparation of ethyl tropate via this route was already published.[5] However, the German workers found that formation of ethyl 2-phenylacrylate was substantial. In addition, no ongoing reduction of methyl tropate to PPD was described (Scheme 2).

Our Chemical Development team, under Dr. Chou-Hong Tann, energetically and creatively undertook a vigorous laboratory effort to try to improve the above process to enhance the yield of methyl tropate and also to investigate the reduction of this compound to PPD. Study of the formaldehyde reaction did not quickly yield much improvement, so within weeks and not without overcoming some reluctance to abandon the methyl tropate route, we phased in an exploration of the reaction of methyl formate with methyl phenylacetate, followed by reduction with sodium borohydride. This route almost immediately showed great promise (Scheme 3).

Within a matter of 4–6 weeks after initiation of the methyl formate program, we had defined an outline of a process and gathered sufficient results to initiate

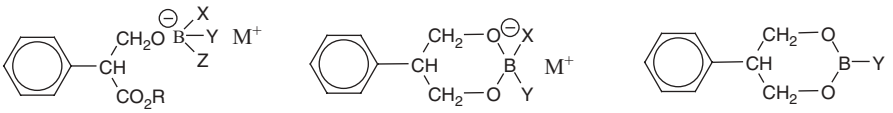
(b) Choi, Y. M., Emblidge, R. W., Kucharczyk, N., and Sofia, R. D. *J. Org. Chem.*, 1989, **54**, 11194. (c) Choi, Y. M., and Emblidge, R. W. *J. Org. Chem.*, 1989, **54**, 1198. A somewhat lower cost process via 2-nitro-2-phenyl-1,3-propanediol [Stiefel, F. J., U.S. Patent 4,868,327, 1989 (to Carter–Wallace)] was also practiced commercially.

[5](a) Schwenker, G., Prenntzell, W., Gassner, U., and Gerber, R. *Chem Ber.*, 1966, **99**, 2407. (b) USSR Patent Application 322,988,1976; this describes a method for preparing tropic acid by the reduction of alkyl esters of formyl phenylacetic acid using borohydrides. No reference is made to the reduction of both CHO and $CO_2C_2H_5$ groups in this patent.



SCHEME 3. Methyl formylphenylacetate route to PPD.

preparation of patent applications[6] supporting our earlier calculations that the cost of PPD might well be reduced to one-third the cost of PPD made by the commercial process. We also perceived environmental and quality advantages. A priority patent application covering this route was filed in the U.S. Patent office on September 18, 1992.[6(a)] In addition to claiming the overall process outlined above, and the best range of reaction conditions, we also sought claims for boron intermediates:



wherein X, Y, and Z independently represent H, OH, $O^{\ominus}$, OR^2 or $OCOR_2$
wherein R is alkyl or aralkyl
wherein R_2 is C_1 to C_6 alkyl (a further definition of Y in the nonionic formula above is $OCH_2CH(Ph)CH_2OH$)
wherein M is a metal of groups I, II, or III of the periodic table

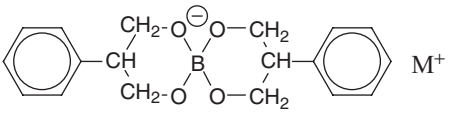
The Schering U.S. priority application dated September 18, 1992 formed the basis for an international Patent Convention Treaty (PCT) application, covering Europe, which was filed eight months later.[6(b)]

As should be common practice when working in a competitive field, we maintained a watch worldwide for relevant third-party patents and patent applications as they were published. In Europe and most other countries, patent applications are published 18 months from the earliest priority date. In the United States, at that time, patents were not published until grant (the law has recently changed[7]), but grant can often occur earlier in the United States than in other major countries. That was the

[6](a) The original U.S. Patent Application, filed September 18, 1992, by Walker, D., Babad, E., and Tann, C.-H., was not pursued to the publication stage when Schering–Plough abandoned the Felbamate project. (b) Walker, D., Babad, E., Tann, C.-H., Tsai, D. J., Kwok, D-I., Belsky, K. A., and Herczeg, L. International Patent Applications WO 94/27941, Priority date May 25, 1993 and WO 94/06737 (March 31, 1994) to Avondale Chemical Company Division of Schering–Plough.

[7]In keeping with the worldwide patent law harmonization effort, the U.S. House of Representatives and the Senate Judiciary Committee approved a Bill in 1997 requiring the publication of Patent Applications in 18 months; the 1997 House version did, however, carry an amendment exempting individual inventors (not companies) and Universities.

case here when the U.S. patent[8(a)] to Johnson et al. was granted and published on August 24, 1993. With that publication, we realized that unbeknownst to us, Johnson et al. had been working along similar lines to ourselves. The Johnson et al. patent was similarly concerned with 2-aryl-1,3 propanediols, more specifically PPD. It essentially disclosed the preparation, isolation, and reduction of methyl tropate (prepared from methyl phenylacetate) and claimed a priority date of September 16, 1992 (versus our September 18, 1992 for the reduction of methyl 2-formylphenylacetate). Of most concern, however, was that the U.S. Johnson et al. patent, in addition to having claims to the process of its invention, also had product claims to boron intermediates of the structure:



wherein M+ is a metal of Groups I to III of the periodic table, or quaternary ammonium. There was no spectral or other evidence to support the structure claimed. We realized that should Johnson et al. obtain grant in Europe of valid claims to those boron intermediates, then those claims could be an impediment to our proposed manufacture of PPD in Europe; Johnson et al. had a priority date two days earlier than ours!

We anticipated that Johnson et al. would file in the PCT countries within the permitted one year period expiring September 16, 1993. We needed to see what Johnson et al. would claim in Europe. In Europe, in contrast to the United States, the patent prosecution file is open to public inspection. It was thus possible to find out that Johnson et al. had indeed filed a corresponding patent application[8(b)] in Europe and to see what patent claims they were pursuing. We found that the claims being pursued were essentially the same as those in the United States. Thus, only the claims to boron intermediates were a potential impediment to our planned European manufacture. Could Johnson et al. obtain valid claims to such intermediates?

In considering this question, we noted the following. It seemed to us that Choi, in his earlier 1991 disclosure of the lithium borohydride reduction of diethyl 2-phenylmalonate, may well have produced boron intermediates falling within the Johnson et al. intermediate patent claims. If this were so, then the Johnson et al. patent claims to boron intermediates would be invalid if they were the same as the boron intermediates previously produced by Choi. In short, the Johnson et al. claims would be open to attack as lacking novelty. We investigated. We undertook a boron NMR analysis of the following fully reduced solutions:

- Reduction of diethyl 2-phenylmalonate with lithium borohydride precisely following the Choi procedure.[4]

[8](a) Johnson, F., and Miller, R. U.S. Patent 5,239,121,1993 (filed September 16, 1992 to Ganes Chemicals). (b) Equivalent European Patent Application 588652 A1 (filed September 16, 1993).

- Reduction of ethyl tropate with sodium borohydride precisely following the Johnson et al. procedure.[8(a)]
- Reduction of methyl 2-formyl 2-phenylacetate with sodium borohydride using the Schering procedure.[6]

All three solutions showed the presence (NMR) of the same boron intermediates. In light of this evidence, it was clear that Johnson et al. could not obtain a grant in Europe of valid patent claims to boron intermediates that would be an impediment to us. (Incidentally, for the same reason, Schering could not obtain such intermediate claims.) On the other hand, the Johnson et al. methyl tropate reduction process was patentable over the disclosed Choi diethyl phenylmalonate reduction process and Schering's formyl phenylacetate process was patentable over both the disclosed Choi and Johnson et al. processes. Both were novel and both had a basis for showing nonobviousness.

Johnson et al. likely became aware that they could not obtain valid intermediate claims in Europe that would impede Schering because eventually they withdrew their European patent application.

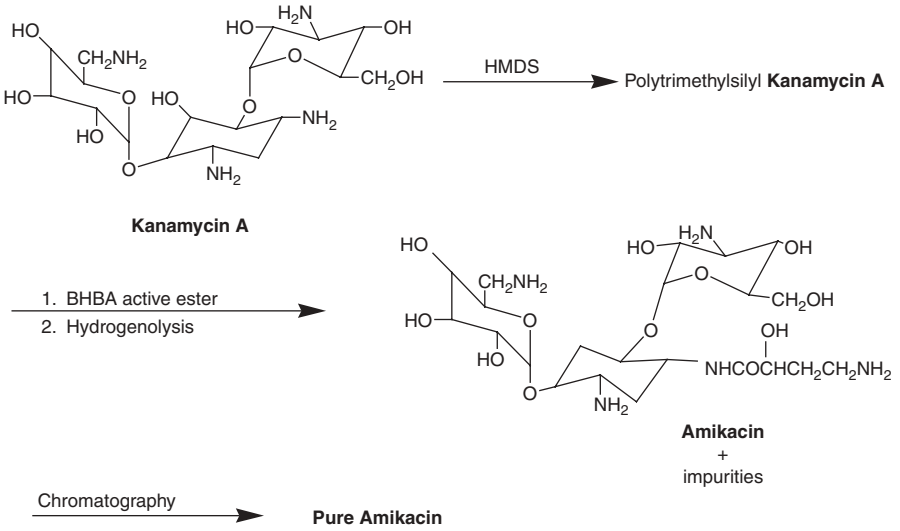
Johnson et al. had attempted to cover the Schering reduction process in a later patent filing[9] having a priority date of November 17, 1992. But they were too late. Schering had beaten them with a priority date of September 18, 1992. Thus the speed with which Dr Tann and his group phased in the methyl formyl phenylacetate approach provided Schering with the lowest-cost technology and a vital patent position.

THE DEFENSE OF PATENT PROPERTY

As indicated, pharmaceutical companies protect the fruits of their research—valuable new drugs—by patents. Where countries provide product protection for new drugs, the protection is strong. However, in days gone by, and to a lesser extent even now, some countries only provided, or still only provide, protection for the patentee's disclosed process for making the drug. Such "process protection" is not strong protection because generic companies can frequently devise other different processes, outside the process patent, for producing the drug—for instance, by reversing the order of process steps specified in the process patent claim.

Alternatively, where the basic patent to the new drug has expired, and hence others are free to use the old process disclosed in the patent, the generic company can assert that it is using that old process to prepare the drug even though in the meantime the patentee will have devised newer, more efficient improved processes, the subject of later patents, and the generic company is really using one of those newer patented processes. In such circumstances, the patentee is faced with the question, Which process is the generic company using, the less efficient off-patent process or the improved patented process?

[9]Johnson, F., and Miller, R. U.S. Patent 5,250,744,1993 (filed November 17, 1992, to Ganes Chemicals).



SCHEME 4. Bristol–Myers process for the production of Amikacin.

The most widely used method of challenging the legitimacy of the process used to manufacture the generic product is to undertake an "impurity profile" study of the drug substance extracted from the competing product, in short to check its impurity "fingerprint" vs. your own product. Most companies can describe cases. One in my experience occurred when an Italian company decided to market Amikacin, at that time a patented Bristol–Myers' product, in Korea.

After years of work, we in Bristol–Myers created an elegant and very practical process for the manufacture of Amikacin which we commercialized. In brief, the process involves solubilization of Kanamycin A in organic solvents by trimethylsilylation (hexamethyldisilazane-HMDS) followed by acylation with *S*-4-benzyloxycarbonyl amino-2-hydroxybutyric acid activated by formation of an active ester with *N*-hydroxynorbornene-2,3-dicarboximide (BHBA active ester) (Scheme 4).

The impurities were primarily compounds which carried the 4-amino-2-hydroxybutyric acid side chain on other than the C-1 amino group of Kanamycin A, including diacyl products. One extraordinary and unexpected result of using the trimethylsilylation approach to solubilizing Kanamycin A in organic solvents preparatory to acylation was the total absence of any acylation at the C-3 amino group. Thus the impurity profile of the Amikacin prepared via polytrimethylsilyl Kanamycin A was quite unique—no other of the several processes described for the acylation of Kanamycin A gave Amikacin containing no C-3-amino product. Our work was patented[10] and published.[11] Later, at a meeting on another subject with the

[10]Cron, M. J., Keil, J. G., Lin, J. S., Ruggeri, M. V., and Walker, D. U.S. Patent 4,424,343, 1984 (to Bristol–Myers).

[11]Cron, M. J., Keil, J. G., Lin, J. S., Ruggeri, M. V., and Walker, D. *Chem. Commun*., 1979, 266.

Italian company which was about to market generic Amikacin in Korea, they congratulated me, on the side, for our work on the Amikacin process. As soon as the Italian company's Amikacin appeared on the Korean market, we obtained samples and analyzed them. When the result came back showing that the Italian Amikacin contained the same profile of impurities as the Bristol–Myers product, and specifically that it contained no C-3-amino product, we were able to force the Italian product off the Korean market on the grounds of their infringement of the Bristol–Myers patent.

DESIGNING AROUND PROCESS PATENTS

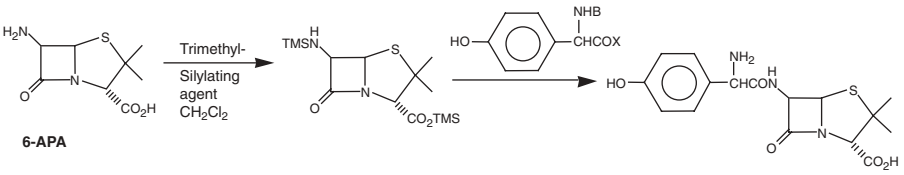
The competitive nature of the pharmaceutical industry often results in lead compounds being identified which are picked up by many companies working to grow their franchises in core businesses. Thus there are many companies with substantial business based on the same molecules. Three of the major molecular foundations of my experience are as follows:

Steroids	Pfizer (Upjohn), Aventis (Roussel), Glaxo–Smith–Kline, Schering–Plough, AKZO (Organon), Hofmann LaRoche (Syntex), Merck, American Home Products (Wyeth), etc.
Penicillins/cephalosporins	Eli Lilly, Glaxo–Smith–Kline (Beecham), Bristol–Myers–Squibb, Pfizer, Shionogi, Fujisawa, Takeda, Aventis (Roussel/Hoechst), Merck, Novartis (Ciba), etc.
Aminoglycosides	Meiji, Eli Lilly, Schering–Plough, Pfizer, Bristol–Myers–Squibb

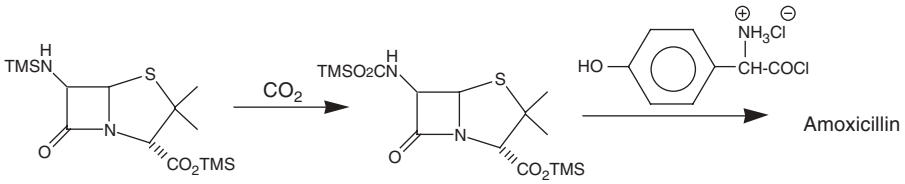
There are many companies working on many other molecular foundations—for example, alkaloids, peptides, proteins, benzodiazepines, statins, and so on.

Companies working on the same core molecule build patent franchises to protect their positions, often designing around the patent positions of competitors. One such situation arose when Beecham saw Bristol–Myers enter the Japanese Amoxicillin market. Beecham's belief was that Bristol–Myers was using its patented process for the manufacture of Amoxicillin (Scheme 5).

Beecham commenced court action in Japan to get Bristol–Myers off the market, accusing them of infringing its patented process. As the reports of that litigation show,



SCHEME 5. Beecham process for the production of Amoxicillin.

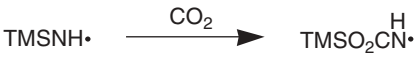


SCHEME 6. Bristol-Myers process for the production of Amoxicillin.

Bristol–Myers denied the Beecham accusation, stating that it had a process of its own which did not involve the acylation of the bis-trimethylsilyl derivative of 6-APA. However, Bristol–Myers refused to disclose its process to Beecham on the grounds that the process was still under patent prosecution with the U.S. Patent Office. This dilemma was resolved when Bristol–Myers and Beecham agreed that the Japanese judge presiding over the court action could visit Bristol–Myers' plant in Sermoneta, Italy, where the process was being run, to judge whether or not patent infringement was occurring.

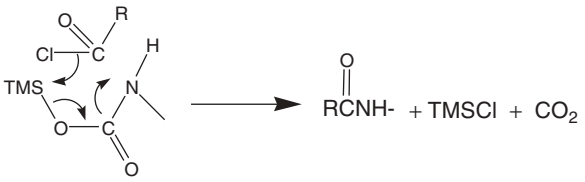
In reaching its decision to launch Amoxicillin on the Japanese market, Bristol–Myers had recognized the need to design around the Beecham patent and identify and develop a process which would be competitive.

Our Chemical Development group in Bristol–Myers had earlier held many brainstorming sessions to find a solution to the problem. The solution came from a reading of Russian literature[12] describing the conversion of TMSNH· to $TMSO_2CNH$·

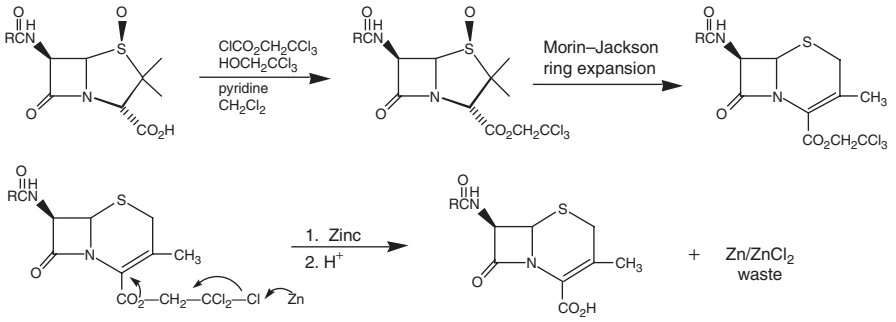


We found that the bis-trimethylsilyl derivative of 6-APA reacted quantitatively with dry CO_2 to give a trimethylsilylcarbamate intermediate which in turn reacted almost quantitatively with *p*-hydroxyphenylglycyl chloride to give Amoxicillin (Scheme 6). The formation of the carbamate could be readily followed by NMR, and sufficient spectral evidence was gathered to allow Bristol–Myers to unequivocally claim the trimethylsilylcarbamate derivative of monotrimethylsilyl 6-APA.

The mechanism of the acylation reaction was never studied. We, perhaps naively, hypothesized the mechanism involved:



[12](a) Sheludyakov, V. D., Kirilin, A. D., Gusev, A. J., Sharapov, V. A., and Mironov, *V. F. Zh. Obschei Khim*., 1976,46,2215. (b) Sheludyakov, V. D., Rodionov, E. S., Kirilin, A. D., and Mironov, *V. F. Zh. Obschei Khim.,* 1976,46,2265.



SCHEME 7. 2,2,2-Trichloroethyl protection of carboxyl: Protection and deprotection.

However, since a process patent was granted to Bristol–Myers[13] no further work was undertaken.

Assertion of property rights of a different kind occurred in the late 1960s in the then commercially important era of penicillin sulfoxide ring expansion to cephalosporins. An early focus of commercial attention was finding a commercially viable blocking group for the 3-carboxyl group of the penicillin. Ciba, through its Woodward Research Institute in Basel, found that the trichloroethyl ester of penicillin sulfoxides could be produced in high efficiency, the product ring could be expanded to the cephalosporin, and the trichloroethyl ester protection could be removed by treatment with zinc.[14] The process is outlined in Scheme 7.

The use of the 2,2,2-trichloroethyl (TCE) group for carboxyl protection became of interest following publications by Woodward et al.[14(c,d,e)] As a result, TCE protection was used by Glaxo in the early stages of developing a process for Cephalexin manufacture. At the same time, Glaxo initiated work to find an alternative to TCE, recognizing that Ciba may patent its TCE-based process, and also recognizing that TCE protection was unsuitable from an industrial standpoint. Glaxo's plant in Montrose, Scotland, where the step of removing the TCE group was being carried out, was encountering zinc/zinc chloride waste disposal problems owing to the spontaneous combustion properties of this waste.

Glaxo initiated evaluation of two other carboxyl protecting groups, namely diphenylmethyl (DPM) and *p*-nitrobenzyl (PNB). Of these, development of the PNB group was already well-advanced by Eli Lilly, with whom Glaxo had a working relationship through the U.K. National Research Development Council (NRDC). [The NRDC held the patents on Cephalosporins and licensed rights to several companies, including Glaxo and Eli Lilly.] Evaluation of the two blocking groups was resolved

[13] Walker, D., Silvestri, H. H., Sapino, C., and Johnson, D. A. U.S. Patents 4,240,960,1980; 4,278,600,1981; 4,310,458,1982 and 4,351,796,1982 (all to Bristol–Myers).

[14] (a) Woodward, R. B. British Patent 1,155,016,1969. (b) Woodward R. B. U.S. Patent 3,828,026,1974 (to Ciba–Geigy). (c) Woodward, R. B. *Science*, 1966, **153**, 487. (d) Woodward, R. B. *Angew. Chemie,* 1966, **78**, 557 (e) Woodward, R. B., Heusler, K., Gosteli, J., Naegeli, P., Oppolzer, W., Ramage, R., Ranganathan, S., and Vorbrüggen, H. *J. Am. Chem. Soc.,* 1966, **88**, 852.

in favor of the DPM ester since we in the Chemical Development Group (in Glaxo's Ulverston manufacturing plant in the United Kingdom) had created and developed a novel low-cost process for introducing DPM ester protection. We also demonstrated its value in the manufacture of Cephalexin DPM ester and showed that the DPM group was readily removed to give high-quality Cephalexin. The new process was patented.[15] Glaxo paid a royalty to Ciba during the short period of its use of the Woodward patent.

PATENTING VERSUS TRADE SECRETS

Most improvements to commercial processes are not patented. These generally result from efforts by the process improvement and development groups on the production site to increase productivity and reduce costs. These efforts include increasing yield by better understanding of the chemical transformations, increasing reaction concentration, minimizing isolations (e.g., by combining process steps), recycling waste more efficiently, changing solvents to harmonize with other plant processes, improving environmental compliance, improving product quality, and finding lower-cost, quality sources of raw materials. Not infrequently, better chemistry may be devised, steps reversed advantageously, and other innovations made which could create a patentable situation. Often the judgment call is made to keep such innovations as trade secrets. This can be dangerous and expensive, since if others obtained a patent covering the technology, those who practice the innovation as a trade secret could be considered infringers who may be forced to either stop using the technology or pay royalties to the patent holder! Happily, this way of thinking is being outmoded to allow the original trade secret user to keep using the technology without license. Europe now recognizes prior use as a defense to an infringement action, and the United States is moving toward recognizing the right of prior use.

PATENT ASPECTS OF THE DEVELOPMENT OF PROCESSES FOR FLORFENICOL MANUFACTURE

Introduction

Several patent situations emerged during the course of the development of a process for the manufacture of Florfenicol. Those described in this section illustrate the importance of the following:

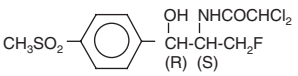
1. When third parties are involved in process research and development work, agreements are needed to cover both the objectives of the joint program of work and definition of the ownership of intellectual property (patents) discovered by the third party. Such agreements benefit all parties.

[15] (a) Bywood R., Gallagher, G., Sharma, G. K., and Walker, D. German Patent 2,201,018,1972 (to Glaxo). (b) Bywood, R., Gallagher, G., and Walker, D. German Patent 2,311,597,1973 (to Glaxo).

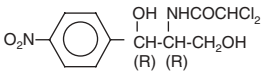
2. The company that owns the patents is in charge of the technology that develops; this is vital for controlling Active Pharmaceutical Ingredient (API) or Intermediate supply and provides flexibility in selecting manufacturing partners—for example, to obtain the lowest cost of goods (COG).
3. Quality issues can raise questions that galvanize the search for improved *processes*, often leading to new and patentable *technology*.
4. Failure to demonstrate a chemical synthesis idea in one laboratory need not discourage others who believe they can make that idea work.
5. Designing around the patent positions of others frequently requires the kind of thinking that identifies new and sometimes revolutionary approaches to a synthesis; competitive instincts and seemingly insurmountable obstacles stimulate new insights and speed innovation.

Initial Process Exploration with Third Parties

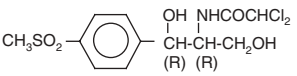
Florfenicol (IX) was patented by Schering–Plough as a broad spectrum antibiotic with Gram-positive and Gram-negative activity comparable to chloramphenicol (X). Chloramphenicol had become severely restricted in use, owing to its propensity to cause blood dyscrasia (aplastic anemia) in some patients.



IX



X



XI

Florfenicol was believed to be more like thiamphenicol (XI), which appeared to be free of the blood toxicity problems associated with chloramphenicol. The toxicity of chloramphenicol was loosely linked to the presence of the nitro group. Nevertheless, Schering regarded Florfenicol as too risky to develop for human use, leaving the compound to be picked up by Schering's Animal Health Division for use as an animal antibiotic.

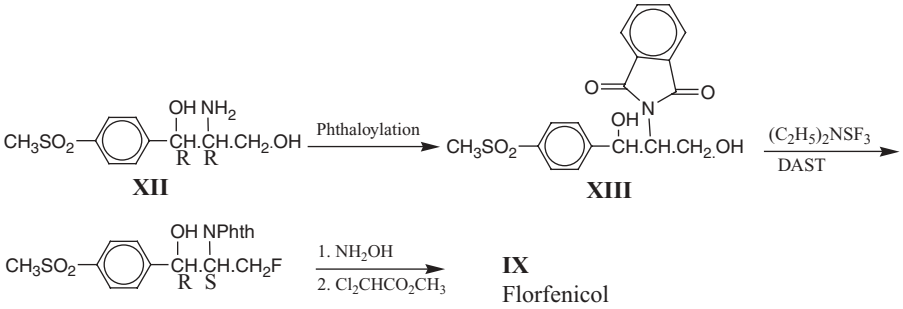
In order to progress the development of Florfenicol, Schering produced its earliest needs (for safety and early clinical studies) using a process based on thiamphenicol (Scheme 8):[16]

Schering–Plough undertook a broad-based effort with third parties, both university and industrial, to search for a more practical process than that outlined in Scheme 8. The most important collaboration was that with Zambon S.p.A in Italy.

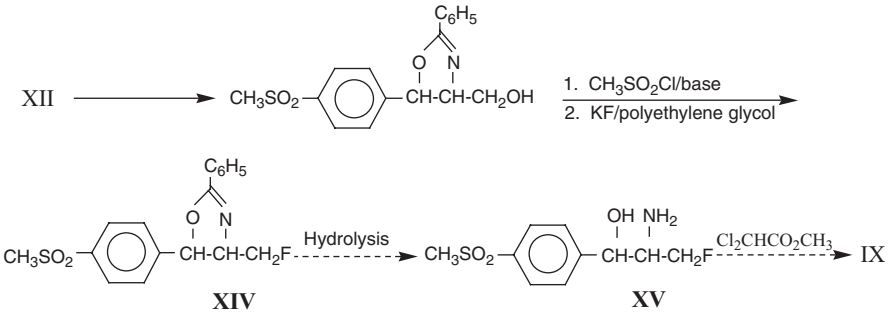
Zambon already marketed Thiamphenicol, which it produced in Italy via the chiral intermediate XII.[17] In 1980 Zambon undertook the search for a synthesis scheme

[16]Nagabhushan, T. L. U.S. Patent 4,235,892, 1980 (to Schering–Plough).

[17](a) Kleeman, A., Engel, J., Kutscher, B., and Reichert, D. *Pharmaceutical Substances; Syntheses, Patents and Applications*, 4th edition, Georg Thieme Verlag, Stuttgart, 2001, p. 2016. (b) Jacquez, J., Collet, A., and Wilen, S. *Enantiomers, Racemates and Resolutions*, John Wiley & Sons, New York, 1981, p. 223.



SCHEME 8. Conversion of Thiamphenicol to Florfenicol.



SCHEME 9. Zambon process for producing Florfenicol.

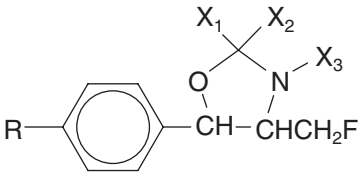
which would give a less expensive product than that afforded by Scheme 8. The major problems with Scheme 8 lay in the cost and potential hazard associated with the production and use of the DAST reagent, and also with the expense of removing the difluoro impurity resulting from "fluorination" at both the primary and secondary alcohol positions of XIII.

Zambon devised the "fluorination" process outlined in Scheme 9, and used the new intermediate XIV to produce useful quantities of Florfenicol for Schering–Plough's ongoing development programs.

The process steps up to compound XV were the subject of disclosure in a Zambon patent.[18] The Zambon patent was part of a family of patents that Zambon was to build up over time, in both the United States and Europe, covering its process R&D work. Claim 1 in Zambon's patent, covering the process to compound XIV is provided to illustrate the breadth and complexity of their coverage. It can be adduced that compound XVI in Claim 1 embraces the key intermediate XIV. Claim 1 reads as follows:

[18]Jommi, G., Chiarino, D., and Pagliarin, R. U.S. Patent 4,743,700,1988 (to Zambon S.p.A.).

A process for preparing a compound of formula XVI (formula III in the U.S. Patent[18])



XVI

where

R is a methylthio, methylsulfoxy, methylsulfonyl, or nitro group, and

X_1 is hydrogen, 1–6 carbon alkyl, 1–6 carbon haloalkyl, 3–6 carbon cycloalkyl, phenyl or 1–6 carbonphenylalkyl, whose phenyl ring may be substituted by one or two halogen atoms, 1–3 carbon alkyl, 1–3 carbon alkoxy or nitrogroups; or

X_1 together with X_2 is an oxygen atom or an alkylene having from 2–5 carbon atoms; and

X_2 is hydrogen, 1–6 carbon alkyl, 1–6 carbon haloalkyl, 1–6 carbon cycloalkyl or phenyl which may be substituted by one or two halogen atoms, 1–3 carbon alkyl, 1–3 carbon alkoxy or nitro groups; or

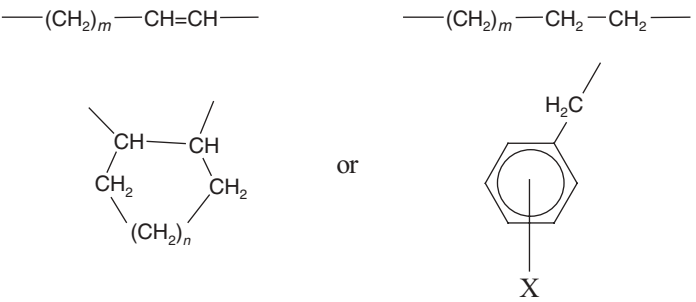
X_2 together with X1, is an oxygen atom or an alkylene having from 2–5 carbon atoms; or

X_2 is covalently linked to X_3; and

X_3 is hydrogen or $–COR_4$ wherein

R_4 is hydrogen, 1–6 carbon alkyl, 1–6 carbon haloalkyl, 3–6 carbon cycloalkyl, phenyl or 1–6 carbon phenylalkyl, which phenyl ring may be substituted by one or two halogen atoms, 1–3 carbon alkyl, 1–3 carbon alkoxy or nitro groups; or

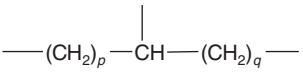
R_4 together with X_2 is



where

n is 1 or 2; *m* is 0 or 1; X is hydrogen, a halogen atom, 1–3 carbon alkyl, 1–3 carbon alkoxy or nitro groups; or

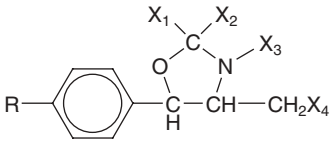
R_4 together with X_2 and X_1 is a chain of formula



where

p is 3 or 4 and *q* is 1 or 2; or

X_3 is covalently linked with X_2; a process that comprises reacting one mole of a compound of formula

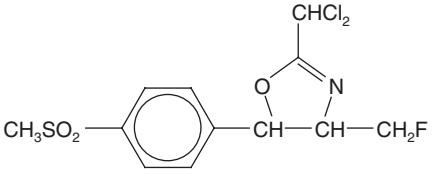


where

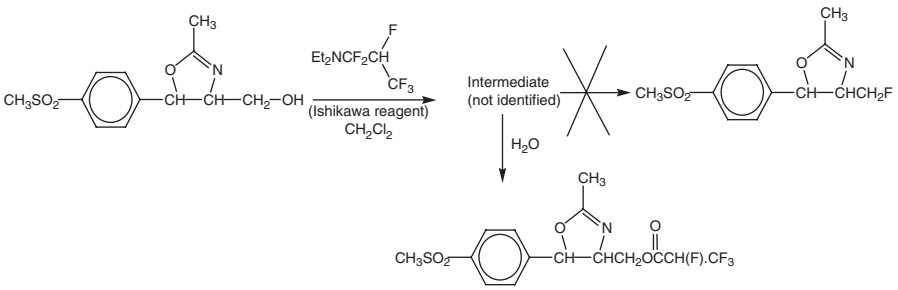
R, X_1, X_2, and X_3 are as is defined above, and where

X4 is –OSO2R6 where R6 is methyl, trifluoromethyl, phenyl, *p*-methyl phenyl, 2-, 4-, 6-trimethylphenyl, 2- naphthyl, or 2-pyridyl with 1–15 moles of a non-gaseous inorganic fluoride in a polyglycol having at least four alkylidene oxide units at a temperature of 40°C to 150°C and retaining said compound of formula III formed in the reaction mixture until completion of the reaction.

This broad claim covers processes to compound XIV and XVII the compounds most germane to Schering–Plough's subsequent Florfenicol process interests (see later):



XVII



SCHEME 10. Use of new fluorinating reagents in the synthesis of Florfenicol intermediates.

The Zambon U.S. Patent[18] covered processes only. Product claims to intermediates were divided out from that parent patent, in both the United States and Europe, and became the subject of a later patent.[19]

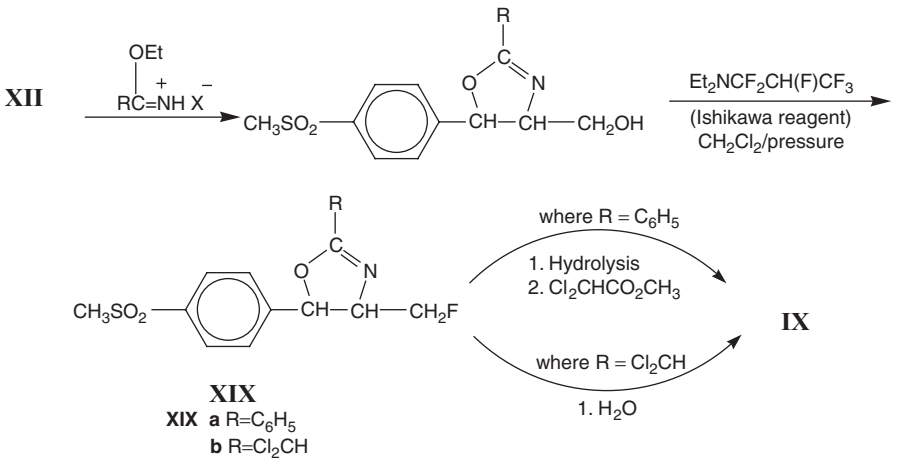
One interesting feature of Zambon's U.S. Patents, which might have become fortuitous as far as Schering–Plough was concerned, was that no examples or claims were made to the use of intermediates, produced according to their process, in the production of Florfenicol. In short, the dotted line process steps in Scheme 9, covering the production of Florfenicol using the process and intermediates of its U.S. Patent, were not claimed by Zambon. Thus, had Schering decided to import Florfenicol produced in a country that did not recognize patents (e.g., China or India at that time), Zambon could not have prevented this. In short, Schering would not have been infringing Zambon's process claims in the United States by importation since Zambon in this patent did not claim Florfenicol made by its process!

In regard to other process exploration work carried out in Universities under Schering–Plough auspices, it is pertinent to mention the work of Professor Szarek and his postdoctoral student at Queens University in Kingston Ontario. One particularly interesting reaction carried out by them[20] is outlined in Scheme 10. This work was carried out in 1982. Although the hydroxymethyl methyloxazoline did not appear to give the desired fluoromethyl compound with Ishikawa reagent, we later found that other similar oxazolines did.

The Search for a Better Process for Florfenicol Manufacture

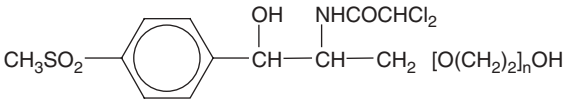
The Schering–Plough chemical process development group was drawn into the Florfenicol clinical supply program in 1984 with a view to determining whether a lower-cost process might be found which would overcome the need to routinely recrystallize the Florfenicol produced by Zambon. Recrystallization had proved necessary to

[19] Jommi, G., Chiarino, D., and Pagliarin, R. U.S. Patent 5,153,328,1992 (to Zambon S.p.A.)
[20] Szarek, W. A., and Matsuura, D. Unpublished results, November 1982.



SCHEME 11. Schering–Plough process for the manufacture of Florfenicol.

remove an impurity we identified to be XVIII.



XVIII

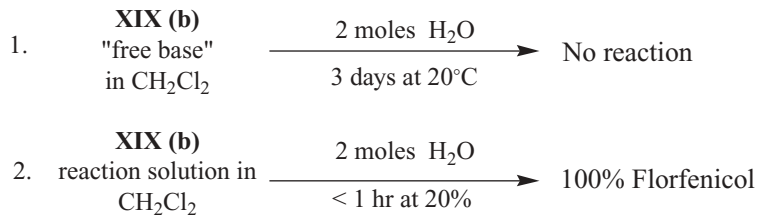
resulting from step 2 of the Zambon process outlined in Scheme 9.

Work to improve the cost of goods and the quality of Florfenicol led to the process outlined in Scheme 11. The Schering process exploration program, led by Dr. Doris Schumacher, is noteworthy for the striking success of the Ishikawa reaction identified in Scheme 11 versus the results obtained in Scheme 10. Dr. Schumacher's initiative nicely illustrates a homily I often use: Never let theory abort an experiment.

This process was the subject of two process patents,[21] one for the selective oxazoline formation step and the other for the "fluorination" step. The key factor in obtaining a patent for the "fluorination" step was the use of pressure. Application of process conditions previously described by Ishikawa and co-workers[22] gave poor yields. When the reaction was carried out in dry methylene chloride at 100°C in an autoclave, the yield of high-quality Florfenicol intermediates (XIV or XVII) was almost quantitative.

A study of the hydrolysis of XIX(b) revealed that the "free base" form was very stable to the action of water, whereas the Ishikawa reaction mixture (containing HF)

[21](a) Clark, J. E., Schumacher, D. P., and Wu, G.-Z. U.S. Patent 5,382,673,1995 (to Schering–Plough).
(b) Schumacher, D. P., Clark, J. E., and Murphy, B. L. U.S. Patent 4,876,352,1989 (to Schering–Plough).
[22]Takaoka, A., Iwagiri, H., and Ishikawa, N. *Bull. Chem. Soc. Japan* 1979, **52**, 3377.



SCHEME 12. Hydrolysis of XIX b.

was rapidly hydrolyzed to Florfenicol (Scheme 12). This work led to the establishment of a "one-pot" process for the manufacture of Florfenicol.[23]

Schering–Plough's Improved Process in Relation to Zambon's Patent Rights

During the period leading to Schering–Plough's new process for the manufacture of Florfenicol, Zambon had continued its efforts to complete its process and compound claims to the intermediates disclosed in its U.S. Patents. In order to ensure the best possible patent protection for Florfenicol processes and intermediates thereto, Schering–Plough acquired rights to the Zambon patents, thus closing a chapter of fruitful collaboration.

A LIGHTER SIDE OF THE PATENT LITERATURE

As the patent system harmonizes and more countries recognize the importance of patenting intellectual property, the value of patents grows. This leads to more people and companies seeking patents for even the most abstruse and maybe bizarre inventions. Patents issued by the U.S. Patent Office can be viewed in some large libraries or on the Web at www.uspto.gov. The following patents indicate there are no limits to human imagination:

U.S. Patent 5,911,805. The inventor claims a "unique die-cut confetti that has unusual aerodynamic features that create visually pleasing flight patterns that have not been previously observed with confetti." To achieve the pleasing flight patterns, the inventor merely stamps a hole into the middle of each piece of paper, which itself can be any desired shape (e.g., a bell, dove, etc.).

U. S. Patent 5,876,995. The inventor claims a way of making glow-in-the-dark party drinks such as champagne. The glow is created by the interaction of luciferin and luciferase as in the bioluminescence process, which lights the firefly's tail. One way of achieving this is to clone the luciferase gene into the

[23](a) Example 7 in Reference 21(b) describes the "one-pot" process. (b) Wu, G., Schumacher, D. P., Tormos, W., Clark, J. E., and Murphy, B. L. *J. Org. Chem.*, 1997, **62**, 2996.

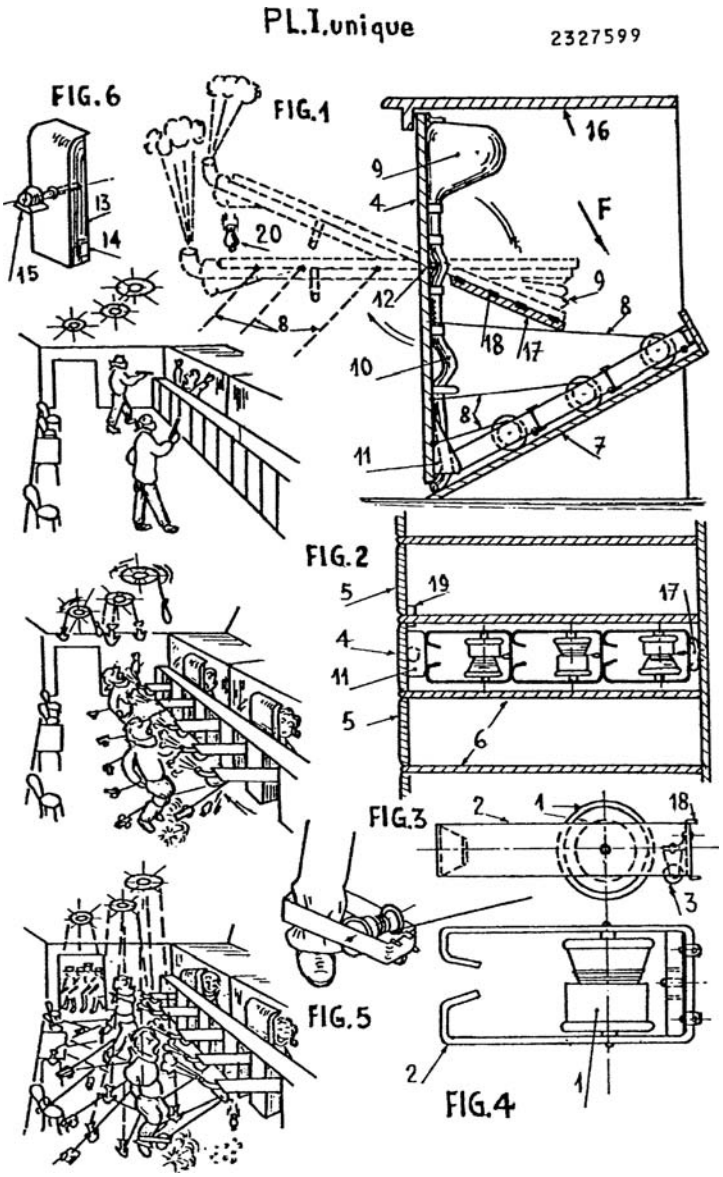


FIGURE 1. Illustration from French Patent 2,327,599.

yeast that makes champagne and arrange for luciferin to be introduced when the cork is popped. One imagines that the product would require FDA approval!

My own all-time favorite bizarre patent I owe to Dr. Ken Kerridge, librarian at Bristol–Myers. He and his colleagues recognized, in sending out a weekly summary

of relevant new patents, that the Bristol–Myers scientists needed occasional light relief from scanning the almost mind-numbing torrent of patent information. The following patent abstract served the need:

French Patent 2,327,599 (1977) to E. Kimmerle. This patent describes a new bank security system:

> The bank counter conceals an automatic system for seizing robbers, encircling them with cables, releasing tear gas, etc. When a pedal behind a counter is pressed, alternate sections of the counter screen tip over, bringing tear gas tubes to the robbers' head level—tear gas is released automatically as this happens. At the same time, bullet-proof screens are raised in front of the staff. In tipping, the counter screens/sections release reels of cable stored behind them, the reels roll down ramps and then circle, some to the left and some to the right, encircling the robbers legs. Some reels roll straight across the banking hall; their cables catch in the legs of furniture fixed to the floor and serve as trip wires. Small balls are distributed over the floor, and stupefying gas is released. These measures are added to those described in the parent patent (Figure 1).

Unfortunately, today, few chemists appear to have the time to read the patent literature. The proliferation of journals and the pressure to accelerate projects appears to create neglect of patents as a source of technical information. Process development chemists and engineers do get involved in cases of patent interference, extending patent life, and in situations where new processes for important compounds have some priority. However, these are relatively minor activities. Neglect of the patent literature is seen in the paucity of reference to patents in publications in the major journals. Even in journals such as *Organic Process Research and Development* (OPRD), one finds relatively few references to patents. This situation is recognized by the editor of OPRD,[24] and initiatives[25] to bring patents to the attention of readers of this journal have been taken. In view of the growing importance of intellectual property and the increasing strength of a harmonizing patent system, the reading and understanding of patents needs to be given more attention. Certainly, chemists involved in creative/inventive endeavors need to see their work in the perspective of patent applications. Patents are more than just a nuisance slowing the publication of scientific findings. They are the pillars on which companies around the world build their businesses.

[24]Laird, T. *J. Organic Proc. Res. Dev.*, 2000, **4**, 61.
[25](a) Turner, K. *J. Organic Proc. Res. Dev.*, 2000, **4**, 68; (b) *idem ibid.*, 2000, **4**, 246.

8

CHEMICAL ENGINEERING

> The philosopher may be delighted with the extent of his views, the artificer with the readiness of his hands, but let one remember without mechanical performance refined speculation is but an empty dream and let the other remember that without theoretical reasoning, dexterity is little more than brute instinct.
>
> ——Samuel Johnson (1709–1784)

INTRODUCTION

Though the chemist may not be the philosopher in Samuel Johnson's sense, nor the chemical engineer merely an artificer, the quotation aptly reinforces the need for the closest possible integration of the chemist's and chemical engineer's skills in the creation of a chemical process.

The descriptive approach to illustrating the chemical engineer's contribution to chemical process development, which is presented in the following pages, provides no more than an introduction to the chemical engineering discipline. There is no substitute for a dialogue with a professional chemical engineer when developing a process for scale-up. Published texts—for example, Griskey's *Chemical Engineering for Chemists*[1] and Perry et al.'s *Perry's Chemical Engineers Handbook*[2]—provide more fundamental information on the field. I have personally found

[1]Griskey, R. G. *Chemical Engineering for Chemists*, American Chemical Society, Washington, D.C., 1997.
[2]Perry, R. H., Green, D. W., and Maloney, J. O. *Perry's Chemical Engineers Handbook*, 7th edition, McGraw-Hill, New York, 1997.

The Management of Chemical Process Development in the Pharmaceutical Industry by Derek Walker
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Perry's Handbook to be particularly useful. It gives masses of physical and chemical data on chemicals and learned information on topics such as heat and mass transfer, pumping, flow measurement, liquid–liquid extraction, distillation, evaporation, fractionation, reaction kinetics, membrane separation processes, chromatography, crystallization, filtration, drying, process control, materials of construction, corrosion, waste water management, biochemical engineering, pollution, accounting, and more. More recently, a splendid publication by McConville[3] provides an excellent source of chemical engineering information and, more particularly, a chemical engineer's insights and perspective on chemical process scale-up. For a more formal chemical engineering education, The American Institute of Chemical Engineers offers a wide range of courses (see www.aiche.org/education).

The process of developing the chemistry needed to produce a target molecule usually starts with the research chemist's raw chemical transformation (a notebook "*Recipe*"). Building on this, development chemists, analysts, and chemical engineers work to better understand the chemistry and modify or change it to make it safer, more efficient, and more suitable for larger-scale operation—during this exercise the *Recipe* generally becomes a *Method*. Transformation of the *Method* into a *Process* is a major endeavor often taking many years of close collaboration between chemists, analysts, chemical engineers, and chemical manufacturing people. Nor does the work end when the developers of a production process transfer the technology into the manufacturing plant. The manufacturing group responsible for producing the chemical generally achieves substantial cost reduction over the years by increasing productivity, in particular by reducing labor costs, minimizing equipment usage, and generally reducing plant overhead. Thus the development of a plant process is a continuum requiring dedicated teamwork over a long period of time.

Chemists start by manipulating the chemistry, in concert with analysts. Chemists, however, are not usually trained in chemical engineering such that integration of the chemistry and chemical engineering disciplines is often unwittingly delayed to the detriment of process development. As an aside, in my experience, the practical aspects of creating and developing a chemical process are hardly studied at all in Universities except in a small number of colleges that offer courses in industrial chemistry or chemical technology.

The chemist does not think much about how he or she manipulates the mechanics of a process, how chemicals are transported to the site, how they are moved from store to bench, how these often noxious chemicals are moved from their containers and weighed, how they are added to flasks, how the flasks are stirred and heated and cooled, how reflux and distillation are carried out, how and even why solvent recovery is done, how crystals are formed for the best filtration, how filtrations are done and products washed and taken from the filter to a drier and how the drier is operated, how dry powders are handled or offloaded, and how they are milled or micronized. In reality, the differences between the chemist's view of the preparation of a chemical and the chemical engineer's view are profound. In scale-up, the chemist

[3]McConville, F. X. *The Pilot Plant Real Book*, FXM Engineering and Design, Worcester, MA, 2002.

not unnaturally looks on the chemical plant as a scaled-up laboratory. In contrast, the chemical engineer looks at laboratory equipment in terms of a scaled-down plant.

This is not to denigrate the chemist and his glassware. The chemist grew up drawing chemicals from a store, manually pouring or scooping them from their containers into graduated receptacles or onto a balance, manually adding them to flasks set up in heating mantles or cooling/heating baths in a fume hood, manually setting up condensers, soxhlets, Dean-Stark traps, distillation receivers, and so on, carrying out chemical additions, heating and cooling, crystallizing and manually lifting the flask and pouring the contents into a Buchner filter and manually washing the filter cake, sometimes eliminating cracks in the cake with a spatula, digging out the wet cake and loading it thinly onto a dish or paper for drying, and so on. Having grown up with glassware and having been trained in laboratory manipulations and chemical reactions observed through glass in a fume hood, the manual approach to running chemical reactions is almost second nature to the chemist. He doesn't have to think much about solvent recovery, the handling of chemicals, or the exposure of plant operators. The trained graduate chemist has a fair knowledge of hazards and a rudimentary experience of safety, and he knows from Material Safety Data Sheets (MSDSs) the dangers of handling chemicals. The chemist thinks mostly about the molecular transformations going on and how to manage and improve them to get the best reaction yield and product quality.

The process development chemist, by dint of exposure to scale-up, rapidly becomes aware of the challenges posed by chemical operations on a larger scale and recognizes the need for thinking about how to carry out routine laboratory manipulations in larger equipment. In this domain the chemical engineer provides an educational resource in respect of identifying the large-scale equipment needed to meet the requirements of the process. The engineer also provides considerations for changing the process to meet the limitations or harness the advantages of operating in large-scale equipment.

SCALE-UP

In the pharmaceutical industry, scale-up of a chemical *recipe*, *method*, or *process* invariably comes before chemists or chemical engineers are fully ready for it; this is generally because of the urgency of the clinical supply program and the relentless need for speed in defining and implementing a process suitable for commercial operation. Clearly, raw chemical recipes pose the greatest problem especially from the safety, environmental, regulatory, and logistics points of view. So little is generally known about the chemicals, the chemical sources, outsourcing possibilities, the chemistry involved in manipulating the transformations, the effects of changing reaction conditions in larger-scale equipment, the limitations of available equipment, what equipment modifications are needed to reproduce defined reaction conditions, and how long all the necessary steps needed to commence scale-up will take. A written procedure for every step in order of their proposed implementation is provided, along with the chemicals, to enable a hazard analysis and hazard operability study to be undertaken before a procedure can be approved for scale-up—the safety of

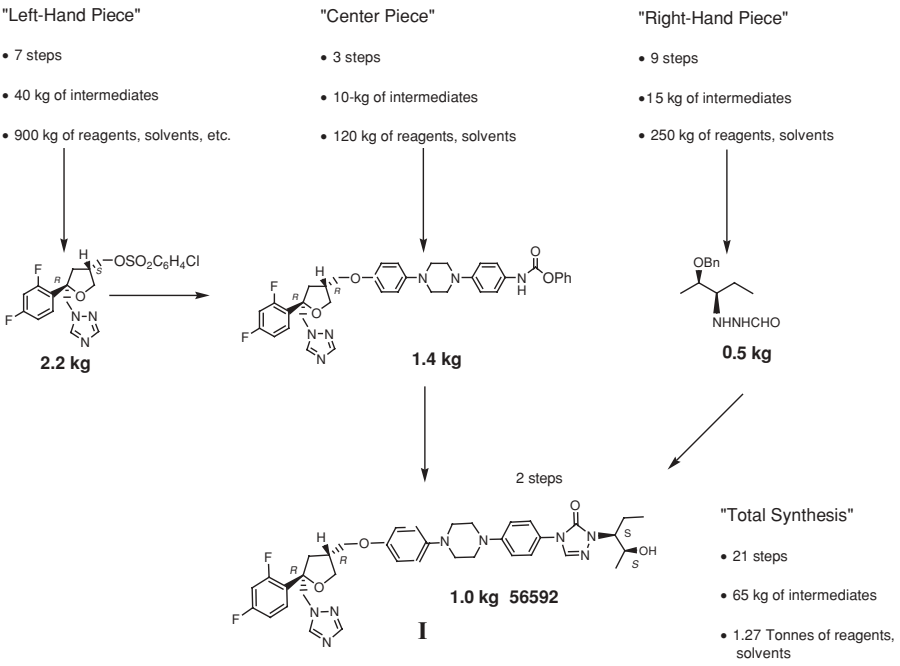
operators, chemists, and chemical engineers is paramount. The best available procedures for analyzing the reactions and products are vital for control of the process. It bears repeating that the thorough preparation of the batch sheet (manufacturing directions) is a team effort that reflects the input of all those who will be involved in running the process.

The project team in charge of scale-up usually comprises chemists, chemical engineers, and analysts. These people are responsible for asking the sourcing specialists to order needed chemicals, for modifying the large-scale equipment, for working out analytical methods, and for prioritizing and scheduling. They are also simultaneously called on to provide a likely timeline for operations to commence and for delivery of the final active pharmaceutical ingredient (API), meeting the desired quality criteria. At the same time, they are exhorted to do everything possible to stay within budget! The timeline, kilos expected, and product quality are the main interests. This information enables others, and especially those involved in toxicology, pharmaceutical dosage form development, pharmacology, and drug metabolism, to plan their own programs for the prioritized development of the API.

The formal program outlined above, leading to delivery of the API, meeting the desired quality criteria, varies with the length and difficulty of the API synthesis. Chemical engineers may not be involved to any extent in the provision of the first kilo if the API synthesis is relatively short and straightforward. At the other extreme, the synthesis of the first kilo may immediately require the input of chemical engineers. One such example was provided by the synthesis of the Schering–Plough antifungal **I**, wherein 1.2 tonnes of chemicals, including solvents, were required for the synthesis of the first kilogram (Scheme 1).

The chemical engineer's "laboratory" is a physical world apart. Chemicals arrive in drums, containers, and cylinders requiring closely regulated storage; large warehouses have separate areas for new chemicals, for released (analyzed) chemicals, for in-process chemicals, for quarantined chemicals, and for final APIs (often requiring refrigerated storage). Dangerous and controlled chemicals all need special (lock-up) storage. Chemicals are moved by forklift trucks (often with explosion proof motors) or "dollies," to weighing areas (properly ventilated) for weighing or measuring the amounts required by the operating procedure. Frequently the weighing scales are set by the reaction vessels, allowing weighed chemicals to be directly delivered to the vessel (sometimes the last API step chemicals have to be delivered through a glove box or protected system to minimize microbiological contamination). Operating staff are also trained and are issued with special protective equipment as needed, to ensure their own protection from exposure to chemicals at all appropriate steps of the operation.

Suitable reaction vessels are selected by the chemical engineers. These may be glass-lined steel, steel (for good heat transfer), or vessels made of corrosion-resistant materials (e.g., Hastelloy, teflon-coated steel, etc.). Reaction vessels in pharmaceutical pilot plants may range from a few liters to thousands of liters and are generally equipped for multipurpose use. Although reaction vessels come in many different configurations, they preferably have a variable-speed agitator, attachment to an emission control device, a sight-glass, a thermometer pocket, a pressure gauge, a nitrogen



SCHEME 1. Initial chemical usage in the preparation of Sch 56592.

(or argon) blanketing port, a pressure relief line (with bursting disc), condenser access, inlet(s) for the addition of chemicals, and capabilities for measuring liquid levels. They are usually also connected to a similarly equipped receiver vessel for distillation and, subsequently, process work-up. Heating and cooling are provided by an external jacket (often split level in larger vessels), sometimes supplemented with capability for pumping the reactor contents through an external heat exchanger. A baffle is often a valuable addition to aid mixing, especially in large vessels. A bottom valve (most frequently a ball valve, a rising stem valve, or a butterfly valve) enables removal of vessel contents. A typical multipurpose pilot plant reactor package is outlined in Figure 1.

Since most chemical processes use flammable organic solvents, the electrics in all pilot plant and plant facilities are invariably explosion-proof.

There are many differences between pilot plant and laboratory operation. These can be illustrated by reference to the following operations:

Heat Exchange

The scale of pilot plant operations results in slower heating and cooling rates since the ratio of cooling or heating surface to reaction volume is much smaller in a plant versus in small-scale laboratory equipment. This can pose serious problems in controlling strongly exothermic reactions, especially if the chemist has found that the rate of

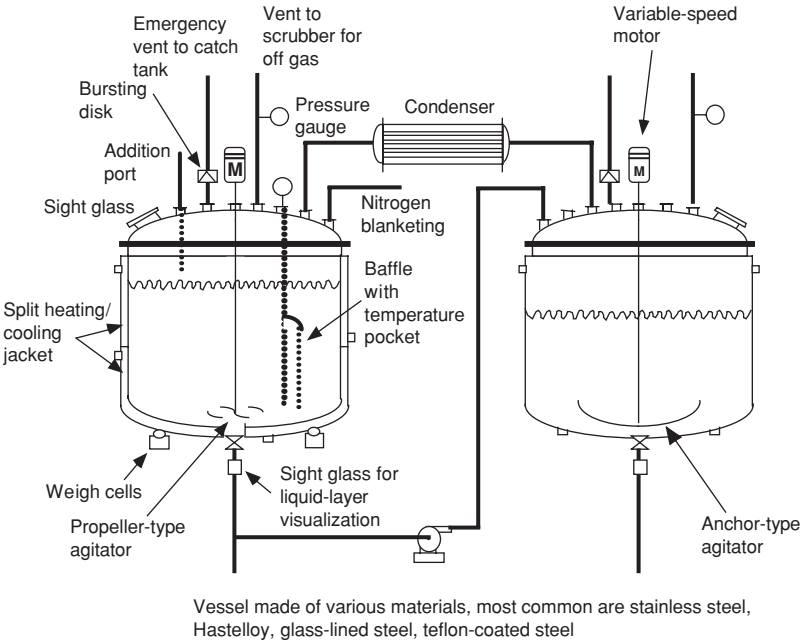


FIGURE 1. Typical multipurpose pilot plant reactor package.

addition of one reactant to another has to be done quickly for the best result. The heat exchange problem is exacerbated if the reaction mixture is corrosive, necessitating the use of glass or teflon-lined vessels. Such a situation can be accommodated to some extent by the use of a corrosion-resistant external heat exchanger or by greater dilution, though the latter, using a large volume of solvent as the heat sink, is not favored by those who eventually want to create high productivity in a process. The chemical engineer's approach may be to pump solutions of the reactants continuously into a cooled mixing chamber and immediately through an appropriately sized heat exchanger into the reaction vessel.

In most pilot plants, the reactor jackets are equipped for heating with hot water or steam under varying degrees of pressure. Similarly, in cooling, ice water (0°C) or ice/methanol (−20°C) are frequently employed, with lower temperatures being obtained through the use of dry ice/acetone. These systems are familiar to the chemist, but water-based heating and cooling systems in particular bring a sense of unease, especially to the chemical engineer asking the "what if" question, What if water leaked from a failing reflux condenser into say a Grignard reaction?

For the safety reason, new pilot plants are often equipped with inert cooling/heating fluids in reactor jackets and condensers. Aromatic compounds and mixtures thereof and silicones are widely used as heat exchange fluids. The range of operating temperatures desired generally dictates the choice of heat exchange fluid. Aromatic heat

exchange fluids are generally made up from biphenyl–terphenyl diphenyloxide combinations or from di- or polyalkylated benzenes. Two drawbacks of these fluids lie in their odor and their propensity to burn in a fire. On the other hand, the more expensive silicone fluids are somewhat safer and less odorous. The use of single fluids for temperature control also avoids the discontinuity inherent in two media systems (e.g., water and steam) where heat exchange is lost in switching from one medium to another.

In other situations, the heat of reaction in, say, a water quenching step may be simply accommodated by feeding a reaction mixture into a vessel containing crushed ice.

Agitation

The mixing of chemicals in a pilot plant vessel, especially when a reaction is heterogeneous, can be critical such that the design of the agitator in the pilot plant reactor is important—for example, to avoid local concentrations of a reactant or to quickly disperse reaction heat. The most commonly used agitators are of a propeller or anchor type, but the chemical engineer is well-versed in setting up continuous external reactant mixing and heat exchange devices or fabricating items such as a submerged perforated pipe to enhance the distribution of a reactant in as even a way as possible.

Extraction

Reaction quenching (e.g., with water) or solvent extraction of wanted or unwanted reaction products from an aqueous solution generally leads to the need for the separation of aqueous and organic solvent layers. The laboratory approach, manually shaking a conical separating funnel and separating layers, often repeating a solvent extraction several times for the best efficiency, is not an option in the plant. Separating aqueous and organic layers in a plant setting poses no difficulty, using the vessel's bottom sight glass, when the separation of layers is clean, but poses great difficulty when a "rag" or emulsion confuses layer separation. The development chemist works to overcome or minimize the problem using techniques to enhance layer separation such as the use of solvents with much higher or lower density than the water layer, or adding salts to promote separation by increasing the ionic character of the water layer, or by using nonpolar solvents. The chemical engineer can help by using devices to detect major differences in the conductivity of organic and aqueous layers.

If multiple solvent extraction operations are a necessity, the chemical engineer usually recommends a less labor-consuming process. A frequently used approach, which can generally be automated, is to build a simple low-cost solvent extraction column (Figure 2), wherein efficient mixing of organic solvent and aqueous layers in a countercurrent flow system elegantly serves the purpose.

Improvements on the simple device have been patented, such as the use of a gentle vertical agitation of the passing layers with perforated plates to improve contact of aqueous and organic phases, thereby increasing the theoretical plate capability of

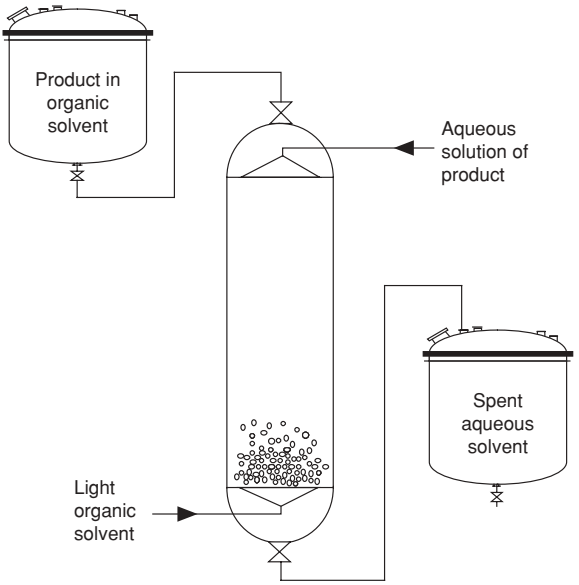


FIGURE 2. Simplified sketch of a liquid–liquid extraction column.

the column; the agitated device is known as a Karr column, after its inventor. Other, even more sophisticated extraction equipment has been invented to meet the needs of the fermentation industry. This is especially impressive in the penicillin fermentation industry wherein the relatively stable penicillin salts and mycelium in the broth are mixed with an organic solvent and acidified to give a very unstable penicillin acid in the water medium. The penicillin acid is then immediately extracted into the organic solvent in a mixer chamber and centrifugally separated to give a more stable organic solution of the free penicillin acid, which is quickly precipitated as a relatively stable salt, filtered, and dried (Figure 3). The whole mixing/acidifying/extracting/separating process is engineered to be carried out in a few seconds, thereby minimizing decomposition of the penicillin molecule. The major process equipment firms in the centrifugal mixer separator field are Westfalia and Alfa-Laval.

From a commercial point of view, there is an environmental downside to the commonly used solvent extraction of aqueous solutions, namely that the extracted aqueous layer needs to be processed (often by no more than stripping volatile solvents) before being sent on to standard wastewater treatment systems.

There are many ramifications to solvent extraction, especially from aqueous processing streams. Sometimes a polar, water-soluble molecule can be advantageously rendered lipophilic by carrying out a chemical reaction to nullify solubilizing factors; for example, zwitterionic amino acids can be converted to extractable acids by acylation of the NH_2 group, rendering the molecule suitable for conventional solvent extraction. One commercial example of this is the extraction of Cephalosporin C **(II)** from a filtered fermentation broth by first acylating the amino group with isobutyl chloroformate and extracting the resultant isobutyloxycarbonyl

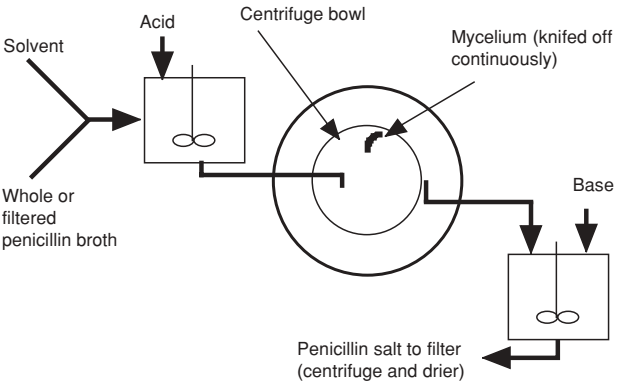
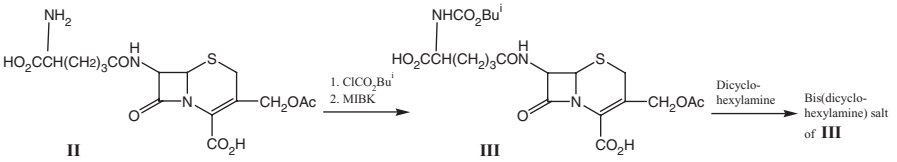


FIGURE 3. Simplified sketch of centrifugal separation system used for the extraction of penicillin from broth.



SCHEME 2. Process of the extraction of a Cephalosporin C derivative from fermentation broth.

derivative **(III)** with methyl isobutyl ketone.[4] A pure salt of **II** is produced by precipitation with dicyclohexylamine[5] (Scheme 2).

Another major application of extraction techniques lies in the use of resins to recover polar and nonpolar materials from both aqueous and nonaqueous process streams, commonly using solid ion exchange resin beads or, increasingly, macroreticular resins, often packed in columns. The writer is most familiar with the recovery of cephalosporin C itself from filtered broth using IRC-50/IRA-68 Resins. In addition to removing desired, and also undesired cephalosporins (Figure 4), by absorbing and concentrating them on the resin beads, the elution of the cephalosporins from the resin affords some opportunity for chromatographic separation, although in practice only lactone and desacetoxycephalosporin C can be significantly reduced by such elution.

In the case of cephalosporin C extraction, chemical engineers played the major role in designing the large plant needed to meet the projected tonnage off-takes. Plant design was based on the results of resin evaluation and selection, hydraulic studies on the resin bead size and column dimensions, Cephalosporin C loading capacities,

[4]Johnson, D. A., Richardson, E. J., Rombie, J. M., and Silvestri, H. H. U.S. Patent 3,573,296,1971 (to Bristol–Myers).

[5]Brooks, T. J. U.S. Patent 3,830,809, 1974 (to Bristol–Myers).

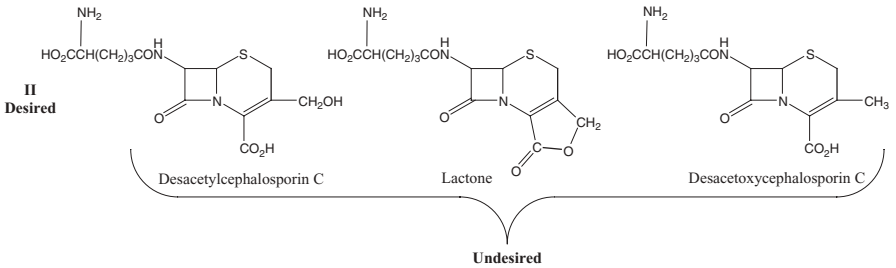


FIGURE 4. Desired and undesired Cephalosporins removed by absorption on ion exchange resins.

elution conditions, resin regeneration, and sizing of the columns and associated equipment, including the selection of equipment for the evaporation, crystallization, filtration, and drying steps needed to produce the isolated cephalosporin C potassium salt. Activities of this kind, in any scale-up or plant design project, are often regarded as the core activities of chemical engineers in the chemical process development field and would make an interesting case study. Such a study is beyond the introduction provided in this presentation.

Distillation/Evaporation

Although widely practiced both in the laboratory and in the plant, it is always necessary to consider the consequences of subjecting a reaction mixture being distilled to heat. There are safety concerns, product stability issues, environmental considerations, solvent recycling or disposal factors, time limitations, and cost constraints.

Safety and product stability issues associated with the distillation/evaporation process are discussed in Chapter 4.

Distillation is carried out for many reasons: concentration of a substrate in a solvent, removal of one solvent from a mixture and often its replacement by another, azeotropic removal of unwanted solvents (very frequently azeotropic drying), fractionation to separate a pure solvent for reuse, and removal of a low-boiling product of a reaction frequently to prevent its further reaction with the initial substrates or product (e.g., removal of water by passing a wet distillate through molecular sieves).

In distilling mixed solvents it is generally necessary to consult azeotrope data books[6] for mixture compositions. Chemists generally prefer to carry out reactions in relatively low-boiling low-cost solvents. Most of the common solvents are listed in Table 1, with a few notes on issues.

Vacuum distillation of solvents is frequently undertaken to reduce the temperature of the solution, thereby reducing the risk of decomposition. Vacuum distillation also speeds the removal of solvents. In a pilot plant, setting vacuum is usually generated through a great variety of sealed mechanical pumps, or, simply, using steam

[6]Horsley, L. H. *Azeotropic Data—III*, Advances in Chemistry Series 116, American Chemical Society, Washington, D.C., 1973.

TABLE 1. Common Reaction Solvents, Costs,[a] Boiling Points, Flash Points and Comment

Solvent	Cost ($/unit)[a]	B.Pt. (°C)	Flash Point (°C)	Density	Comment
Methylene chloride	1.65/kg	40	—	1.325	Suspected carcinogen-declining use
Acetone	1.10/kg	56	−17	0.79	
Methanol	0.37/kg	65	11	0.791	
Isopropanol	1.50/kg	83	12	0.785	
Tetrahydrofuran	4.03/kg	67	−17	0.887	
Ethyl acetate	1.54/kg	77	−2	0.90	
Isopropyl acetate	2.66/kg	89	4	0.87	Less water-soluble than ethyl acetate
Dimethyl carbonate	2.78/kg	90	18	1.069	Underutilized, but note m.p. = 4°C
Diethyl carbonate	2.95/kg	128	31	0.975	
Propylene carbonate	2.05/kg	239	123	1.205	
Tert-butyl methyl ether	2.39/kg	56	−25	0.742	Increased cost due to phase out in gasoline
Heptane	1.75/kg	99	−4	0.684	Concerns re static charges in working with plastic equipment
Toluene	0.61/liter	111	4	0.867	A perennial favorite
Chlorobenzene	1.54/kg	133	29	1.107	
Xylenes	0.60/liter	137–144	29	0.860	Boiling Points: o-145°C, m-139°C, p-138°C
Water	Virtually free	100	—	1.0	The preferred solvent
Acetonitrile	2.31/kg	81	5	0.786	
Methyl isobutyl ketone	2.75/kg	118	13	0.80	
Methyl ethyl ketone	2.15/kg	103	−6	0.805	
DMF	0.93/kg	153	57	0.946	All are water-soluble. Recovery from aqueous solutions is fairly expensive
DMA	2.04/liter	166	70	0.938	
DMSO	2.85/liter	189	95	1.102	

[a]Commercial costs for bulk quantities. Data from Dr. P. Savle, Schering–Plough, 1Q '07, and Chemical Market Reporter.

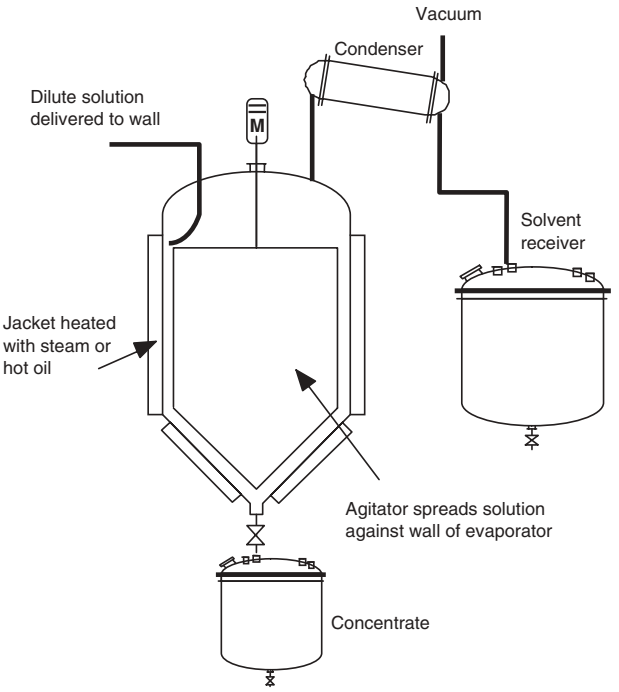


FIGURE 5. Thin-film evaporators.

ejectors. The use of vacuum distillation always raises environmental concerns: solvent contamination of the oil in a vacuum pump or of water in a steam ejector system. Generally, in small-scale pilot plant operations, contaminated oil, distilled waste solvent, and aqueous solvent wastes are sent to outside specialists for incineration: Non-halogen-containing solvent wastes are segregated from halogenated wastes, with the latter being incinerated in furnaces constructed to withstand hydrogen halide attack.

Another vacuum distillation technique, including for water removal in large-scale operations, is evaporation. Thin-film evaporators are designed to expose large surface areas of liquid to heat and/or vacuum in order to speed the evaporation process. The design principle is illustrated in Figure 5.

When a chemical process becomes a manufacturing proposition, chemical engineering data on solvent recovery may well be needed in order to make the capital investments necessary to achieve cost reduction and meet environmental requirements. Frequently, however, one arrives at the manufacturing stage with minimal solvent recovery data, necessitating the continued incineration of solvents using environmentally approved waste disposal protocols. In those cases where relatively small quantities of waste solvent are being generated, incineration often remains the most economic option. In other situations, efforts are made to reuse solvents stripped from processes; however, the main justification for cost saving and waste reduction

is negated if contaminants in the distilled solvent have an adverse effect on the yield or quality of the desired product.

In creating a manufacturing process for a given site, solvents are often changed to harmonize with the solvent recovery capabilities of that site. This process is not always straightforward when contaminants from various process streams compromise the analytical specification of the solvent required for a given NDA process. Under such circumstances, contaminated solvents often have to be qualified to meet FDA requirements, with the extent of qualification usually depending on whether the solvent is used for production of an early intermediate or for an API. In a manufacturing setting, where large volumes of waste solvent are generated, solvent recovery to meet the desired specification is often contracted out to third parties.

Distillation is one of those unit operations that assumes its importance based on the scale of operation. Clearly, distillation is one of the most important operations in a petroleum manufacturing plant where separations of closely boiling liquids require sophisticated distillation column design, built upon detailed theoretical plate determinations, material of construction issues, and secondary distillation requirements. In the pharmaceutical industry, the recovery and recycle of a solvent (versus incineration) depends on process scale. Further insight into the problems that might be faced in recovering solvents (and reagents) is provided in the section entitled "Dilevalol Hydrochloride: Development of a Commercial Process."

In conclusion, it is worth digressing to describe another widely used technology that can be used as an alternative to some distillations, namely the concentration of a chemical, particularly in aqueous solution, by reverse osmosis (RO). This technology depends on reversing the normal osmosis process, wherein water, on one side of a semipermeable membrane, will flow through the membrane to dilute an aqueous solution of such as a salt on the other side of the semipermeable membrane. Reversal, in commerce (e.g., obtaining potable water from brackish water), is achievable by applying pressure generally of many hundreds of psi to the salt solution, so that water will flow back through the membrane, concentrating the salt solution. RO is widely practiced in the chemical, pharmaceutical, and wastewater treatment industries. The technology of producing strong semipermeable membranes and their supports is a critical requirement, especially in cases where membrane materials may be compromised by the presence of organic solvents. In some endeavors (e.g., RO of sea water to produce potable water), energy costs are a major operating consideration.

Crystallization

Crystallization is one of the most important unit operations in the manufacture of APIs and to a lesser extent in the manufacture of intermediates for APIs (since later process steps often provide opportunities for purging impurities).

An API is closely controlled in terms of crystal form, polymorph identity, particle size, impurity profile and content, solvent, and water levels. All of these "quality parameters" are defined in creating a drug product that has the desired pharmacological properties (e.g., tablet dissolution rate to give needed blood levels) and desired physical properties (e.g., stability and compatibility with drug delivery systems).

Solid API intermediates are crystallized, and thereby purified, to meet specified quality standards. The specification may cover no more than appearance, identity, and purity parameters; these are often set by finding the right solvent that consistently provides the needed crystal qualities or, in some instances, an amorphous solid product. In contrast, the crystallization of APIs themselves is usually the subject of intensive research efforts in collaboration with the pharmaceutical scientists to provide a desired crystalline (rarely amorphous) API that will consistently allow production of a dosage form meeting the criteria needed for the marketplace. Every API has its own specific requirements, all of which need chemical engineering input to one degree or another. Sometimes the attention to detail can be very demanding. One case in the author's experience concerned a process for the crystallization of an API·hydrochloride (API·HCl) that required major reengineering after production had commenced.

Crystallization of an API·HCl. Chemical engineers in process research and development operations gain specialist expertise in a great variety of process problems such that they are often called upon to solve production problems. Areas of involvement include increasing the productivity of a plant to delay the need for further equipment investment, reducing manufacturing costs by reducing labor requirements and helping resolve regulatory issues.

When production problems persist for a long time, especially if an FDA inspection references the chronic aspects of a problem, a sense of urgency is created which encourages the involvement of chemical process R&D engineers. One such event occurred when the hydrochloride salt of an active pharmaceutical ingredient (API·HCl), being produced by a third party manufacturer, proved difficult to dry to the solvent level needed (<0.1% ethyl acetate) to avoid the development of an ethyl acetate odor in tablets of the API·HCl.

During the period of developing the process for the manufacture of the API·HCl, the ethyl acetate level was set at <0.2%. This level was filed in the New Drug Application (NDA). However, over the course of time, it became apparent that the tablets made from API·HCl containing <0.2% ethyl acetate developed an odor of ethyl acetate—an issue manifested in customer complaints (as an aside, the FDA generally targets customer complaints as one of its focus areas in initiating a production plant inspection).

As a result of these findings, the ethyl acetate specification was reduced to the <0.1% figure based on an investigation of ethyl acetate levels in the API·HCl versus odor development in the product tablets; in practice the API·HCl was dried to a target specification of <0.08% ethyl acetate to provide a comfort level. However, since the API·HCl tenaciously held onto ethyl acetate, the drying times to meet the new target varied from 100 hr to as much, on rare occasions, as 300 hr even under extreme drying conditions—110°C under vacuum! The FDA regarded the process as out of control.

Fortunately, in our particular case, the API·HCl proved sufficiently stable, even under the extreme temperature condition, to permit bulk drug production within the desired specification. Nevertheless, the extension of the drying time from ~24 hr,

to get down to an ethyl acetate level of <0.2%, to the 100–300 hr needed to reach the 0.08% figure proved to be quite unacceptable. A rough comparison of API·HCl particle size versus drying time to meet the <0.08% ethyl acetate specification revealed that the routine API·HCl production material contained ~80% of crystals > 200 μ. Micronizing the API·HCl to reduce the particle size greatly reduced the drying times, but this approach introduced another step, adding unwanted GMP qualification requirements and, even more important, creating safety and industrial hygiene concerns associated with dusts and worker exposure.

As a result of the above, we defined the objective as improving the process while staying within the process filed in the NDA. This essentially defined our objective as one of finding crystallization conditions that would give a smaller crystal of the same polymorph as that described in the NDA.

The NDA process for preparing the API·HCl comprised addition of 100 mol.% of 35% hydrochloric acid to a stirred solution of the acetate salt of the API in ethyl acetate (65%), water (35%), and methanol (5%) at a temperature of 24–28°C. This process produced crystals of variable size, with the said >80% being over 200 μ.

A solution to the problem was created as a result of the initiatives of two chemical engineers, Ray Werner and Lydia Peer. Their crystallization process studies led them to the following variant of the NDA process:

Addition of 50 mol.% of the 35% hydrochloric acid at 24–28°C to the stirred solution of the acetate salt of the API in the same composition of ethyl acetate, water, and methanol as in the NDA process gave a solution of the mixed salts. Interestingly, most of the heat evolution in formation of the API·HCl occurred during this first half addition. More important, the resulting solution could be cooled virtually to −10°C without crystallization of API·HCl. In short, the mixture of salts was far more soluble than API·HCl on its own. In practice the solution was cooled to −5°C to ensure that ice crystals did not crash out before the final addition of the remaining 50 mol.% of 35% hydrochloric acid. In the laboratory the final 50 mol.% of 35% hydrochloric acid was added over about 1 min, resulting in fine crystals of API·HCl which dried to <0.08% ethyl acetate in approximately 12 hr or less. In the first plant trial, addition of the hydrochloric acid was carried out over 45 min and still produced much smaller crystals of API·HCl than those produced by the third-party manufacturer, despite the addition time being far longer than the 1 min used in the laboratory. The plant trial was based on holding the temperature at −5°C rather than adding the 35% hydrochloric acid as rapidly as possible. Although the plant trial produced beautiful, perfectly formed fine crystals, they, disappointingly, dried to the <0.08% ethyl acetate level at the lower end of the time range (i.e., approximately 100 hr) of the API·HCl prepared by the third party manufacturer. Microscopic comparison of the two lots of crystals revealed that those formed over 45 min were uniformly dense, whereas those formed in 1 min were much more fractured. Further physical comparison showed that both lots of crystals were of the same polymorphic form and identical in most other ways, principally in melting point, stability, and overall particle size range. When the plant trial was repeated using a 1-min addition, the fine fractured crystals produced were identical to those formed in the laboratory. The filtration and washing of both types of crystals were similar and close to times observed with API·HCl prepared by the

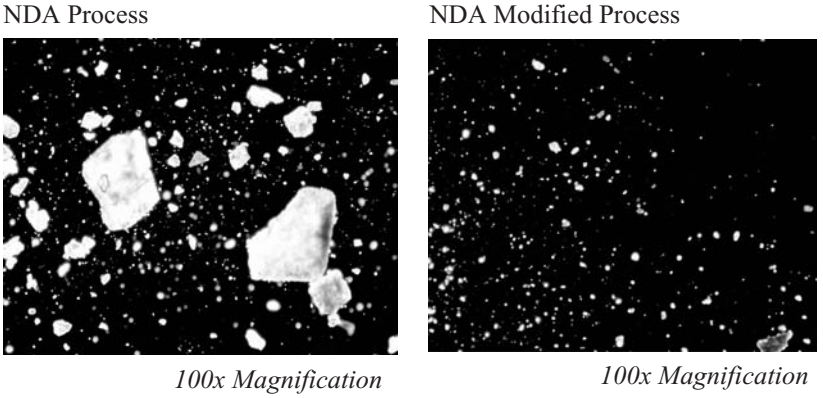


FIGURE 6. Comparison of photomicrographs of API·HCl prepared using the NDA process and the modified NDA process.

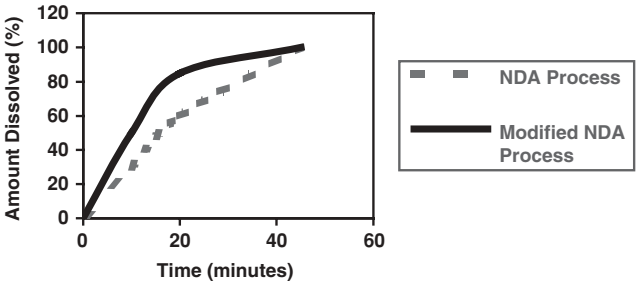


FIGURE 7. Comparison of rate of dissolution of API·HCl prepared by the NDA process and the modified NDA process.

third-party manufacturer. The photomicrographs in Figure 6 illustrate the enormous differences in the appearance of the crystals.

The range of drying times for various plant lots of fractured crystals, to meet the <0.08% ethyl acetate specification, was 8–24 hr. The heat generated in the process using a 1-min addition of the last half of the 35% hydrochloric acid did not prove problematic, being held in the range -5 to $+15^{\circ}$C under full jacket cooling using coolant at a temperature of approximately -20°C. The particle size range of the desired fractured crystals was generally 80% $<150\,\mu$. The process for preparing API·HCl by the modified NDA process was not without its detractors since one difference found versus the API·HCl prepared by the NDA process was in the relative rates of their dissolution (Figure 7).

Roughly 85% of the API·HCl prepared using the modified NDA process was dissolved in 20 min versus 45 min for the API·HCl from the NDA process. Although the drug is administered on a twice-a-day regimen, the concern was raised that there may be an earlier spike in the blood level of the API·HCl from the modified

NDA process. A medical review of the data led to the conclusion that in the 12-hr time frame between API·HCl administrations the 25-min difference in reaching the specified 85% dissolved material was of little consequence. It was also observed that by the use of a higher pressure in tablet production, a tablet dissolution rate conforming to tablets of marketed product could be created.

The modified NDA process was adopted.

Although the above case centers on the creation of a desired crystalline product that dries well, similar permutations of solvent, solvent mixtures, salt selection, and crystallization conditions (temperature, concentration, pH, seeding, stirring, rates of addition, etc.) are generally applicable in creating crystals that filter and wash well. The chemical engineer is a vital ally of the chemist in such work.

Filtration, Washing, and Drying

These unit operations are closely integrated in plant practice. The chemist's Buchi filter, with choice of the best filter paper, manipulation of the wet cake on the filter with a spatula (to improve washing), and smoothing to eliminate cracking of the cake, is a far cry from the situation faced by the chemical engineer dealing with large volumes of crystal slurry, or a hot solution of a product being carbon treated, say before crystallization. In the latter case, the carbon is removed in a closed filter system—for example, a Sparkler filter at a temperature above the crystallization temperature of the product. Not infrequently, when carbon peptization has occurred, it is necessary to add a filter aid to prevent clogging of the closed filter and to ensure that fine-particle carbon is held by the filter aid – many APIs are subjected to a filter test in concentrated solution, a gray filter paper usually signaling that a batch is carbon contaminated and must be reworked.

In engineering practice at the pilot plant stage, the chemical engineer employs a great variety of Buchi-type filters. Whereas open large Buchi filters are still used in pilot plant practice (with "elephant trunking" exhaust to remove fumes and with worker protection as needed, all the way up to "breathing air" suits), the equivalents favored by chemical engineers are closed filters of various types.

The simplest are closed filters of the Sparkler or Aurora type. The most versatile is the Rosenmund type, which can undertake increasingly sophisticated functions: These range from stirring the filter cake in a slurry mode, to building in a drying operation via hot nitrogen passed upwards through the filter plate, and on to offloading through side ports into containers, with the whole system being virtually closed to minimize bacterial contamination and worker exposure. Sketches indicating the design features of the major Buchi-type closed filters are provided in Figure 8.

Most of these filters, especially the closed ones, are relatively easily cleaned, usually by flooding the filter with an appropriate hot solvent.

Centrifugation is one of the most widely employed types of filtration, notable for operational speed (assuming the solid packs well on the filter cloth, or sintered metal bowl, and the porosity of the solid cake is maintained to allow thorough washing) and for producing a relatively dry cake—it is not uncommon for a centrifuged filter cake to be "dried out" to a solvent content of approximately 20%. Sometimes

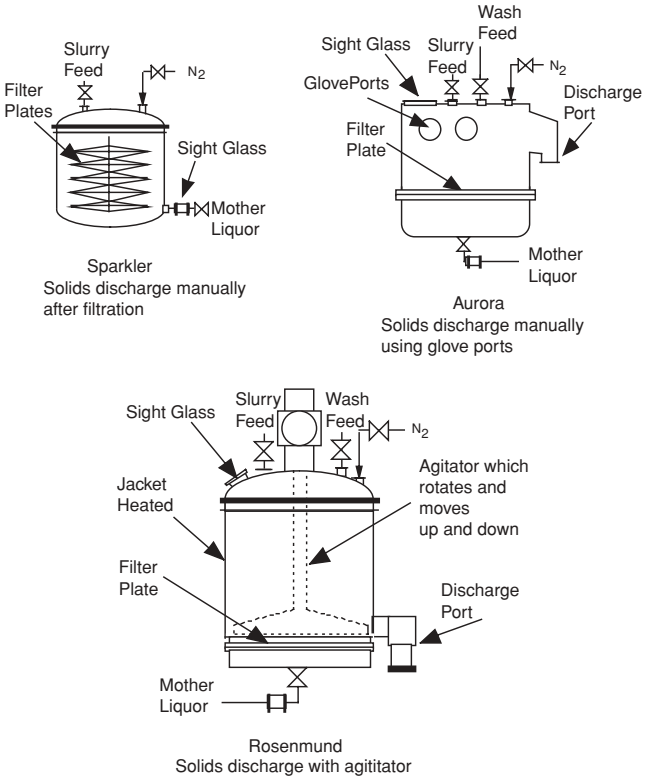


FIGURE 8. Buchi-type closed filters.

centrifugation causes dense packing of a solid product, making washing slow and inefficient; occasionally this can be overcome by loading the original crystal slurry on to the centrifuge at relatively low revolutions/minute, or if the solid is an unwanted product of a process (e.g., a fermentation broth mycelium) by mixing the slurry with a filter aid. In some cases, unwanted products that do not filter (e.g., muddy materials) can be removed by centrifugation in a solid bowl centrifuge, wherein the mud is retained in the centrifuge bowl and the needed liquid flows out over the edges.

One of the major considerations in operating a centrifuge for the filtration of crystal slurries in flammable organic solvents is to eliminate the possibility of explosion by using safeguards such as a nitrogen blanket to provide oxygen levels below the critical level. Oxygen sensors are usually installed that switch off the centrifuge if prescribed oxygen levels are exceeded.

The unloading of a centrifuge once the spin-dry cycle has been completed is best accomplished without exposing process operators to harmful fumes, while at the same time minimizing the biological contamination of the product. In this regard, bottom-offloading centrifuges minimize product handling by process operators, but do not

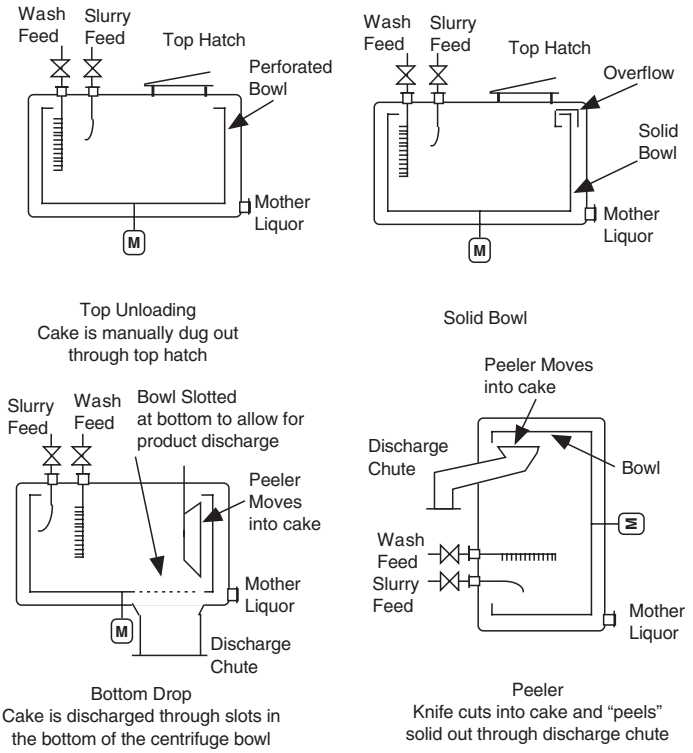


FIGURE 9. Types of conventional centrifuge.

overcome the handling needed in transferring the product to a conventional dryer. Sketches indicating the design features of conventional centrifuges are provided in Figure 9.

A valuable variant of the conventional centrifuge is the horizontal spindle centrifuge, especially the Heinkel type. This centrifuge has a unique offloading feature in that the filter cloth loaded with washed filter cake is pulled out to allow a reversed centrifugal removal of the solid as illustrated in Figure 10.

The most advantageous features of the Heinkel-type centrifuge are the ability to handle difficult-to-filter materials by building up and washing thin cakes and offloading them rapidly. Thus, the Heinkel-type centrifuge is generally more versatile and can be faster in operation than the conventional type. As is the case with conventional centrifuges, the windage release of solvent vapors requires that solvent capture systems (e.g., carbon beds or air scrubbing) be in place.

A few other kinds of filters are used in manufacturing plants (Figure 11), particularly for intermediates. One is the plate and frame filter press, which is relatively low in cost but labor-intensive. Another is the vacuum rotary filter wherein the filter cake rotates through a washing segment, as well as through a "pulling-dry" segment

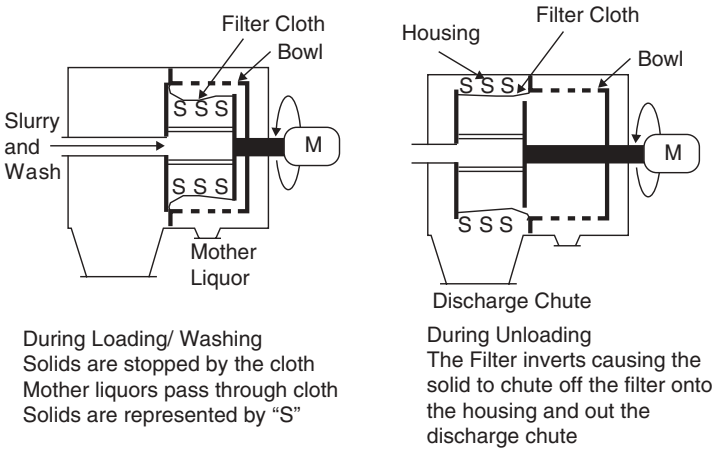


FIGURE 10. Operation of a Heinkel-type centrifuge.

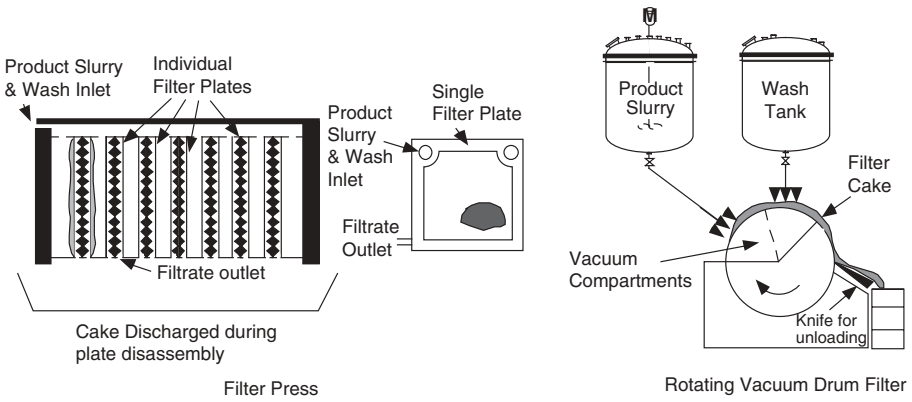


FIGURE 11. Other filters used in commerce.

prior to being knifed-off or blown-off. These two filters are somewhat tedious to operate and environmentally problematic, though enclosed versions of rotary filters are marketed.

A very large assortment of ovens and dryers is in use in chemical and pharmaceutical plants. Simple forced-air-heated tray dryers are increasingly required to have solvent capture attachments; old permits allowed specific levels of solvent in the emitted air and a finite emission rate and time for each individual drying operation. Such environmental strictures often persuade the chemical engineer to use a centrifuge for filtration in order to minimize the amount of solvent needing removal in the drying

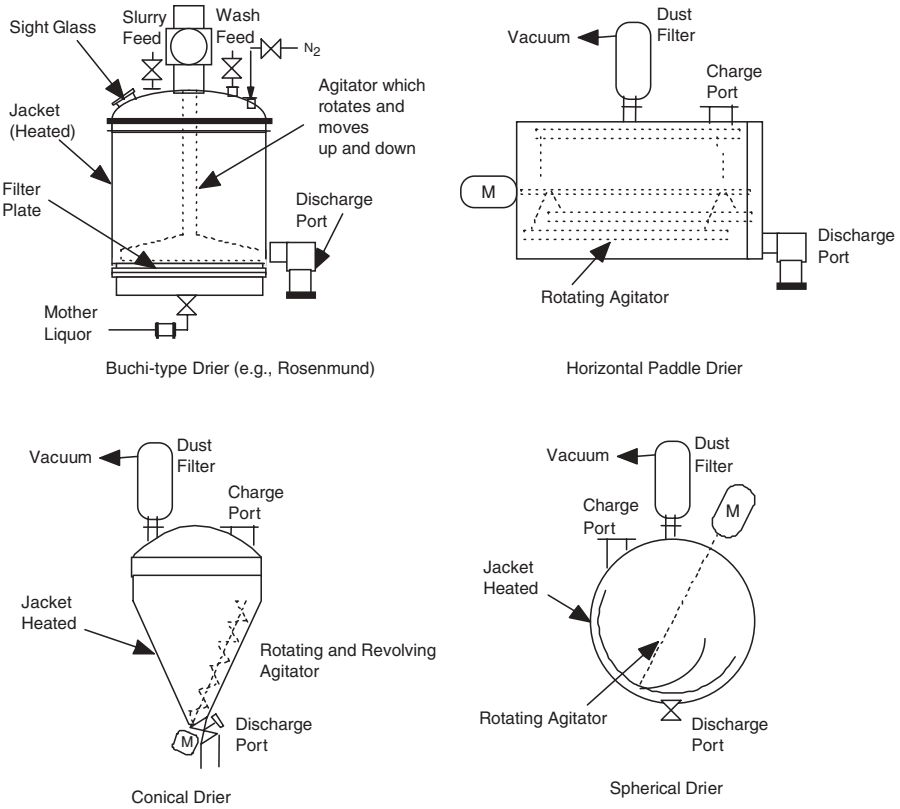


FIGURE 12. Popular vacuum dryers with a mechanical "paddle."

step. However, as mentioned, solvent capture from windage emissions is also needed here.

Vacuum drying is the most popular drying option, and dryers of many different types equipped with appropriate emissions capture devices have been designed to suit all manner of requirements. One of the most versatile is the vacuum tray drier, which can accommodate solids that dry at variable rates. Greater sophistication, not infrequently leading to a loss of versatility, has been introduced with the addition of paddles to mechanically move the solid during the drying period, accelerating the rate of drying. In many cases the paddles also function to break up lumps; however, the reverse can also occur, leading to balling and/or lining the dryer wall with a veneer of solid—obviously undesirable mechanical and insulating situations. Dryers with various types of mechanical stirring devices are available, notably in Buchi-type, horizontal, or conical paddle configurations, the latter with couplings allowing the screw flights to turn and sweep round the wall of the drier at the same time (Figure 12).

Spherical dryers have recently become more popular in the drying of APIs, one reason being that hold-up of API in the discharge process is less than that with other types of drier.

Fluid bed dryers (wherein hot air or a hot gas is driven upwards through a bed of wet crystals to fluidize the mass, with fine material being caught by filter socks) are particularly useful for drying water wet filter cakes. Spray dryers are also normally employed for the removal of water, though in this case the rapid drying process (from a spray of an aqueous solution falling in a countercurrent or co-current flow of hot air or gas) often leads to an amorphous material. Similarly, lyophilization of an aqueous solution under high vacuum at low temperatures (freeze drying) is often employed for the production of drug substances, again often in an amorphous form.

There are environmental (and sometimes safety) concerns with evaporative techniques of the above types whenever the solid to be dried, or the solution to be spray dried or lyophilized, contains volatile organic solvents. Of the above three drying techniques, spray drying is probably the most widely used, especially in recovering water-soluble drug substances from water solution (e.g., the aminoglycosides).

A variety of dryers is often available in model pilot plants since not every product will dry without causing problems of the balling or veneering type, or in the case of the conical dryer without clogging at the bottom outlet. Test drying in a variety of dryers is often needed to determine the optimum dryer and optimum drying conditions. Drying tests often lead to the reinvolvement of the chemist in efforts to change the crystallization to improve the handling properties of the crystal.

Frequently, filtration, washing, and drying operations are integrated especially where noxious substances are being handled or when a crystal slurry of an API is being processed to a dry solid in a controlled environment room (CER). In the latter case, all types of combinations of filters and dryers are used (Figure 13).

The operation of CERs is governed by validated SOPs covering topics such as cleaning and microbiological testing, ingress and egress protocols (for both people and materials), air quality and air pressure differentials and equipment calibration, and maintenance, inter alia. The entire operation is covered by a comprehensive documentation program.

Pilot plants generally produce APIs using controlled environment rooms of the above type. Manufacturing units also often operate using this basic type of controlled environment room. However, when specific large-scale operations are designed, it is often desirable to minimize operator involvement by integrating filtration, washing, drying, and product offloading steps into a single closed unit. In short, the enclosed plant is the clean room. This strategy of containment has many advantages, including:

1. Elimination/minimization of exposure of both product and operators to contamination
2. Enhancement of process safety
3. Minimization of solvent and product releases into the environment

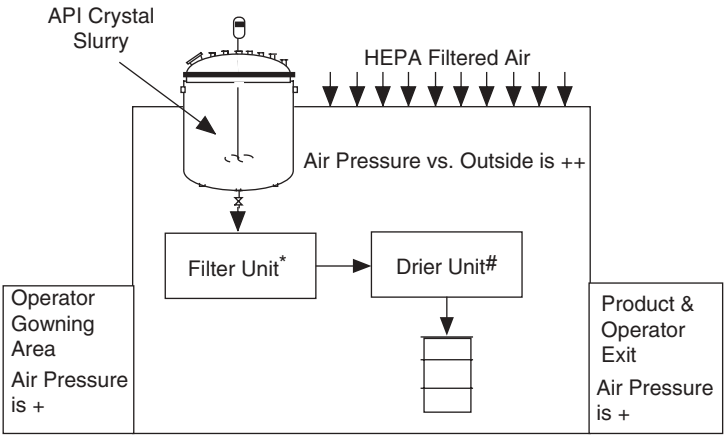


FIGURE 13. Illustration of major features of a controlled environment room. Controlled environmental rooms (CERs) are operated by gowned, specially trained operators working to standards/guidelines identified as appropriate for producing APIs meeting specific quality criteria including microbiological and particulate requirements for each specific drug form or use—parenteral, inhaler, oral, or topical (in practice the standards applied routinely may be the more exacting requirements).

4. Closed system recovery of solvents
5. Process automation
6. Enhanced GMP compliance

There are some downsides too:

1. Containment systems are often inflexible, thereby making them unattractive for multiproduct use.
2. When two or more products are produced in a contained system, the turnaround time from one product to another is generally very long, owing to the need to thoroughly clean the entire equipment train and to validate that it is clean.
3. Long, large-scale product cycles are usually needed to justify the investment.
4. Purpose-built containment units are generally best for single-product operations, though industry has overcome the "one-product" downside in many instances.

The use of a Kraus–Maffei type of containment unit is described in the case study entitled "Dilevalol Hydrochloride: Development of a Commercial Process" (q.v.). The

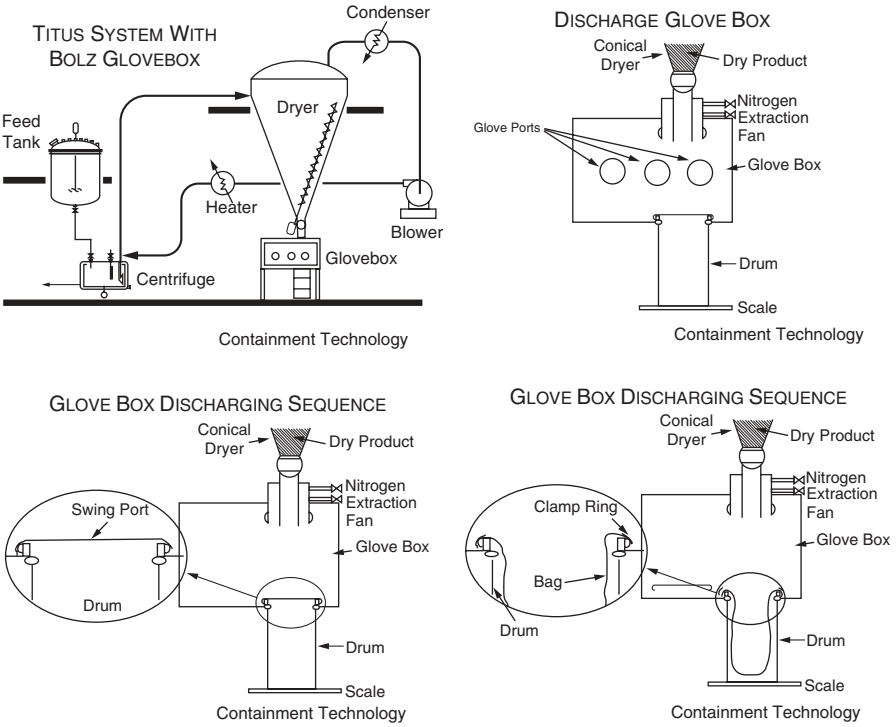


FIGURE 14. Sequence of steps in the contained off-loading of a drier.

operation of the Krauss–Maffei Titus System, diagrammatically outlined in Figure 3 of this case study (Chapter 10), is basically as follows:

> The process for producing the crystals of product to be filtered is carried out in a closed system in such a way as to virtually eliminate any microbiological or particulate contamination of the crystals. The crystal slurry is filtered and washed using the closed centrifuge. The filter cake is knifed off and picked up by circulating hot nitrogen gas and carried to the conical drier for the final drying operation. The hot nitrogen passes through the filter socks to a condenser where solvent is condensed for recovery and recycle. The nitrogen is then blown through the heater for repetition of the cycle. For complete containment of the product, wherein the plant equipment itself becomes the controlled environment room, the offloading of the drier is carried out through a glove box into a plastic container (bags stored inside the glove box) within a drum as depicted in Figure 14.

Other ingenious efforts have been made by chemical engineers to integrate crystallization with filtration, washing, and drying operations. One such unit built by Rosenmund AG in Switzerland is their "Nutrex" unit. This unit is designed to carry out a reaction—namely a crystallization—and, by inverting the unit on gimbals and

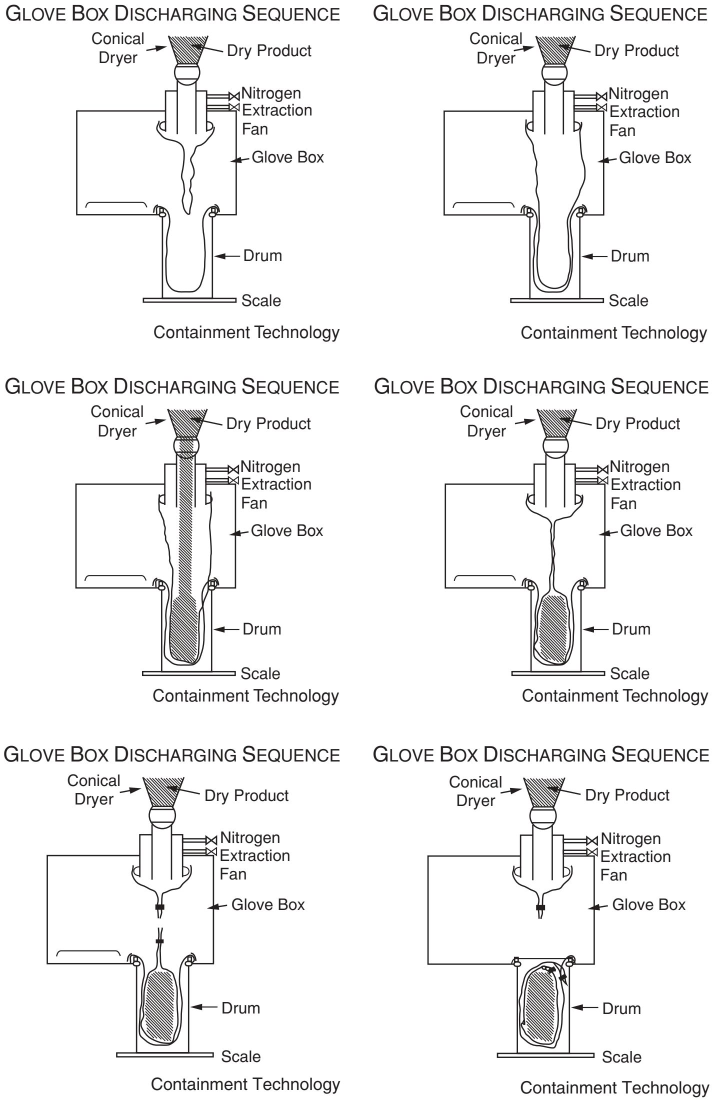


FIGURE 14. (*Continued*)

lowering the stirrer, to also undertake filtration, washing, drying, and offloading steps. A sketch illustrating the cycles is provided in Figure 15.

Although the Nutrex unit is a testimonial to the creativity of chemical engineers, it is obvious that inflexibility increases as more potentially problematic unit operations are integrated. In addition, the mechanical and operating requirements (e.g., piping) for large-scale production do not lend themselves well to the operating principles of the Nutrex unit.

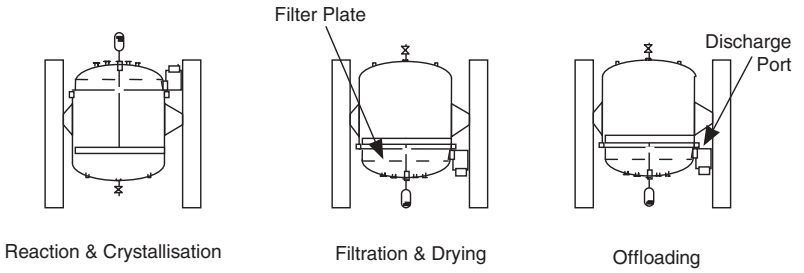


FIGURE 15. Operating cycles in the use of a Rosenmund "Nutrex" unit.

Producing a Product of Small Particle Size (Milling, Micronization, and Precipitation)

Reducing the particle size of a material for heterogeneous reactions or for preparing a drug product from a very insoluble API is an important area of endeavor.

Delumpers and hammer mills are frequently used to reduce the particle size of products, thereby creating a manageable physical form for ongoing processing, usually improving rates of dissolution or an even distribution of a product when blended in a mixture.

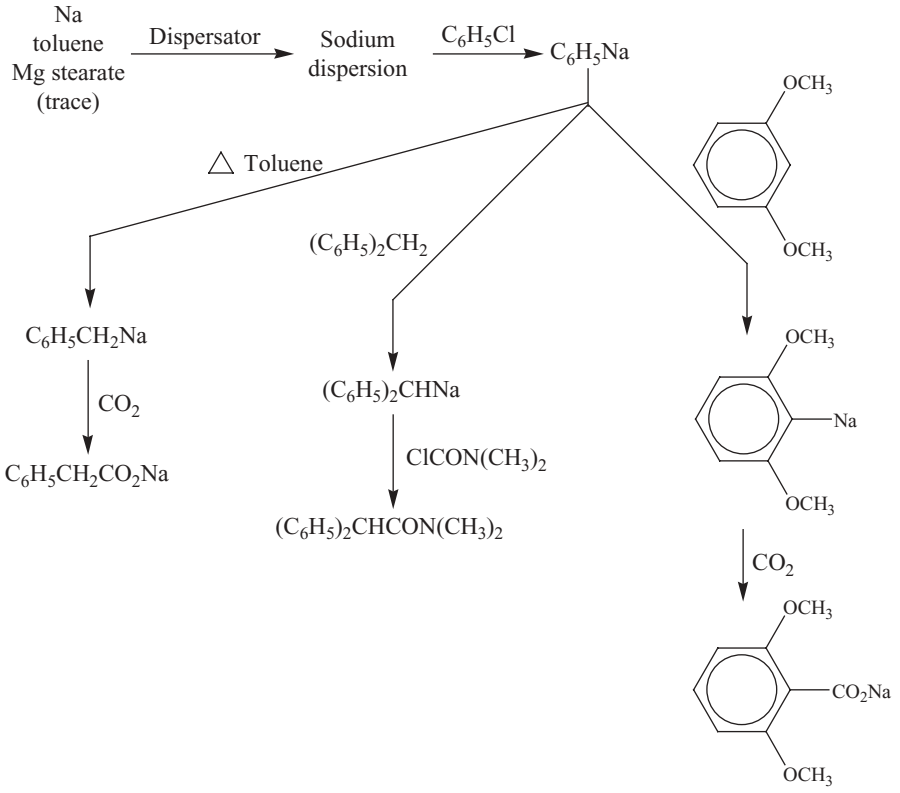
On occasion, it is necessary to produce a very fine particle size in order to effect a reaction—for example, reactions where a reagent is insoluble in the medium used for a reaction. In this case, a very small particle size (e.g., 5–10 μ) can enhance chemical reactivity by exposing a very large surface area of an insoluble chemical to an appropriate reactant. One example of this is the preparation of a so-called sodium dispersion, which has been used in a variety of commercial processes (Scheme 3).

Sodium dispersion is prepared by melting sodium in toluene at just over 100°C in a reactor equipped with a high-speed stirrer engineered to maximize shear of the liquid sodium. On cooling, stable particle sizes of 5–10 μ can be achieved. The stirrer design may be any of the types illustrated in Figure 16.

Micronization in the pharmaceutical industry is most often associated with producing an API, generally a water-insoluble compound, of very small particle size to enhance its absorption into the bloodstream. The design principles of the commonly used micronizers are illustrated by reference to Figure 17.

Chemical engineers are the principal managers of micronization studies, as well as of other technologies used in producing a fine particle size product. The following case study describes the work involved in producing an insoluble API in a fine particle form suitable for dosage form preparation. The case specifically illustrates the importance of observation and also looking beyond traditional micronization for methods to produce fine particle size products.

A Micronization Study. The particle size of an API is often a key parameter to control to ensure consistency in bioavailability of the API in the drug product. For this reason, micronization of APIs has become a standard operating procedure, at



SCHEME 3. Uses of sodium dispersion in commerce.

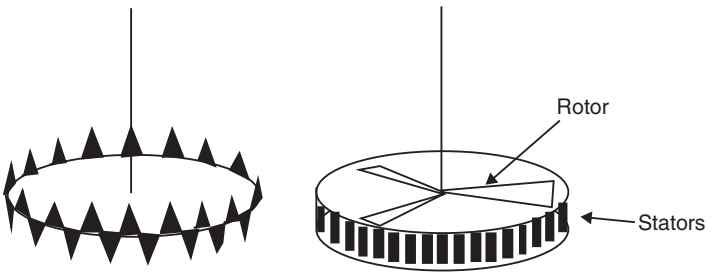


FIGURE 16. Stirrer designs for the production of sodium dispersion.

the research stage, in a number of pharmaceutical companies, especially for water-insoluble molecules. The particle size of an inhaled steroid, for example, is carefully controlled to meet the exacting consistency standards set by a company and approved by the Pulmonary Division of the FDA.

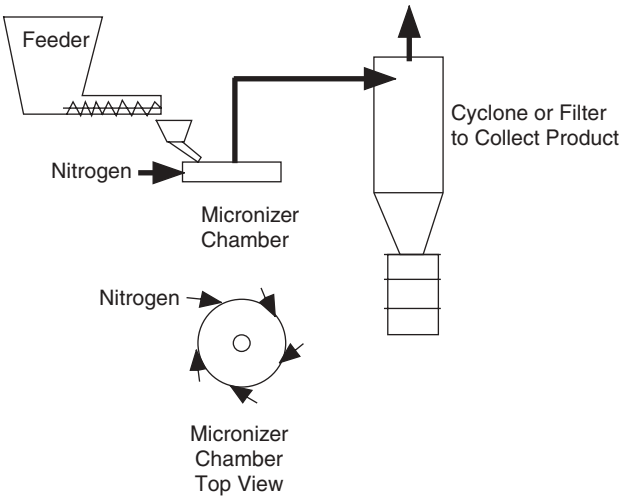


FIGURE 17. Design feature of commonly used micronizers.

Setting a particle size specification for an API is seldom straightforward. Many factors have to be considered, such as the flow properties needed for tableting, capsule filling, and filling inhalation devices, the tendency of the API to pick up a static charge, the achievement of desired rates of dissolution to meet blood level requirements in the body, the availability of equipment on the manufacturing sites, and even the stability of the API and any propensity to change polymorphic form during micronization. Although many APIs can be micronized without difficulty, it cannot be predicted that all of them will. For example, one needs to know whether a commercially viable API feed rate to a micronizer can be achieved, and whether the crystal of the API will clog the feed device or, after micronization, the micronizer itself.

In overcoming problems in the crystallization and micronization of a water-insoluble antifungal compound, we first tried to meet desired particle size specifications by conventional means such as adding a solution of the compound in an acceptable GRAS (Generally Regarded as Safe) water-soluble solvent into water under conditions that might lead to a fine particle size, in an acceptable crystal form and with acceptable filtration and drying characteristics. Unfortunately, this work did not initially lead to desired particle size requirements, although the product filtered well. Drying of the product in an INOX-GLATT dryer with wet milling capabilities led to caking. Drying in a regular vacuum tray dryer followed by delumping gave a uniform product suitable for use as the feed to a micronizer, but not fine enough for use in a dosage form.

Micronization of our antifungal using the favored Jet pulverizer micronizer (Figure 17) led to the desired particle size product; however, the micronizer Venturi feed mechanism rapidly (1–3 min) became clogged by a ceramic-like coating on the

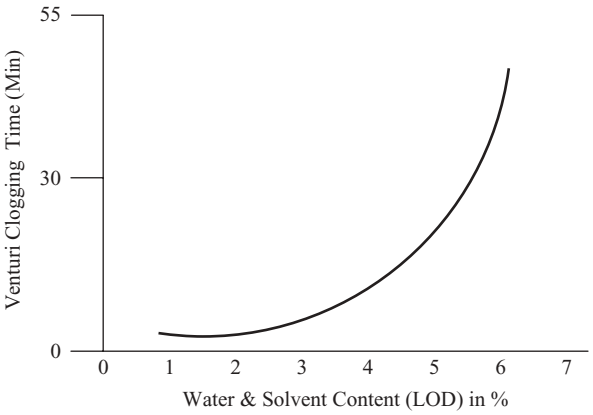


FIGURE 18. Relationship between Venturi clogging time and Water/Solvent content of an antifungal API.

wall of the Venturi nozzle, just beyond the Venturi outlet. This necessitated frequent dismantling of the micronizer for cleaning, severely hampering the drug delivery program and necessitating rework of the recovered material; this also created an analytical nightmare. A different feed device (obtained from a Hosokawa mill) gave no better results, nor did we find that efforts to embrittle the particles by pre-cooling them in a dry-ice box were any more successful. These failures led us to initiate an urgent program of work to find a way of producing product of an acceptable particle size. The chemical engineers in charge of the project (Noel Dinan and Steven Yu) examined the pilot plant data generated in every phase of the project. Noel Dinan observed that the caking occurring in the INOX-GLATT dryer did not happen until quite late in the drying cycle. He went on to show that the transition from a free-flowing crystal to the caking stage occurred when the water level in the solid dropped below approximately 5%. This key observation led to the proposal that product of water content >5–6% be used as micronizer feed. The engineers' suggestion was not accepted at first for various reasons. Some pointed out that since the crystal used as input for the micronization step came from a process in which a methanol solution was added to water, it seemed likely that methanol levels in the final micronized API would be unacceptable. Others raised questions on the crystal form of the product: Would it be a hydrate or be in a different, perhaps even metastable, crystal form? Analytical studies using differential scanning calorimetry and infrared showed that no new polymorph or hydrate form was produced. Noel Dinan undertook a study feeding material of various water contents into the micronizer (Figure 18). No clogging of the Venturi inlet occurred when the water of the API was >7%. Moreover the water and methanol levels were greatly reduced during the course of micronization owing to the sweep of dry nitrogen through the micronizer. The study results are summarized in Table 2.

TABLE 2. Micronization Studies[a] with "Wet" API Using a Four-Inch Jet Pulverizer

Water/MeOH Content (LOD[b]), %	Particle Size Distribution % <2 μ	% <7.5 μ	% <30 μ	LOD (%) Post Micronization	MeOH Content %	H_2O Content %
2.0	39.0	91.0	99.9	0.2	0.01	0.3
3.75	48.8	96.9	100.0	0.21	0.01	0.25
9.8	58.2	99.1	100.0	0.22	<0.01	0.77!
12.8	65.2	98.9	100.0	0.22	0.01	0.17

[a]Feed rate 50 g/min. Injector pressure 120 psi. Milling pressure 100 psi. Venturi 316 SS.
[b]LOD, loss on drying.

Use of a smaller micronizer (3/4 in.) gave anomalous results. As seen from Table 2, the water methanol and particle size targets set for the product were routinely met:

Target particle size: 98% ≤ 30 μ, 75% ≤ 7.5 μ, and 30% ≤ 2 μ
Target methanol content: 0.01%

Most important, the micronizer clogging problem was overcome. The success of the project owed everything to the simple observation that in the drying step a marked adverse change in the rheological properties of the API occurred when the water level dropped below approximately 5%. In further engineering work to try to simplify the process and to generate an optimal production process, Noel Dinan reinvestigated the original (failed) precipitation concept by producing an acceptable particle size range using a continuous crystallization scheme. A 10% solution of the API in methanol (1 part) was fed simultaneously and equivalently with a stream containing 25% methanol and 75% water (40 parts) into a mixing chamber and on into a stirred crystallizer containing 2.5% of the batch weight in seeds to produce a very uniform crystal: 100% <40 μ, 80% <7 μ.

The methanol level in the precipitation vessel (25%) was optimized in studies of process conditions for the precipitation: When methanol levels below 25% were used, gumming of the product was observed. The product of the above precipitation process filtered and washed well, did not agglomerate during drying, and, physically, appeared and behaved the same as micronized material. Such a continuous process was operationally attractive despite the dilution, since it shortened the time cycle (a large crystallizer was available) and avoided the labor intensive and dusty micronization process. However, the micronization process using "wet" API was adopted since it was deemed useable on all production sites.

In concluding this section on producing small particle size powders, I would like once again to pay tribute to the chemical engineers' ability to grasp the practical significance of observations made regarding the properties of materials. Earlier I passed over the idea of embrittling a solid as a technique for making it suitable for milling. It is pertinent to recount one case where embrittling is used commercially on

a tens of thousands of tonnes/annum scale. The Mayekama Manufacturing Company, Ltd., Tokyo, Japan, uses embrittling via a secondary cooling system to cool used tires to the point where they can be milled easily to a powder for recycle. A two-stage refrigeration system using ammonia on the high side and ethane on the low side chills a hydrofluoroether, $C_4F_9OCH_3$, which in turn cools air to $-87^{\circ}C$. This cold air is passed over incoming tires, cooling them to the point that they shatter easily. Selection of $C_4F_9OCH_3$ was made because of its low-temperature properties and because it is nonflammable, non-ozone-depleting, and low in toxicity. This cooling system was found to be cheaper and actually friendlier to the environment than liquid nitrogen systems used earlier.

OTHER UNIT OPERATIONS

It is worth describing other operations where differences between the chemist's laboratory and the chemical engineer's pilot plant and plant create the need for different approaches. Pumping, flow measurement, and reactor volume measurement are a few of the more common operations deserving the chemist's attention.

Pumping

The chemist's manual pouring techniques are necessarily replaced in large-scale operation by more practical techniques. The preferred method of moving liquids (solutions) during operation of a chemical process is by gravity through a multistorey train of reactors. However, very frequently the lifting of liquids to elevated levels to permit gravity movement is done using pumps. Pumps are of many types and are designed to handle all types of flammable, noxious, viscous, and corrosive liquids, as well as heavy slurries and gases. Delivery of the latter is more often handled by weight from a cylinder of the compressed gas.

The major kinds of pumps used in the chemical and pharmaceutical industries are centrifugal, positive displacement, and turbine pumps.

In a centrifugal pump, rotating flared blades in the pump housing essentially suck in a liquid from a delivery pipe at the eye of the driveshaft, ejecting it outwards from the blades into the shell of the housing carrying the outlet pipe. Centrifugal pumps are probably the most widely used pump types and are available for capacity needs as small as 2–3 gals/min and as large as 100,000 gals/min!

A positive displacement pump is equipped with both valve inlet and outlet pieces: The inlet opens with the suction of liquid in the priming stroke of the piston, and it closes as the outlet valve opens in the discharge stroke. The drive for movement of the liquid may be a piston, a plunger, or a diaphragm, the latter being a flexible material fabricated of rubber, plastic, or metal. Rotary pumps can be considered as positive displacement pumps. Such pumps depend upon the mechanical displacement of liquid by rotation of an "impeller" within a stationary housing. In a gear pump the impeller is a pair of rotating meshed gears that impound liquid from the inlet pipe in the outer tooth gaps and carry it a round the periphery of the housing to the outlet pipe.

Although the capacity of positive displacement pumps is not as great as centrifugal pumps, they are more efficient because internal losses are minimized. Far greater pressures can be exerted on a liquid with a positive displacement pump, leading to such pumps being widely used for pumping to high heads. Diaphragm pumps have great appeal for handling hazardous and toxic liquids since their construction eliminates exposure of seals and packing to hazardous and noxious liquids. Diaphragm pumps are also popular for pumping slurries, especially where gentle handling of suspended solids is required to minimize crystal degradation. The major downside to the use of a diaphragm pump is the inevitability of failure of the membrane; such pumps therefore require that a rigorous inspection and maintenance program is in place. Peristaltic pumps, despite their weak point of potential failure of the flexible hose, have found some favor where nonaggressive liquids, or slurries in such liquids, are being pumped. Pumping rates of 350 gals/min at over 2000 psi have been routinely achieved in a 24-hr-a-day operation. Again a rigorous inspection/maintenance policy needs to be in place to ensure that flexible hoses are changed before they fail.

Turbine pumps mix features of a simple propeller (axial flow) pump with a centrifugal pump and are often referred to as units with mixed flow. A simple turbine pump carries curved vanes on a central rotating spindle. Such pumps are often immersed in the liquid and find use in closed-loop circulation systems, in condenser circulating water, and in sumps and wells. Turbine pumps have noteworthy pumping capacity, and like positive displacements pumps are often used for heads up to about 100 ft/stage with capacities of up to several hundred gallons/minute.

Flow Measurement

The chemist's "eyeballing" a graduated dropping funnel to deliver reactants at desired feed rates into a glass reactor, or setting up precise delivery using a validated peristaltic pump, is generally replaced by quite different flow measurement systems in the pilot plant and plant worlds.

Pumps, such as piston pumps, can meter liquids into a reactor fairly precisely, but the chemical engineer uses a flow measurement device for greater precision. The most commonly used flowmeters are rotameters that are calibrated to translate the lifting of a float in a vertical slightly tapered tube (small diameter at the inlet of the flowmeter) into a measure of the amount of liquid delivered in a given timeframe. For greatest precision the rotameter is calibrated with the specific fluid being metered. Most modern rotameters are provided with a calibration plot that corresponds to performance.

There are many other flow measurement devices including Orifice/Venturi meters, turbine meters, and more sophisticated instruments using ultrasonic, magnetic, and Coriolis effect techniques. Orifice/Venturi type meters have a restriction causing a pressure drop related to the flow rate of liquid. Such meters are popular because of their low cost; however, their accuracy can be compromised by upstream elbows and valves. Turbine meters are designed so that rotation speed varies linearly with the

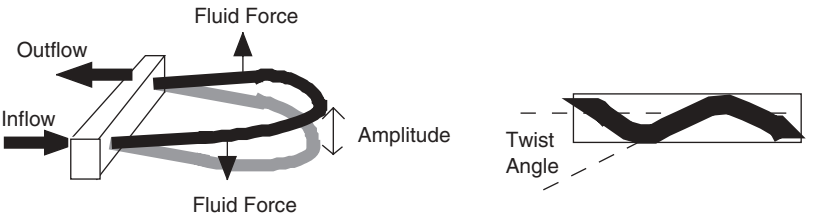


FIGURE 19. Mass flowmeters.

flow rate. Magnetic pick-up of turbine blade rotation is translated into voltage pulses, which in turn are converted into a measure of flow rate. Again, such meters operate best in situations where flow is not restricted.

Ultrasonic flowmeters depend upon measuring time delays in received sound waves from a pair of opposing transducers, one set downstream from the other in a pipe carrying liquid. The transducers measure the difference between the velocity at which sound travels with the flow of liquid and against the flow of liquid, the signals being translated into a measure of liquid flow. Another ultrasound flowmeter for liquids containing bubbles or particulates utilizes the Doppler effect—that is, the change in frequency of a returned sound wave bounced from a particle or bubble moving away. Ultrasonic flowmeters, like magnetic flowmeters and Coriolis mass flowmeters, have no moving parts and can be used for measuring flow within a broad range of viscosities and temperatures. Magnetic flowmeters sense the voltage induced when a conductive fluid flows through a magnetic field. The induced voltage, proportional to the flow velocity, is fed to a measuring amplifier by a pair of electrodes. Coriolis mass flowmeters (Figure 19) depend on creating and measuring Coriolis acceleration in a flow loop.[7] This is done by passing flowing liquid through a flow loop that is being vibrated, usually with an amplitude of approximately 2 mm at a frequency of approximately 80 cycles per second.

The inflowing liquid exerts a small opposite directional force on the upward and downward vibrations of the tube. Going in at an upward vibration, the liquid assumes the force of the up motion halfway around the loop. This upward flow force exerts the opposite effect on the down cycle of the vibration the net effect, causing the tube to twist. Electromagnetic velocity detectors located on each side of the flow tube measure the velocity of the tube. The twist results in a time difference between the tube velocity signals; this time difference is directly proportional to mass flow. From once being regarded as esoteric and expensive, Coriolis flowmeters are now in the mainstream, largely because of their accuracy of mass flow measurement and the

[7]The discovery of the Coriolis effect resulted from work done by Gaspar Gustav de Coriolis (1792–1843) at the behest of Napoleon, who wanted to know why his cannon balls never went straight. There is no historical record to indicate that Coriolis cast any light on Napoleon's problem but, as often happens in research, unexpected findings can stimulate curiosity and lead to other useful outcomes—as Pasteur once said, "Chance only visits the prepared mind."

availability of lower priced meters which deliver almost the same performance level as higher priced units.

In modern plants it is important to add that reliance on pumping liquids through flow measurement devices to deliver precise weights or volumes is often replaced by load cells that weigh the process vessel and its contents and accurately record weights of incoming reactants and solvents.

In a point of validation it is worth saying that all weight or volume measurement devices need to be well maintained, calibrated, proven, and regularly audited to ensure that the device is delivering what the operations people running a process batch sheet say it is delivering.

Reactor Volume Measurement

The chemist operating a laboratory experiment in glassware relies on the use of balances for weighing reagents and graduated cylinders or dropping funnels for measuring volumes. Although graduated glass vessels are used to control the addition of liquid reagents and solutions to a reactor, the chemical engineer, operating a pilot plant reactor in which volumes cannot be checked by eye, works to ensure that a pilot plant standard operating procedure (SOP) is being carried out as well as possible by double-checking reaction volumes.

In past times the dipstick, often made of wood, was widely used to make a volume measurement check even in a calibrated vessel. In reference, perhaps reverence, to the wooden dipstick it is pertinent to mention that the Ford Motor Company, in celebrating its centennial in 2003, built six all-new Model T's, each being equipped (as was the original) with a ruler for checking the fuel level in the tank! (*New York Times*, May 18, 2001, page F1). Today, opening a reactor for liquid level checks, or for sampling the contents, is considered to be undesirable. (In regard to sampling, contained devices can be fitted to draw reaction samples for the chemist's process monitoring work.) In measuring reaction volumes, reactor calibration is often used. There are also a great number of both simple and sophisticated level measurement devices.

A simple device is based on the pressure required to slowly bubble a gas (nitrogen or air) through a dip tube to the bottom of a vented reactor the pressure differential being translated into a level measurement. At the other extreme, the application of ultrasonic and radar technologies has led to much more sophisticated devices.

Ultrasonic level measurement depends on a transducer sending an ultrasonic pulse to the liquid surface which is reflected back to the transducer. Electronics convert the ultrasonic lag time into a distance (D) corresponding to depth. Ultrasonic level measurement is based on the equation

$$D = V \times t/2$$

where D is a function of the round-trip time (t) required for an electronic pulse to travel at the speed of sound (V) from the face of the transducer to the reflecting surface.

Although ultrasonic level indicators require little maintenance and are unaffected by the nature of the liquid (acidity/basicity, dielectric constant, or specific gravity), they cannot be used in circumstances of excessive foaming or turbulence or in high-temperature situations where stratified vapor layers may be present.

On the other hand, radar detectors can be used in vessels exhibiting a wide variety of conditions: Radar energy passes through air or vapor space with imperceptible changes. The greatest limitation to the use of radar detectors is price, because of the complexity of the microwave and timing circuitry. In an advanced measurement unit, the radar level gauge sends out a continually swept microwave signal with varying frequency. The transmitted signal is compared with the signal sent back in a microwave mixer device, the difference in frequency being directly proportional to the distance. It will be obvious that high-quality signal processing is necessary since the liquid surface in a working reactor is never calm and unwanted echoes within the reactor need to be separated out.

GENERAL OPERATIONS

The chemical engineer is the best process technology team member to oversee the general operation of a plant. In addition to managing the chemistry and engineering, this oversight also covers GMP, Safety & Environmental requirements to meet regulatory needs (dealt with separately), and such physical responsibilities as are involved in waste management, plant maintenance, process automation, process containment, plant equipment evaluation (e.g., for capital projects), technology transfer, and all aspects of the management of the human resources. In all of these activities, the chemical engineer collaborates with the needed specialists and experts and is often responsible for the documentation required in validating such operations. A brief outline of waste management, computer applications, and pilot plant/plant maintenance is appropriate here.

Waste Management

As stated earlier, in the process development phase of a project, wastes are generally sent out for disposal by licensed practitioners in the field. Nevertheless, the chemical engineer is required to meet the constraints required by the operating permits for the pilot plant or plant. Thus, it is necessary to ensure that incoming process materials and outgoing products are managed (see earlier) and that in plant operations, all emissions are properly controlled (often by condensation or by validated entrapment, absorption or scrubbing systems) and that wastewater going to the general plant sewer meets the standards set for disposal to a public water treatment facility. For larger operations this may require dialogue with the public treatment facility. In these endeavors some in-house treatment (e.g., pH adjustment, solvent stripping, and filtration) is usually required to meet biological oxygen demand (BOD), carbon oxygen demand (COD), and particulates content standards set for disposal to the public treatment facility. Waste treatment and management work often provides information of immense value

should the process be subsequently taken on to a manufacturing scale. Waste disposal issues are not infrequently a factor in process selection, or in generating a program of work to assist the manufacturing site taking on a process in preparing its own waste treatment operation; this may be no more than the manufacturing plant determining whether the wastewater can be accommodated by the organisms in its own waste treatment facility. It can become much more if waste solvent recovery and recycle become major capital and GMP considerations. In such situations, outside specialists are often engaged to help deal with waste issues—as an aside I remember that in the late 1960s a lorry drove around Ulverston, England, where Glaxo has a large manufacturing facility, which proudly displayed the slogan "We specialize in talking rubbish!"

Computer Applications

The application of computers in the chemical process development industry is a field in itself, beyond the scope of this presentation. However, the following limited overview provides some idea of the chemical engineer's contribution in this area of endeavor.

The chemical engineer is generally the person most involved in the application of computers to process engineering problems, as well as in the application of computers in such areas as process control, process modeling, robotics, cost calculations, and so on. At the pilot plant level of process monitoring and control, the usual practice is to build automation systems into process operations at late stages in the development of a process, when the chemistry is better understood, and provide only limited process control in the early stages of development. The sophisticated modeling of processes is particularly valuable when a process is selected for development to a large-scale production operation.

In the early stages of process operation at the pilot plant level, the parameters that lend themselves well to automation are pH adjustment, pressure control, and temperature control, the latter by automating rates of heating and cooling and rates of addition of reagents. Simple process monitoring by automating sampling and metering to an analytical instrument for feedback to process operators, or for utilizing the information obtained to initiate subsequent process control steps, is also often employed at the pilot plant level. The application of computers in the pilot plant phase of developing a process provides an invaluable opportunity for data collection and analysis, speeding the identification of optimal process conditions.

The automation of laboratory operations to enhance the process development chemist's armory has also grown as an activity. Equipment is available (e.g., Buchi Syncore[8]) to aid in the evaluation and optimization of such as time-temperature cycles in a given reaction, or in combinatorial and parallel synthesis endeavors.

Computer applications also spread to the preparation of batch sheets and other written requirements for Regulatory purposes as well as to training courses for

[8]Buchi Labortechnik AG, CH-9230 Flawil, Switzerland.

operations people wherein instructional programs can aid in the education and testing of workers, such as in Safety, Environmental, and GMP areas.

Pilot Plant and Plant Maintenance

Maintenance is a vital component of all pilot plant and plant manufacturing operations. Any organization that strives to meet deadlines for the preparation of clinical supplies and commercial APIs requires a plant that ideally does not break down. To achieve this, all responsible managements require a strong, well-staffed maintenance department that has the trained manpower, budget, spare parts, mission, and organization to keep the plant operating.

Maintenance is not merely called upon to repair failed equipment (breakdown maintenance). Over the course of time, maintenance workers have teamed with plant operations personnel to develop preventive maintenance (PM), predictive maintenance (PdM), and condition-based maintenance (CBM) programs, all in an effort to get ahead of problems occurring in plant operations, and to do so as efficiently as possible.

Preventive maintenance is probably the most common type of maintenance practiced in chemical manufacturing plants. This usually means carrying out work to ensure that a piece of equipment will operate continuously and efficiently. PM tasks include regularly performed lubrication, parts replacement, and so on. PM is generally carried out routinely at set intervals, usually at a scheduled shutdown. PM has the downside of requiring work that may not be necessary and replacing parts that may still have useful life.

Predictive maintenance (PdM) tries to avoid some of the wasted effort called for in a PM program. Equipment monitoring programs are set up to provide data on a given piece of equipment, with maintenance decisions being based on the data collected.

Condition-based maintenance (CBM) operates more like PdM with an overview philosophy, enabling plant operators and maintenance departments to do the right work at the right time. CBM enables those trends leading to problems to be identified and proactive steps taken to head off breakdowns. An operating history, especially of the critical pieces of equipment and their integration in a processing system, is assembled. This log provides the baseline for plant "health" checks carried out by operations and shop floor maintenance people on a continuous basis; the plant essentially signals when it is getting sick. The charting of sensor outputs from a given piece of equipment can enable operating and maintenance personnel to spot, early on, changes occurring, such as vibration problems, equipment overheating, and deterioration in the analysis of lubricating oil. These changes trigger actions to avoid occurrence of a problem. The documented record of repairs, calibrations, validations, and so on [frequently held in a computerized maintenance management system (CMMS)], is additionally important in providing information to show that the chemical process is being run according to the requirements of the Standard Operating Procedure (SOP); the equipment log is an important component of the documentation needed to establish GMP (Good Manufacturing Practice) requirements for the FDA.

The importance of the chemical engineer's input in a chemical process development program cannot be overemphasized. The chemical engineer is, in every way, a team member and contributor whose input should be sought by every process development chemist. As Samuel Johnson said ". . . without mechanical performance, refined speculation is but an empty dream . . . ."

9

EXCURSIONS IN THE β-LACTAM AND STEROID FIELDS

"Nothing is Forever."

——Allen Read

INTRODUCTION

Some of the most satisfying experiences in chemical process development come from those times when one ventures into a chemical manufacturing process investigation program in a major field. In major fields such as β-lactam or steroid chemistry, the subjects of this chapter, one quickly becomes absorbed by the contributions the founders made to science, medicine, and the understanding of disease. Many of the chemical and biological schemes they devised for the manufacture of their APIs arose from the science of the times. Nevertheless, it is instructive to read the historical beginnings, if for no other reason than to follow the evolution of chemical and microbiological thinking over the decades. More than sharing in the thought processes of the times, chemical process development chemists can contribute from a modern chemistry perspective, even if in only a small way, to the further advancement of the field, especially by creating new, lower-cost, safer or environmentally advantageous molecular transformations. These can be magical experiences, properly tempered by the humbling thought that one is frequently climbing on the shoulders of giants to add to the vast knowledge base which is the historical foundation of the field.

The Management of Chemical Process Development in the Pharmaceutical Industry by Derek Walker
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I have been fortunate over a 43-year career in chemical process development in the pharmaceutical industry to have listened to the thoughts of a few of the greats and to work with many like-minded collaborators, both in R&D and Manufacturing, in proposing and advancing synthesis schemes and achieving practical progress. Useful steps forward bring considerable satisfaction, even if they are not as momentous as the enlightenment which came to those who discovered biological activity or, painstakingly over many years, unraveled the chemical structure of an active compound using degradative methods.

In this spirit, it is pertinent to recount some of the work done under Arapahoe Chemicals/Syntex, Glaxo, Bristol–Myers, and Schering–Plough auspices, much of which illustrates the influence of competition, patent portfolios, business, new discoveries, safety, the environment, and marketing, some of which shows that compelling opportunities can resurrect chemical transformations previously cast off as unworkable or commercially uninteresting.

PART I: PENICILLINS AND CEPHALOSPORINS

The Fermentation of Penicillin G and Cephalosporin C (Glaxo)

In commencing work in the penicillin/cephalosporin field, one is easily enchanted by the excitement attending the original discovery of penicillin by Alexander Fleming and its later applications during World War II. In regard to the latter, one can marvel at the vision of Florey and others who realized the contribution penicillin would make in overcoming infection and, at the basic chemistry level, appreciated the competitive aspects of chemistry in the grudging acceptance by Sir Robert Robinson that Robert Woodward's proposed β-lactam structure for penicillin was indeed correct.

In a much smaller historic way, and from my vantage point of working in Glaxo's Ulverston Penicillin/Cephalosporin factory under the guidance and steadying leadership of Dr. Arthur Best, and with wonderfully committed co-workers, it is worth recounting some of the scientific, manufacturing, and "chemosocial" issues of the times from the mid-1960s.

The intellectual property (the patent portfolio) covering the cephalosporin field was held by the National Research and Development Council (NRDC) in the United Kingdom, largely because early recognition of the value of cephalosporins had resulted from the pioneering work at Oxford University on strains of a microorganism first harvested by Professor Brotzu from a sewage outfall in Sardinia.

The biosynthesis of penicillins and especially cephalosporin C was a hot academic and industrial field during my time in Glaxo (1966–1975). The work of Arnstein and co-workers[1] had more or less established a broad outline of the transformations occurring in the biosynthesis of penicillins, via the oxidative cyclization of the tripeptide, L-α-aminoadipoyl-L-cysteinyl-D-valine (ACV-tripeptide). I had the privilege of sitting in with the fermentation people in the Ulverston factory (notably, Drs. Don Hockenhull, Bob Fildes, and Steve Goulden) during discussions with

[1] Arnstein, H. R.V., Morris, D. *Biochem*. J. 1960, **76**, 357.

Professor Edward Abraham, Oxford University, on his many ideas to determine the precise pathway for the biosynthesis of cephalosporin C and on his several unmet requests that Glaxo provide him with its high-yielding cephalosporin C producing strain for his work on the biosynthesis. Professor Abraham's gentlemanly requests contrasted sharply with the anecdotal stories of earlier rapacious times when opportunistic entrepreneurs tried to obtain fermentation strains by laying agar plates outside Glaxo's Barnard Castle Fermentation Plant in the hope of collecting biological fallout from factory air exhaust systems.[2,3] None of us in Ulverston contributed to the unraveling of the biosynthesis of Cephalosporin C, but work continued in Professor Abraham's laboratories. A few decades later, Professor Jack Baldwin crowned the Oxford work in brilliantly defining the entire Cephalosporin C biosynthesis sequence.[4]

As with most manufacturing operations, the main focus of the technical support work in the Ulverston factory was to:

1. Reduce the cost of fermentation products, primarily penicillin G and Cephalosporin C, by improving process performance—for example, increase the fermentation titer and extraction efficiency at the same time meeting or improving product quality; process improvement frequently involved much troubleshooting work to resolve production problems.
2. Reduce the cost of chemical intermediates by improving existing chemistry. Troubleshooting frequently provided leads for process evolution and also ideas leading to better chemistry for the conversion of fermentation products to chemical intermediates—for example, cephalosporin C to 7-ACA. Again, product quality is the most important guiding parameter.
3. Reduce the cost of manufacturing and improve the quality of bulk APIs made from the chemical intermediates.

Although the chemical development organization in Ulverston had little to do with improving the fermentation processes, it was always necessary to stay vigilant to ensure that when a change was made to the fermentation process, there was no impact on the subsequent chemical transformation steps. Changes were sometimes imposed by natural events outside anyone's control. I recall that the change in fermenter feed from one season's molasses to another could play havoc with the fermentation titer. On another occasion during a drought, the well water level fell to levels that led to high salts content in the water used for fermentation, adversely affecting the titer. Such events only added to the difficulties of making progress in fermentation

[2]Dr. Brian Boothroyd, personal communication.

[3]Fermentation factories are always sensitive to the possibility of industrial espionage negating commercial advantages they had gained from R&D work to improve their fermentation strains. For this reason, before Glaxo would send out waste proteinaceous spent mycelium for animal feed, they always pre-baked it to destroy viable microorganisms.

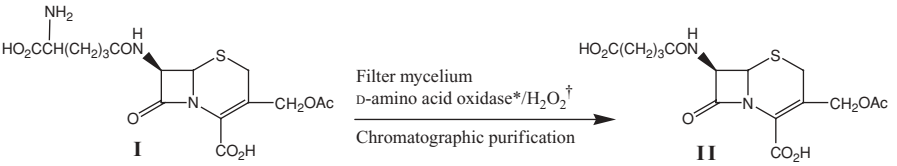
[4]Baldwin, J. E., and Schofield, C. *The Chemistry of* β-*Lactams*, Page, M. I., Ed., Blackie Academic and Professional, Glasgow, 1992, p. 1.

development. In the early days, there was no good method for gas analysis to study oxygen absorption and carbon dioxide expiration during the growth and producing stages of the microorganism. More productive strains were discovered by treating the regular strains with chemical mutants or UV light and plating out the surviving organisms. In the manufacturing plant, stirring rates and the delivery of air were optimized by trial and error. Statistical analysis of plant data played a large part in process improvement.

When problems occurred in fermentation operations, it could take weeks to identify the cause of poor performance and take corrective action. As a result, there was a considerable degree of empiricism and "feel" associated with fermentation development and controlling a "living process." It was therefore not surprising that the filing cabinets of the fermentation development and production staffs contained enormous numbers of reports on problems that came back time and again. Unfortunately, the empiricism associated with managing fermentation development all too often spilled over into the chemical development side of operations, such that one of the greatest managerial challenges was to ensure that a quantitative, rational analysis and testing program was used to resolve the usually more quantifiable chemical synthesis problems.

Despite the turbulence encountered in all process improvement and process development work, there were the occasional triumphs of applied common sense. One of considerable social as well as economic consequence, occurring in the manufacture of penicillin G, resulted from the Ulverston process improvement attending the switch from buying solid phenylacetic acid to purchasing an aqueous solution containing 50% sodium phenyl acetate. In using the solid, our factory workers weighed the required amount of phenylacetic acid and then dissolved it in aqueous sodium hydroxide to produce the aqueous solution used for feeding the penicillin fermenters. The handling of solid phenylacetic acid had created problems for many years, both for the Ulverston factory and for our vendor, Albright and Wilson (A&W). Solid phenylacetic acid introduced an obnoxious, pervasive, sweaty aroma to the penicillin G buildings and the workers' clothes and homes in Ulverston. The odors in Ulverston and surrounding communities were, however, almost trivial besides those encountered by the A&W workers. Keith Partridge, Sales and Marketing Manager for A & W during my time at Ulverston (1966–1975), recounted the privations of process operators manufacturing phenylacetic acid in A&W's Ann Street works in Widnes. They were paid a "social bonus" for working in the plant. Keith said you could walk down the street where they lived and identify their houses by the smell!! No one would sit in their seats at the local public house—even their beer glasses were segregated!! The ultimate indignity occurred when Vernons, the football pool company, asked one worker not to send in his weekly pool coupon because of odor complaints from the clerks who processed it!!!

The common sense use of the 50% aqueous solution of phenylacetic acid virtually eliminated the handling of solid material, though it took some time and a few plant trials to convince the production managers that there was nothing else in the A&W aqueous solution which might have an adverse effect on the penicillin G titer.



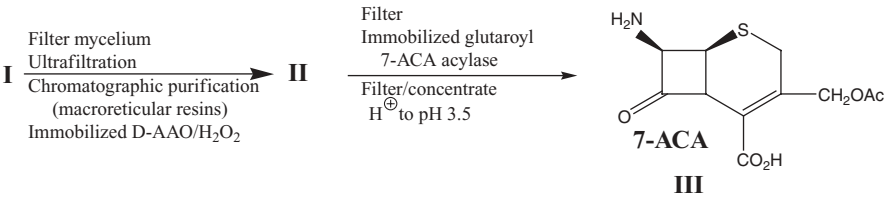
SCHEME 1. *D-AAO derived from *Aspergillus* and *Trigonopsis* strains.
† Added H_2O_2 improves the conversion of the intermediate keto acid to the glutaroyl side chain. Indeed H_2O_2 and a ketone also effect the conversion of I to II.[7]

The scientists and engineers in the Ulverston factory interacted with the Glaxo Research and Development people in Greenford (Chemistry) and Sefton Park (Microbiology/Biochemistry and Fermentation/Extraction)—an interaction that added vitality, good ideas, some rivalry, and great exchanges to the benefit of all who participated. Ultimately, the Ulverston factory benefited the most. A number of notable advances in improving process efficiency came out of the Research Groups, some of which were implemented. Some were before their time, but should not have failed.

One such advance was the work carried out in Sefton Park by Dr. Robert Fildes and co-workers[5,6] on the enzyme-mediated conversion of the zwitterionic aminoadipic acid side chain in Cephalosporin C into a glutaroyl side chain (a process that rendered the molecule more amenable to solvent extraction from filtered fermentation broths; see Scheme 1.

At the time (early 1970s) the enzyme reaction worked well, and the 3-acetoxymethyl-7(*R*)-glutaroylaminoceph-3-em-4-carboxylic acid **(II)** produced could be extracted into *n*-butanol fairly readily. However, isolation of the free acid **(II)** or salt, added to the losses in the extraction step and created only a marginal economic advantage versus the existing process [chromatographic enrichment of cephalosporin C in the filtered broth followed by concentration (Luwa evaporator) and precipitation as the potassium salt]. Glaxo Research, and to a lesser extent the Ulverston staff involved in the recovery of potassium Cephalosporin C, worked on the process for some time but did not succeed in making it practical. The idea was a good one that, finally (almost 30 years later), came to fruition in the hands of Antibioticos S.p.A. in Settimo-Torinese, Italy. Antibioticos succeeded in building on Glaxo's original ideas by finding and immobilizing both an amino acid oxidase and, separately, a glutaroylamidase on polymer supports.[8] These innovations, coupled with the adroit use of macroreticular resins for purifying their cephalosporin intermediates, enabled them to create an all aqueous process for the manufacture of the important cephalosporin intermediate, 3-acetoxymethyl-7-aminoceph-3-em-4-carboxylic acid (7-ACA-III) (Scheme 2).

[5]Arnold, B. H., Fildes, R. A., Gilbert, D. A. U.S. Patent 3,658,649, 1972 (to Glaxo).
[6]Fildes, R. A., Potts, J. R., and Farthing, J. E. U.S. Patent 3,801,458, 1974 (to Glaxo).
[7]Suzuki, N., Sowa, T., and Murakami, M. U.S. Patent 4,079,180, 1978 (to Asahi).
[8]Cambiaghi, S., Tomaselli, S., and Verga, R. U.S. Patent 5,424,196, 1995 (to Antibioticos S.p.A.).



SCHEME 2. Antibioticos' industrial process for the conversion of Cephalosporin C in fermentation broths to 7-ACA.

By combining immobilized enzyme and chromatography technologies, Antibioticos realized the long-standing objective of avoiding intermediate isolations, thereby making 7-ACA the first product isolated from the fermenter. Asahi's position in the same field[7] contributed to the Antibioticos achievement. Biochemie in Austria has also had notable success in a similar, independent program.

Environmentally clean technologies such as those outlined in Scheme 2 have, in addition to reducing the cost of 7-ACA, introduced new opportunities for the preparation of other commercially useful cephalosporin intermediates (see later section entitled "Back to Classical Cephalosporins").

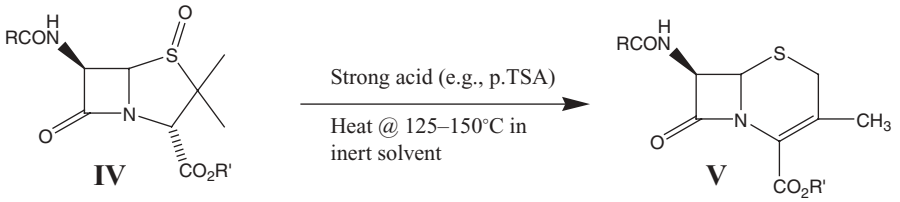
Fifty years ago, the simple molecular manipulation of penicillins isolated from the fermenter (Penicillins G and V) was limited to producing 6-aminopenicillanic acid and acylating the amino group with different acylating agents, thereby providing novel products with an improved biological spectrum. Looked at in the same way, 7-ACA offered two sites for molecular manipulation: the 7-amino group and the 3-acetoxymethyl group. Many cephalosporins with new and improved biological spectra resulted from replacing these groups; the interested reader is referred to books and symposia publications on this subject.[9]

The Ring Expansion of Penicillin Sulfoxides to Cephalosporins

In the early days, much was done by the major pharmaceutical companies to build on the vast chemistry opened up when Morin and Jackson (Eli Lilly) discovered their pioneering process for ring expanding penicillin sulfoxides **(IV)** to 3-methylcephalosporins **(V)**.[10] This breakthrough subsequently led to the discovery, development, and marketing of many new antibiotics.

[9](a) *Cephalosporins and Penicillins: Chemistry and Biology*, Flynn, E. H., Ed., Academic Press, New York, 1972. (b) *Chemistry and Biology of* β-*Lactam Antibiotics*, Morin, R. B., and Gorman, M., Eds., Academic Press, New York, 1982. (c) *Recent Advances in the Chemistry of* β-*Lactam Antibiotics*, Special Publication No. 28, J. Elks, Ed., The Chemical Society London, 1977. (d) *idem*, Special Publication No. 38, Gregory, G. I., Ed., 1981. (e) *idem*, Special Publication No. 51, Brown, A. G., and Roberts, S. M., Eds., 1984.

[10](a) Morin, R. B., Jackson, B. G., Mueller, R. A., Lavagnino, E. R., Scanlon, W. B., Andrews, S. L., *J. Am. Chem. Soc*. 1963, **85**, 1896. (b) *Idem, ibid.* 1969, **91**, 1401. (c) Morin, R. B., Jackson, B. G. U.S. Patent 3,275,626, 1966 (to Eli Lilly).



R = $C_6H_5OCH_2CO.$ or $C_6H_5CH_2CO.$
R' = Readily removed carboxyl protecting group

SCHEME 3. Outline of the Morin – Jackson ring expansion.[10c]

The Morin–Jackson ring expansion discovery led first to the orally absorbed antibiotic, Cephalexin, marketed by Eli Lilly and Glaxo under National Research and Development Council (NRDC) licenses.

The Morin–Jackson ring expansion as first described required that the 3-carboxyl group be blocked by a readily removed protecting group (Scheme 3).

Several companies were involved in the search for the best carboxyl protecting group, notably Ciba–Geigy, Eli Lilly, Glaxo, and later Gist–Brocades. Ciba–Geigy, through the work of Professor R. B. Woodward,[11] discovered the value of the 2,2,2-trichloroethyl (TCE) group. This group, like the β-lactam ring itself, proved to be stable during the conditions used in the ring expansion process, and also the conditions used in the subsequent PCl_5 cleavage reaction to give the 7-aminocephalosporin TCE ester. The TCE group was usually removed by treating the TCE ester with zinc.[12]

At about the same time (early 1960s), Eli Lilly found that the *p*-nitrobenzyl (PNB) group would provide protection equivalent to that provided by the TCE group with the further merit of introducing good crystallinity, and therefore ease of purification, to the products of the ring expansion process. Early ways of introducing the pNB group involved reacting *p*-nitrobenzyl bromide (a vesicant) with the penicillin carboxylate. Reductive removal of the PNB group was also found, by Eli Lilly workers, to give a hazardous waste (allegedly containing carcinogenic tolidines[13]). In its early work on the ring expansion process, Glaxo followed Ciba–Geigy's TCE lead, recognizing that Ciba–Geigy would subsequently patent the process. This enabled Glaxo to get off to a fast start to find a commercially useful ring expansion process and, separately, to undertake work to develop a process based on an alternative protecting group. Glaxo Research chose to follow Eli Lilly's lead to develop a process based on PNB protection since Glaxo had rights, through the umbrella license which the NRDC had

[11](a) Woodward, R. B. *Science*, 1966, **153**, 487. (b) Woodward, R. B. *Angew. Chemie*, 1966, **78**, 557. (c) Woodward, R. B., Heusler, K., Gosteli, J., Naegeli, P., Oppolzer, W., Ramage, R., Ranganathan, S., and Vorbrüggen, H., *J. Am. Chem. Soc*. 1966, **88**, 852.

[12](a) Woodward, R. B. Brit. Pat 1,155,016, 1969. (b) Woodward, R. B. U.S. Patent 3,828,026, 1974 (to Ciba Geigy).

[13]In commercializing the use of pNB protection, Eli Lilly built a special containment facility in its Clinton, Illinois, Cephalexin plant in order to segregate the waste from removal of the pNB group for separate disposal.

created with several companies, including Eli Lilly, to sublicense the findings made by all members of the "NRDC club."

A few of us in the Glaxo factory organization in Ulverston thought that the hazard to process operators that would be introduced by using *p*-nitrobenzyl bromide and by implementing the reductive removal of the PNB group were undesirable in a factory setting. On these grounds, Dr. Arthur Best supported my proposal to evaluate the diphenylmethyl (DPM) group, with the conceptual objective being to introduce DPM via reaction of penicillin G sulfoxide acid with diphenyldiazomethane, produced in situ, and to subsequently remove the DPM group by acid-catalyzed solvolysis.[14]

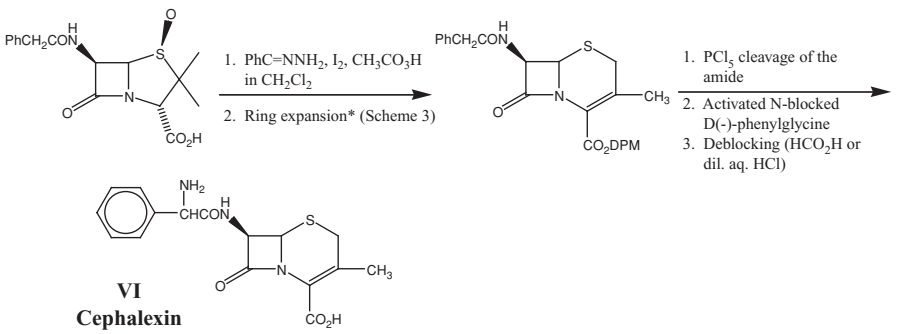
The competition that ensued with the Glaxo, Greenford, chemical development group (developing PNB protection) and the Ulverston team was a healthy, if tortured one. Many in Greenford believed that Ulverston staff should be doing process troubleshooting work on the existing chemical processes and working to increase process yields and reduce costs. But Dr. Best was having none of it, at the same time recognizing that the Ulverston activities were considered heretical by a number of people in Greenford. Looking back, the risks to Ulverston's management were undoubtedly considerable. Nevertheless, joint meetings were organized with Greenford R&D scientists and I personally was given tacit support by Dr. Joseph Elks (at the time the Greenford Director of Chemistry). Dr. B. A. Hems (later Dr. B. A. Hems, FRS), who was the managing director of all R&D in Greenford and himself a visionary,[15] chose to let the Ulverston work go on.

As detailed in our later publications and patents,[16] we found that diphenyldiazomethane (DDM) could be prepared in high yield by the peracetic acid oxidation of benzophenone hydrazone in methylene chloride in the presence of a base. We used peracetic acid in the presence of a nonoxidizable base, tetramethylguanidine being the base of choice. Since, at that time, the separate preparation of DDM was perceived as adding an unsafe step to the process of producing our target molecule, penicillin G sulfoxide diphenylmethyl ester, we quickly moved on to finding a practical process that would enable us to prepare DDM in the presence of penicillin G sulfoxide acid under process conditions wherein the DDM would be immediately scavenged by the sulfoxide acid. We found that this could simply be done by adding peracetic acid to a solution of benzophenone hydrazone and penicillin G sulfoxide acid in methylene chloride. However, we found that the yield to the target DPM ester was quite variable. Fortunately, our Dr. Roy Bywood made the connection between yield of the target ester and the source of penicillin G sulfoxide acid. He observed that old samples of sulfoxide acid gave better yields of ester than new ones and traced the difference to their methods of preparation. Old samples had been prepared

[14]This proposal was based on speculation that the work of Horner, L., and Fernekess, H. *Chem. Ber.*, 1961, **94**, 712 (in which they showed that moderate yields of esters and ethers could be obtained by adding peracetic acid to benzophenone hydrazone in the presence of excesses of carboxylic acids and phenols) may provide a basis for a commercial process to DPM esters.

[15]Jack, Sir D., and Walker, T. *Roy. Soc. Biograph. Mem.* 1997, 217.

[16](a) Adamson, J. R., Bywood, R., Eastlick, D. T., Gallagher, G., Walker, D., and Wilson, E. M., *J. Chem. Soc., Perkin Trans. I*, 1975, 2030. (b) Gallagher, G., and Walker, D. U.S. Patent 4,083,837, 1978 (to Glaxo). (c) Bywood, R., Gallagher, G., Sharma, G. K., and Walker, D., *J. Chem. Soc., Perkin Trans. I*, 1975, 2019.



*Glaxo employed a bidentate catalyst, pyridinium dichloromethylphosphonate, in refluxing dioxane to carry out the ring expansion.

SCHEME 4. Glaxo process for the manufacture of Cephalexin.

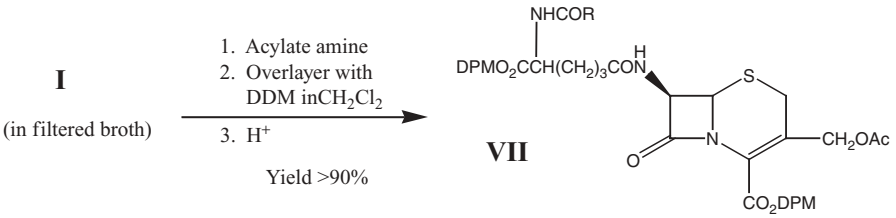
by the oxidation of penicillin G with sodium metaperiodate whereas new samples had been prepared using the much cheaper peracetic acid. He proved that the yield discrepancy was related to contamination of the penicillin G sulfoxide acid by iodide ion. Higher ester yields were obtained in the presence of traces of iodine or iodide ion; typically, when peracetic acid (1.4 mole) was added to a solution of penicillin G sulfoxide acid (1 mole), and benzophenone hydrazone (1.3 mole) in chloroform in the presence of iodine (0.002 mole), an almost quantitative yield of the target DPM ester was obtained. Levels of iodine significantly lower or higher than 0.0015 mole equivalents with respect to the hydrazone gave poorer yields.

This work led on to a Glaxo process patent for the preparation of cephalexin **(VI)** using DPM protection[17] (Scheme 4). The Ulverston process was developed through the pilot plant phase and proven to give high-quality Cephalexin. Moreover, the DPM ester wastes were shown to be readily oxidizable to benzophenone using aqueous nitric acid.[18] Successful plant trials followed to compare both the DPM and PNB options.

At a final process selection meeting in Greenford, Dr. Best presented the case in favor of adopting the DPM process. The process economics vs. PNB were only marginally in favor of DPM. The decision to adopt DPM was based largely on our own patent position and operator safety and environmental considerations. The DPM process was scaled up in Ulverston (through the ring expansion step) and Glaxo's factory in Montrose, Scotland, and served for many years to produce Cephalexin for Glaxo's marketing needs. Later on, Dr. Hems, during a visit to the Ulverston factory, congratulated us for "sticking to our guns" in developing the DPM process.

[17]Bywood, R., Gallagher, G., and Walker, D., German Patent 2,311,597, 1973 (to Glaxo).

[18]The oxidation is carried out by refluxing the "benzhydryl" waste in aqueous 30% nitric acid (see footnote 17, example 37). The benzophenone produced is easily converted to benzophenone hydrazone for recycle to the DDM process. See also Rivkin, S. M. *J. Appl. Chem. (USSR)*, 1938, **11**, 83 (*Chem. Abstr.*, 1938, **32**, 4566). The nitric acid oxidation process was adopted by Albright and Wilson, our benzophenone hydrazone supplier.



SCHEME 5. Extractive esterification of Cephalosporin C derivatives.

We went on, in a lower-key way, to explore the possibilities of using diphenyldiazomethane (DDM) for the extractive esterification of cephalosporins from aqueous solution (Scheme 5).[19] This worked very well. It was not followed up for commercial use at the time, but did find use in a later process development project carried out with Schering–Plough (see later). Two key factors in the decision to further evaluate DDM as a potentially useful reagent for extractive esterification were its better-than-expected stability[20] and the creation of an improved process for producing DDM. Our Ted Wilson[16(a)] discovered that the previously used, and expensive, tetramethylguanidine base could be replaced by aqueous sodium hydroxide and a phase transfer catalyst (Aliquat 336) in a two-phase system with methylene chloride. This process also gave excellent yields of DDM (>90%).

We extended our process work to prepare new polystyrene resins carrying the diazoalkane group (see Chapter 11).

All of this work introduced us to the world of patents and led to a valuable, independent patent portfolio for Glaxo.

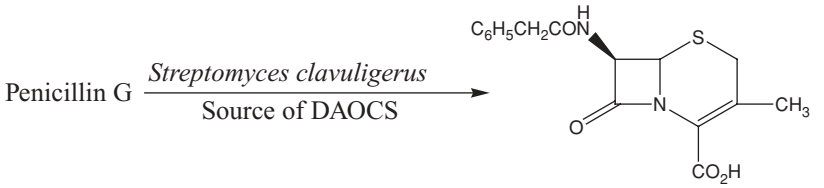
It is pertinent to point out that, after the capital investment program in equipment for the DPM-based process for Cephalexin manufacture was well advanced, we became aware of the pioneering work of Gist–Brocades (now a part of DSM) in using the trimethylsilyl (TMS) group as a temporary protecting group for carboxyl in the ring expansion reaction.[21] Although the TMS group was removed by hydroxylic materials during the work-up of every process step, its advantages of low cost, a very simple procedure for preparing TMS esters (carboxylate and TMS Cl), and its ease of removal (water regenerates the carboxylic acid and hexamethyldisiloxane when a little acid is present) recommended TMS protection to many companies (Bristol–Myers went further in utilizing the even cheaper dichlorodimethylsilane as a protecting group; in practice, the waste polysiloxane was generally disposed of via waste haulers). Gist–Brocades developed their discovery into a very large market for 7(*R*)-amino-3-methylceph-3-em-4-carboxylic acid (7-ADCA). Glaxo looked at the

[19]Robinson, C. H., and Walker, D. U.S. Patent 4,059,573, 1977 (to Glaxo).

[20]Sakamoto, D., Hirayama, Y., Kohno, Y., Sakai, T., Shiraishi, Y., and Saijo, S. European Patent 177,248, 1987 (to Taoka Chemical Co., Ltd).. These workers report that crystalline DDM undergoes no decomposition when held at 5°C for 100 hr, but that solutions in CH_2Cl_2 deteriorate faster: A 50% solution decomposes 4.9% in 20 days and 30.5% in 40 days at 0°C.

[21](a) de Koning, J. J., Kooreman, H. J., Tan, H-S., and Verweij, J. *J. Org. Chem.* 1975, **40**, 1346. (b) Verweij, J., and DeVroom, E. *Recl. Trav. Chim. Pays-Bas*, 1993, 112, 66–81.

possibility of producing Cephalexin via the Gist 7-ADCA process (or to purchase Gist 7-ADCA), but decided that the economics did not justify the change. [*Although the chemical ring expansion of penicillins to 3-methylcephalosporins continues to be used for the manufacture of the orally active 3-methylcephalosporins, there remains that never-say-die belief among biotransformation afficionados, particularly Professor Arnold Demain, that one day the biological ring expansion of Penicillin G to deacetoxycephalosporin G (DAOG) using deacetoxycephalosporin C synthase (DAOCS) will succeed to the point of becoming an industrial process:*



Work published relatively recently[22] *indicates that the yield in this process has been improved to 10%.*

Given a much higher yield, the enzymatic process could save operating costs and reduce waste disposal and environmental problems vs. the established penicillin sulfoxide ring expansion process. However, the major issue is whether an old industry with declining profitability, would be able to justify the cost of investment in better technology (cf. the case of ceftibuten discussed later). In related work, 6-adipoylaminopenicillanic acid has been shown to be convertible to 7-adipoylaminocephalosporanic acid in very low yield by Streptomyces clavuligerus expandase gene.][23]

It was during this period that Glaxo's Research management, and also the Manufacturing management, changed with the retirement of Dr. Hems and with other organizational maneuvers. The effect of these changes on the small Ulverston process development operation was traumatic. It was decreed that all process development work would return to the R&D group in Greenford and that Ulverston would concentrate on troubleshooting and cost reduction. Dr. Robert Fildes, by then head of the Ulverston fermentation operation, left to join the Bristol–Myers Industrial Division. He persuaded me to follow him. Other co-workers departed to join other parts of the Glaxo organization or other companies. The rough organizational trampling by Glaxo's senior management brought to mind Machiavelli's 16th-century observation:

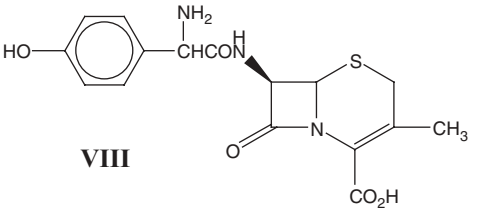
> There is nothing more difficult to carry out,
> nor more doubtful of success, nor more dangerous to handle,
> than to initiate a new order of things.

[22] Adrio, J. L., Demain, A. L., *J. Org. Proc. Res. Dev.*, 2002, **6**, 427.
[23] Crawford, L., Stepan, A. M., McAda, P. C., Rambosek, J. A., Conder, M. J., Vinci, V. A., and Reeves, C. D., *Bio/Technology*, 1995, **13**, 58.

The changes could have been made with more consideration of the consequences —how to keep the talent and experience lost!

Semisynthetic Penicillins and Cephalosporins: Adventures in Product Quality (Bristol–Myers)

Bristol–Myers built on Eli Lilly's discovery of Cephalexin by funding the research that led to the development of Cefadroxil **(VIII)**, just as Beecham had done in building on its own discovery of ampicillin with the invention of amoxicillin. Both amoxicillin and cefadroxil carried the D(-)*p*-hydroxyphenylglycyl side chain which served to extend biological activity and increase blood levels versus ampicillin and Cephalexin.



VIII **Cefadroxil**

All of these semisynthetics had their own quirks in the sense that routinely achieving high quality on a production scale proved very difficult. The major source of most quality problems with all four of these compounds lay in the quality of the 6-APA or 7-ADCA used for their manufacture. Traces of metals such as iron, as well as traces of unknown impurities, affected the color and even the taste of the products.

I recall Bristol–Myers' Managing Director in Brazil, Paulo Mendez, loudly complaining of ampicillin and amoxicillin quality problems that were traced back to the quality of some lots of 6-APA made in Syracuse, New York. "You were supposed to ship 6-APA," he forcefully reminded us, "and I emphasize the 6. Your last shipment was only $5\frac{1}{2}$-APA!!"

Similarly, Banyu in Japan bought Cephalexin from Bristol–Myers' facility in Latina, Italy. In the early days Banyu complained that the taste and odor of Latina's Cephalexin batches varied considerably, with many batches failing to meet Banyu's organoleptic criteria, particularly for taste. Since taste and odor are not quantifiable parameters, the dilemma persisted for some time. During a visit to Latina, Banyu's President, Dr. Iwadare, politely explained that Japanese children actually retched when obliged to take Banyu's Cephalexin oral suspension. The seriousness of the situation became clear to Latina management when Banyu refused to accept free goods that failed their organoleptic tests. The rest of the story was reported to me by my Latina colleague, Dr. Ettore Visibelli. In an effort to resolve the problem, Banyu sent their President's son and their Director of R&D to conduct taste tests on batches of Cephalexin and to "train" Latina people to carry out the taste tests to identify Cephalexin batches suitable for shipment to Japan. Dr. Visibelli said that there was a considerable uproar at the start of the exercise since the Banyu team proved to

be quite persnickety in selecting a room where the taste tests would be performed. They wanted a room with no distracting odors, good air conditioning and excellent lighting—the appearance of the powder was important to them. They sniffed the air in many rooms in several buildings before deciding that the Engineering Department's draftsmen's room met their standards (the story quickly spread around the Latina factory that the draftsmen didn't sweat as much as everyone else!). But that was not all. The Banyu team spent some time in selecting the right Italian water for mouth rinsing after each test.

The taste test itself was a ceremony to behold (as many did, taking turns to look through the window). It seemed to take on the aura of a religious occasion as each taster sniffed his freshly opened bottle and then carefully spooned a very small amount of powder onto a clean plate. After a debate about the powder's appearance, they lifted their plates to their mouths in unison and licked the sample off. A pause followed with exquisite facial expressions registering their reactions to their palates. The mouth was rinsed and the results of the tasting were written down. Only six licks per day could be undertaken such that it took the Japanese several days to lick their way through the assembled batches. The ruling on acceptable batches and unacceptable batches was handed down and arrangements made to ship the acceptable batches to Japan. The use of Latina staff to routinely taste test the Cephalexin batches never happened. Quite apart from the concern that the unions might react to people being used as "tasting guinea pigs," it was agreed that a scientific solution was needed. Indeed, Dr. Visibelli and his staff, working with Latina analysts and production people, found that the presence of acetone in the last process step led to the formation of traces of an unstable Schiff base with Cephalexin which degraded to give unidentified products causing the odor and taste problems.

Beyond quality exercises, there were many patent issues to address, a few of which are detailed in the patents presentation (q.v.). Work in the cephalosporin field continued at Bristol–Myers, but the compounds produced and marketed, cephapirin and ceforanide, were overtaken by products of other companies, notably cefuroxime axetil (Glaxo), ceftriaxone (Roche), and cefotaxime (Aventis—at one time Hoechst Roussel). Later the penems and carbopenems further diminished interest in the earlier cephalosporins.

In 1981, management changes in the Bristol–Myers organization formalized a split in the duties of our chemical process development group. The Research arm of the organization built its own development group to supply the small quantities of its API's for initial screening tests. As the scientific challenges narrowed, several of us left—I being attracted to Schering–Plough (1982).

Penems and Cephalosporins—Flourishing Science (Schering–Plough)

Although Schering–Plough was active in the β-lactam field through its discovery of several interesting penems, none of them made it to the marketplace. However, the period 1982–1996 (when I "graduated" rather than retired!!) was one of the most fruitful periods of my career, notably for the opportunity to work with outstanding people doing great science and to build a chemical development organization of

considerable power, with the indispensable encouragement and support of one of only a few visionaries encountered in my career, Dr. Hal Wolkoff.

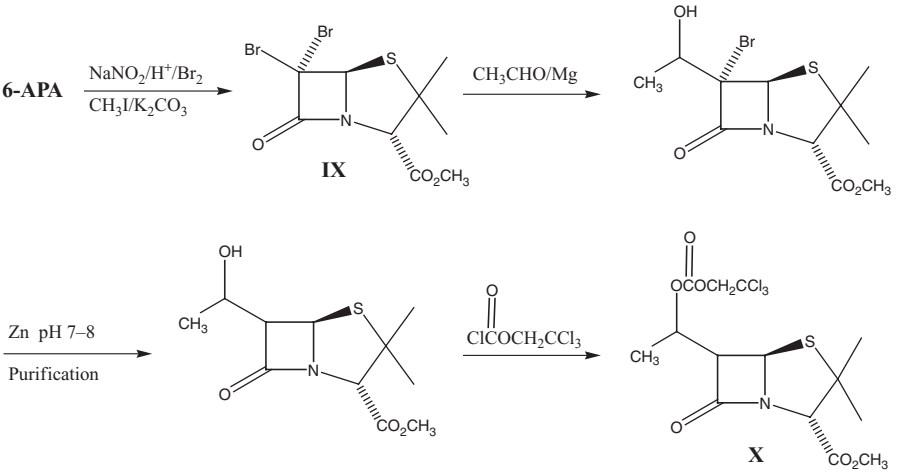
The first few turbulent years were distinguished by our hiring of many chemical engineers and chemists, by the vital acquisition of modern instrumentation (NMR, HPLC, GC, and IR), and by the creation of new laboratories. An adventitious instant increase in plant capacity, enabling chemical development to meet growing demands for bulk APIs, resulted from the transfer of Schering's manufacturing assets in Union, NJ [including personnel and responsibility for continuing production of a few low volume products (albuterol, aurothioglucose, and others)] to chemical development.[24]

Several of my Bristol – Myers colleagues (Bruce Shutts, Steven Yu, Mario Ruggeri, and Dr. Chou Tann) followed me to Schering–Plough. The agreement with Schering was that in addition to meeting our Research commitments and supervising the manufacture of the low volume products, we would also support the manufacturing people in their efforts to improve the performance of steroid manufacturing operations in Mexico City and Manati, Puerto Rico. The manufacturing division funded the chemical development support team in a collaborative effort with Mexico City and Manati scientists. It was agreed that this effort would be ancillary to the main objective, producing quality APIs for Schering Research clinical, toxicology, and pharmaceutical development programs.

Penems

Our work to develop the synthesis methods that would deliver kilos of penems to Research owed much to the brilliant scientific achievements of Schering–Plough Research's Drs. Ashit Ganguly, Stuart McCombie, Viyyor Girijavallabhan (Giri), and Adrian Afonso, who defined the synthesis sequence. However, in reducing their work to practice in the chemical development laboratories and pilot plants, much was owed to the skills and dedication of our own chemists and chemical engineers, notably Ray Werner, Bruce Shutts, Lydia Peer, Stan Rosenhouse, Pete Tahbaz, Bob Jaret, and Drs. Marty Steinman and Dick Draper. None of our own achievements in delivering kilos of penems would have been possible without the starting material, initially methyl 6,6-dibromo penicillanate **(IX)** and later methyl (5*R*,6*S*,8*R*)-6-(1-trichloroethoxycarbonyloxyethyl) penicillanate **(X)** produced with enthusiastic and practical flair in Schering's Union pilot plant by Stan Rosenhouse et al., and subsequently in Schering's manufacturing plant in Ireland by Drs. Brian Brady, Henry Doran, and Maurice Fitzgerald, very ably supported by Michael Miley, who ran the pilot plant. Our Swiss chemical development pilot plant group, enterprisingly led by Phil Ottiger (and later by Dr. Ernst Vogel) and Kurt Jost, were responsible for sourcing the side-chain and blocking groups as well as implementing several of the steps beyond compound **X**. The Irish group became responsible for the implementation of all of Scheme 6.

[24]Such a transfer was made possible by Schering–Plough's investment in new production facilities in Manati, Puerto Rico.



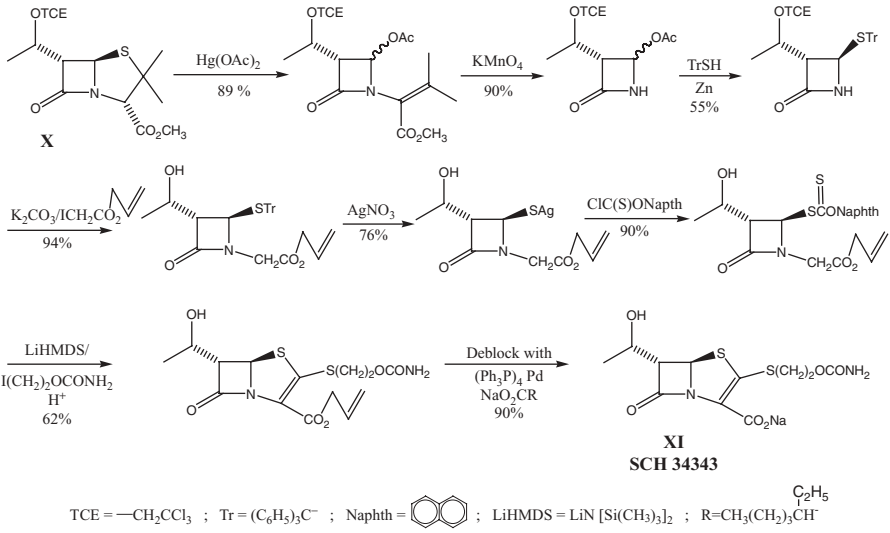
SCHEME 6. Schering–Plough method for the preparation of methyl (6*S*, 7*R*, 8*R*) 6-(1-trichloroethoxycarbonyloxyethyl) penicillanate (X).

Skilled adaptation of the laboratory methodology outlined in Scheme 6 created a practical method for the preparation of high-quality **X** in batches of several hundred kilograms. Ireland went on to become the main supplier of **X**, thus providing the Union, NJ and Swiss pilot plants with all the raw materials needed for the subsequent steps. This strategy also eliminated penicillin contamination concerns from the Union site—at least until the last steps. The Union methodology for converting **X** to Schering penem Sch 34343 is outlined in Scheme 7.

It can be quickly appreciated that the methodology illustrated in Schemes 6 and 7, although radically improved to render it practical, was far from providing the basis of an industrial process. The major burdens were the use and disposal of mercuric acetate, the use of other reagents and solvents such as methyl iodide (suspected carcinogen), allyl iodoacetate (lachrymator), and chloroform (carcinogen)[25] which posed health hazards, and the large number of synthesis steps, some giving relatively poor yields, which created a significant cost of goods problem. Moreover, the synthesis lacked in elegance since only the core β-lactam ring of the starting 6-APA is incorporated into the final penem. In addition, FDA requirements that we use dedicated process equipment in segregated areas to avoid "penicillin" cross-contamination possibilities raised considerable logistics problems.

In progressing the API supply program in the period 1982–1985, we managed to meet rising expectations, mostly for increased kilo requirements, at the same time

[25] Although chloroform is classified as a "confirmed carcinogen . . ." in *Sax's Dangerous Properties of Industrial Materials*, 8th edition, Volume II, Lewis, R. J., Ed., van Nostrand Reinhold New York, 1992, p. 815, its status is questioned by the former director of the Bioassay Segment of the National Cancer Institute (see Weisburger, J. H., *Chemical and Engineering News*, December 17, 2001, p. 8). In addition to giving equivocal results in rat and mice tests, Dr. Weisburger points out that chloroform is neither genotoxic nor mutagenic and does not combine with DNA.



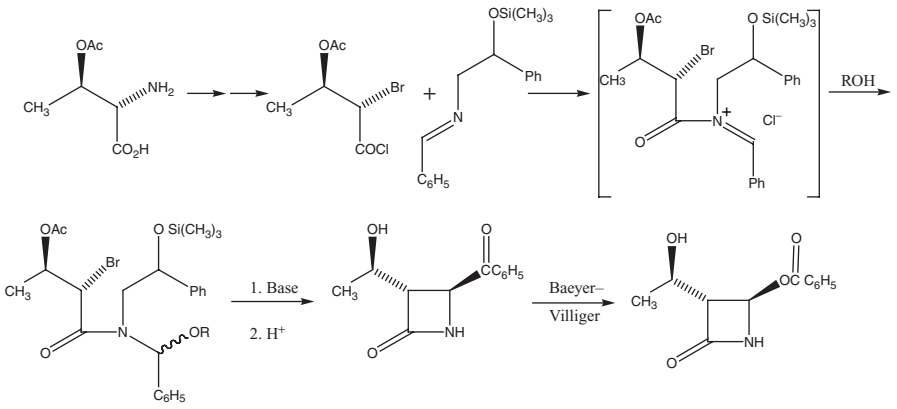
SCHEME 7. Method for the preparation of Schering penem SCH 34343, from intermediate X.

as adding manpower resources, upgrading laboratories and pilot plants, acquiring modern instrumentation, and concurrently intensifying our dialogue with the Analytical Development operation. There was a short respite as we mourned the demise of our first penem, Sch 29482,[26] partly owing to the significant social problems associated with its use.[27] By the time the second penem (Sch 34343, **XI**) was identified, Chemical Development was well advanced in the transition from a largely empirical experimental culture to one based on process innovation and seeking the best possible understanding of the chemistry being scaled up.

In searching for a better synthesis of penems free of the previous need to start with a penicillin, we looked for sources of a starting material that would be relatively low in cost, which would avoid the penicillin cross contamination concerns in the early steps of the synthesis and which would allow us to incorporate as much of the starting material as possible in the final penem. We looked at an L-threonine route devised

[26](a) Girijavallabhan, V. M., Ganguly, A. K., McCombie, S. W., Pinto, P., and Rizvi, R. *Tetrahedron Letters*, 1981, **22**, 3485. (b) Afonso, A., Ganguly, A. K., Girijavallabhan, V. M. and McCombie, S. W. In *Recent Advances in the Chemistry of β-Lactam Antibiotics*, Brown, A. G. and Roberts, S. M., Eds., S. Special publication No. 52, The Royal Society of Chemistry, London; 1984, p. 266.

[27]SCH 29482 carried a 2-ethylmercapto side chain in place of the 2-carbamoyloxyethylmercapto group in Sch 34343. Volunteers enrolled in the clinical trials developed a foul odor, attributed to ethylmercaptan, which contaminated their clothing, offices, and homes. There was one anecdotal story of a volunteer in the American South who was chased by dogs when his wife sent him out to the woods behind their house to relieve himself. Schering tried, unsuccessfully, to mask the problem by formulating Sch 29482 with chlorophyll. Lack of success was predictable. I recall a BBC radio talk given by an expert in the 1950s, debunking the use of chlorophyll as a mouth freshening deodorant in toothpaste. He ended his talk with the lines: "The goat that reeks on yonder hill has browsed all day on chlorophyll!"

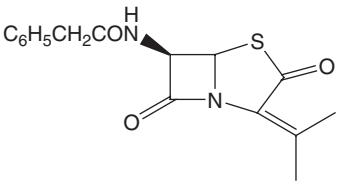


SCHEME 8. Method for the conversion of *O*-acetyl-L-threonine into and intermediate suitable for Sch 34343 preparation.

by our research colleagues, notably Drs. Sam Chackalamannil, Adrian Afonso, and Ashit Ganguly. This is outlined in Scheme 8.

The major virtues of this route to penem XI lie in the low cost of L-threonine and in avoiding a penicillin starting material. However, the route intersects with the Scheme 7 chemistry at too early a stage in the synthesis, with the need to introduce sulfur at C-4. Despite these disadvantages, we did begin an evaluation of the L-threonine route.

We also became interested in the possibility of evaluating sourced phenylacetylanhydro-penicillin **(XII)**, itself obtainable from Penicillin G, since it seemed to us to be outside the usual definition of a penicillin, and may be amenable to elaboration of the 6-hydroxyethyl side chain and conversion of the five-membered ring to the desired penem, retaining the sulfur atom.



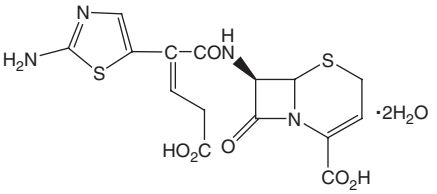
XII

Unfortunately at this time, toxicity and marketing concerns overtook Sch 34343 and finally obliged Schering to abandon its penem program. As so often happens in development work, the end came quickly with manpower and equipment resources rapidly reallocated to other projects. It is usually difficult for all personnel, especially chemists and engineers who have devoted themselves and their energies so totally (often for years) to a project, to suddenly stop thinking and working on the intellectual and company challenges associated with it and be expected to immediately pick

up the next API candidate with the same commitment. Management needs to be especially aware of the need to express thanks and provide explanations, support, and encouragement to employees during such transitions.

Back to Classical Cephalosporins

Several years later (1989), Schering–Plough licensed the oral cephalosporin, Ceftibuten dihydrate **(XIII)**, from Shionogi, Japan.

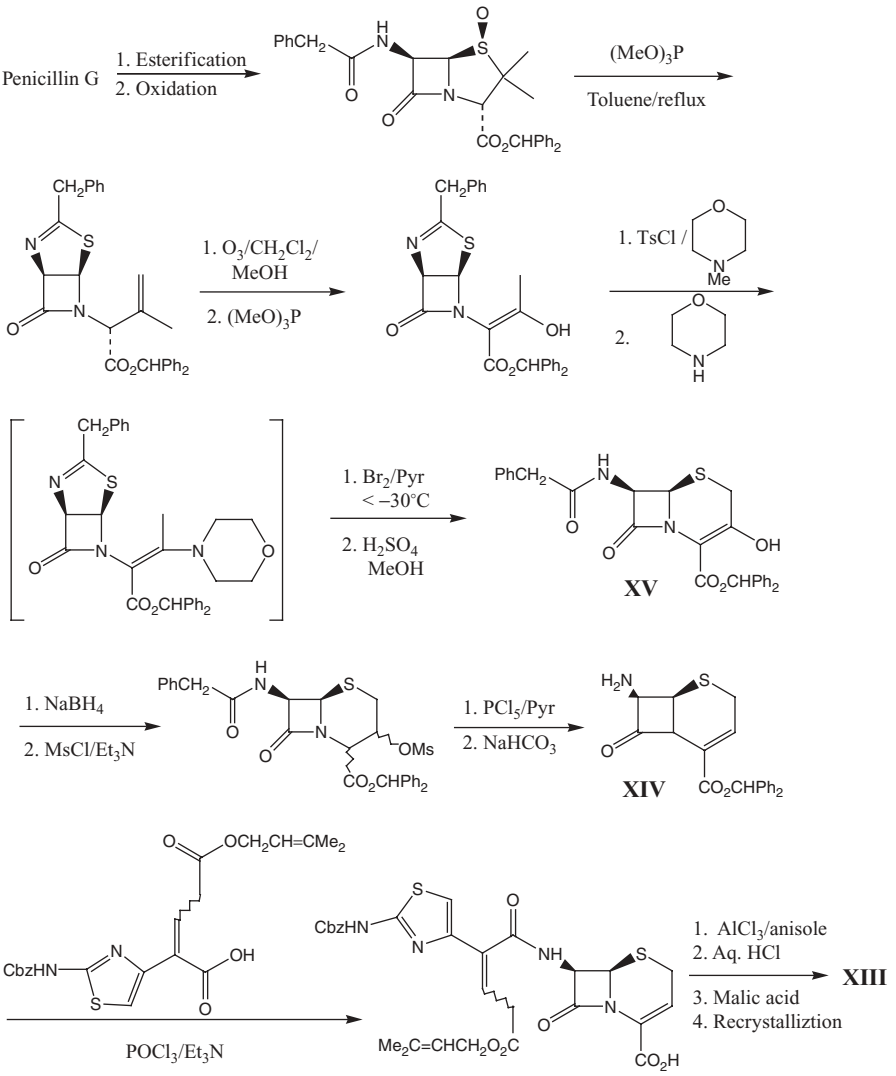


XIII

The contract included a sourcing agreement requiring Schering to purchase the bulk Ceftibuten from Shionogi. Within a year of commencement of the project, the cost of **XIII** had to be raised by Shionogi. This was partly due to Shionogi recognizing the cost realities of their fairly long synthesis and partly due to amortization of their $100 million investment in a Ceftibuten manufacturing plant in Kanegasaki. Our Chemical Development group was called in to help in finding a better (lower cost) process for producing Ceftibuten in collaboration with Shionogi. Clearly, we could do little with the plant depreciation costs unless Shionogi could find a use for the chemical processing equipment that might be idled by moving to a shorter synthesis. The Shionogi process is outlined in Scheme 9.

The thrust of the Chemical Development program was to find a more economical route starting with a low-cost cephalosporin instead of a penicillin. Such an approach would allow us to eliminate the several steps taken by Shionogi to create the cephalosporin ring from their penicillin G starting material (Scheme 9). A further objective was to intersect the Shionogi synthesis by producing the key Shionogi intermediate, diphenylmethyl 7-aminoceph-3-em-4-carboxylate **(XIV)**. By employing precisely the same last few process steps as used by Shionogi, we anticipated eliminating any regulatory concerns regarding new impurities that could arise from a different synthesis.

Our exploratory program, searching for a low-cost cephalosporin starting material, ended with the selection of **II** derived from the process sequence developed by Antibioticos S.p.A., Milan, Italy, starting with fermented cephalosporin C broth (Schemes 1 and 2). To reiterate, Antibioticos had gained considerable commercial advantage by creating and industrializing their Scheme II process to convert cephalosporin C in filtered fermentation broth into the important cephalosporin starting material, 7-amino-3-acetoxymethylceph-3-em-4-carboxylate **(III, 7-ACA)**. By the judicious application of macroreticular resins in the chromatographic purification of cephalosporins in aqueous solution and the use of immobilized enzymes to carry



SCHEME 9. Shionogi synthesis of Ceftibuten.

out efficient transformations without isolating any intermediates, Antibioticos succeeded in industrializing an all aqueous process for the manufacture of 7-ACA (see footnote 8).

Antibioticos agreed to undertake a joint R&D program with Schering to explore chemical synthesis options based on utilizing **II**, preferably in aqueous solution, to produce **XIV**. We reasoned that by continuing to work in water for as long as possible without isolating intermediates, we would maintain Antibioticos' low-cost

processing philosophy. The question then became, What should the new derivative of **II** be?

Initially we evaluated potential routes via the desacetyl derivative of **II**, namely 7-glutaroylamino-3-hydroxymethylceph-3-em-4-carboxylic acid. It was known that several microorganisms deacetylate cephalosporins in high yield. However, evaluation of the literature and review of the production plant requirements to adopt a route to convert 3-hydroxymethyl cephalosporins to 3-H cephalosporins dissuaded us from this option.[28]

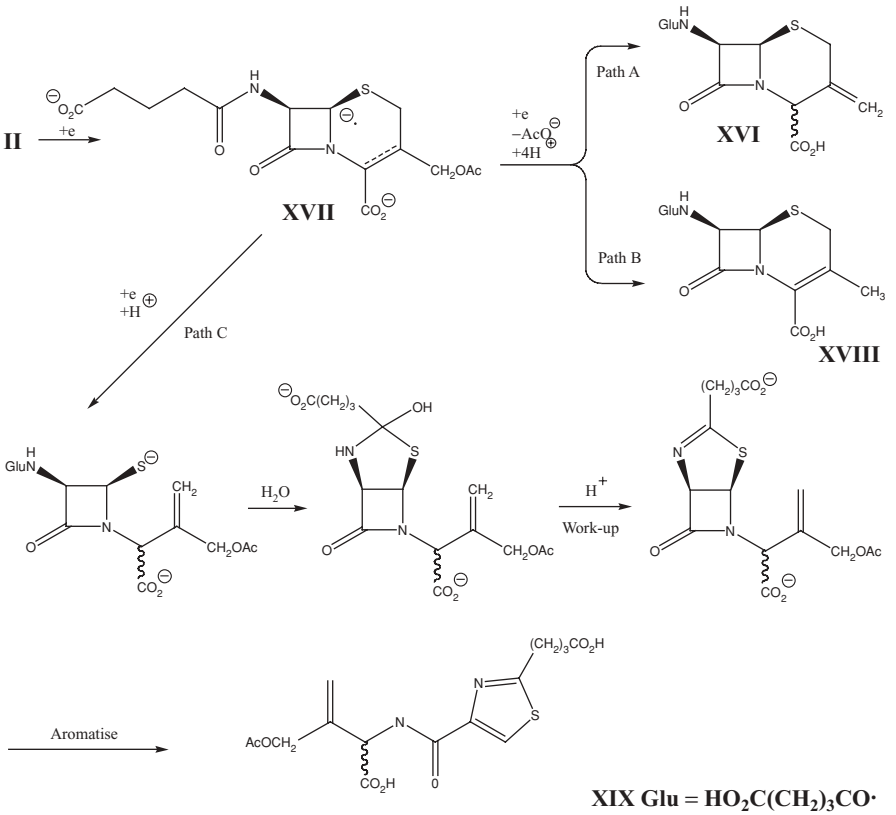
In analyzing the literature, it seemed to me that a shorter and more economical route for the conversion of **II** to **XIV** might be created if we could improve on the 25-year-old electrochemical reduction method for converting 3-acetoxymethylcephalosporins to 3-exomethylene-cephalosporins (e.g., **XVI**) and thence to 3-hydroxycephalosporins **(XV)** via ozonolysis. Shionogi's Dr. Mitsuru Yoshioka and others pointed out that many people, notably at Takeda and Eli Lilly, had published the results of their extensive efforts to achieve such an electrochemical transformation but without commercial success.[29] A review of this literature quickly revealed that the major impediments to commercialization were as follows:

- The use of a mercury cathode
- The low substrate concentration (generally approximately 5 g/liter)
- The low current density
- The inefficiency of the process [the yield of their 3-exomethylene compound was generally <70% with a ring-opened thiazoline as the primary byproduct (up to 30%) and 3-methylcephalosporin **(XVIII)** (up to approximately 7%) as a minor, but difficult to remove, secondary byproduct.

Although the prospects for success appeared daunting, we were encouraged to undertake further evaluation by senior management (Dr. Hal Wolkoff). Our consultant, Professor Sir Derek Barton, suggested that we engage Professor Charles R. Martin [Colorado State University (CSU)] as an electrochemical consultant. Professor Martin's enthusiastic endorsement of our proposed program led us into three years of fruitful collaboration with him through a funding program for several excellent postdoctoral students, Drs. Haiyan Zhang, Vinod Menon, and Piotr Zelenay. Later on as the project developed, we engaged the services of the Electrosynthesis Company (ESC) (primarily Drs. David Genders and Guillermo Zappi, with further input from Dr. Norman Weinberg). They carried out the definitive pilot plant work to validate the

[28] See Bernasconi, E., Genders, D., Lee, J., Longoni, D., Martin, C. R., Menon, V., Roletto, J., Sogli, L., Walker, D., Zappi, G., Zelenay, P., and Zhang, H. *Org. Proc. Res. Dev.*, 2002, **6**, 158.

[29] (a) Ochiai, M., Aki, O., Morimoto, A., Okada, T., and Shimadzu, H. *J. Chem. Soc., Chem. Commun.*, 1972, 800. (b) Ochiai, M., Aki, O., Okada, T., Shinozaki, K., and Asahi, Y., *J. Chem. Soc., Perkin Trans.* I, 1974, 258. (c) Ochiai, M., Aki, O., Morimoto, A., Okada, T., Shinozaki, K., and Asahi, Y., *Tetrahedron Lett.*, 1972, 2341. (d) Ochiai, M., Aki, O., Morimoto, A., Okada, T., Shinozaki, K., Asahi, Y., and Masuda, K. U.S. Patent 3,792,995, 1974 (to Takeda). (e) Hall, D. A. *J. Pharm. Sci.* 1973, **62**, 980. (f) Hall, D. A. U.S. Patent 4,042, 472, 1977 (to Eli Lilly). (g) Hall, D. A., Berry, D. M., and Schneider, C. J. *J. Electroanal. Chem.*, 1977, **80**, 155.

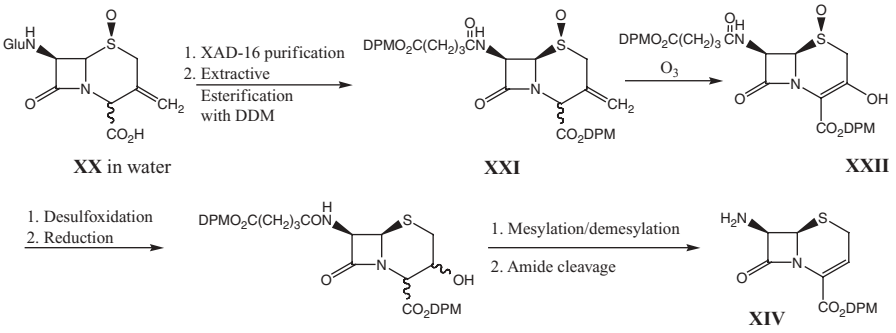


SCHEME 10. Electrochemical reduction of 7-glutaroylamino-3-acetoxymethylceph-3-em-4-carboxylic Acid (II).

laboratory process. Most of the technical work carried out in Schering laboratories was undertaken with great skill and dedication by Dr. Junning Lee. Dr. Lee was also responsible for the day-to-day liaison with all outside laboratory operations (in CSU, Antibioticos and ESC), a task carried out with thoroughness, imagination and enthusiasm.

In beginning work in CSU laboratories, using **II** sourced from Antibioticos, we quickly confirmed the process yield and byproduct profile results obtained by Takeda's Ochiai et al. and Eli Lilly's Hall et al.[29] (Scheme 10).

I reasoned that it may be possible to change the pathway for breakdown of radical ion intermediates such as XVII by either changing the acetoxy leaving group in **II** to one which would leave more readily (e.g., halide, SCN or pyridinium) or by changing the electronic character of the sulfur atom (e.g., by oxidation to the sulfoxide). The use of the sulfoxide of **II** as the electrochemical reduction substrate proved to be most successful, eliminating both of the unwanted pathways B and C in Scheme 10. Work at CSU on the other major practical objectives (increasing

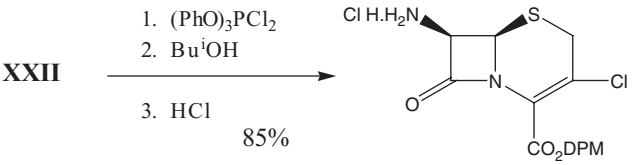


SCHEME 11. Conversion of the sulfoxide of XVI (compound XX) to key intermediate XIV.

the substrate concentration and current density, and finding an alternative to the mercury cathode) enabled us to identify tin as a promising cathode, and to increase the substrate concentration to 50–100 g/liter and the current density to 120–200 mA/cm^2. Finally, ESC (suggestion of Dr. David Genders) showed that a high-surface-area tin mesh cathode would give virtually the same result as mercury, thereby completing the picture and enabling us to create a very efficient process (>90% yield) for the production of the needed intermediate, the sulfoxide of **XVI** (i.e., **XX**) free of previously process-compromising byproducts (the reduced solution contained no **XIX** or **XVIII** sulfoxide). The process was validated by ESC on a pilot plant scale using solutions of **II** sulfoxide obtained from Antibioticos' manufacturing plant in Italy.[30] We were thus able to keep Antibioticos' low-cost processing philosophy going for one more step by carrying out the electrochemical reduction very efficiently in water. The stable sulfoxide **XX** may have been amenable to ozonolysis in water, but we did not test this, preferring instead to undertake the reaction steps to desired intermediate **XIV** according to Scheme 11.

In practical terms, the purification of aqueous solutions of **XX** on Rohm and Haas macroreticular resin XAD-16 proved to be very efficient (95–98% recovery of material with a purity of approximately 95%) and economical to carry out. This chromatographic purification step removes salts (especially phosphates) introduced at earlier processing steps in Antibioticos' plant (Schemes 1 and 2), thereby enabling us to minimize the amount of DDM needed to fully esterify both carboxyl groups of **XX**; 2.3 to 2.5 moles DDM per mole of **XX** generally proved sufficient.[31] Although DDM is a relatively stable molecule (see footnote 20), its separate preparation does introduce some safety concerns. In practical terms, it should be possible to prepare

[30]Chai, D., Genders, D., Weinberg, N., Zappi, G., Bernasconi, E., Lee, J., Roletto, J., Sogli, L., Walker, D., Martin, C. R., Menon, V., Zelenay, P., and Zhang, H. *Org. Process Res. Dev.*, 2002, **6**, 178.
[31]Bernasconi, E., Lee, J., Sogli, L., and Walker, D. *Org. Proc. Res. Dev.*, 2002, 6, 169.

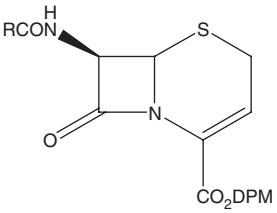


SCHEME 12. Outline for a process for the manufacture of a key intermediate for Cefaclor.

and use DDM in situ,[32] but this option was not pursued in this initial phase of the development of our ceftibuten process.

The ozonolysis of **XXI** was straightforward and very high yielding. The indications were that this step could have been carried out at a much higher temperature than the –65°C temperature we used, since the substrate **XXI** was already in the sulfoxide form.

The sodium borohydride reduction of the C-3 enol **XXII** did not give good yields, necessitating that the sulfoxide be first reduced to the sulfide before reduction. Several desulfoxidation reagents were used successfully, notably Lawesson's reagent, acyl chloride/iodide, and PCl_3. From this point we intersected the established Shionogi chemistry, the only query being whether the trace impurity **(XXIIIa)** in the key intermediate **XIV** prepared by the electrochemically based route would be as readily removed as **XXIIIb** produced in the Shionogi synthesis (Scheme 9).



XXIIIa $(C_6H_5)_2CHO_2C(CH_2)_3^{\bullet}$, DPM = $(C_6H_5)_2CH^{\bullet}$

XXIIIb R = $C_6H_5CH_2^{\bullet}$, DPM = $(C_6H_5)_2CH^{\bullet}$

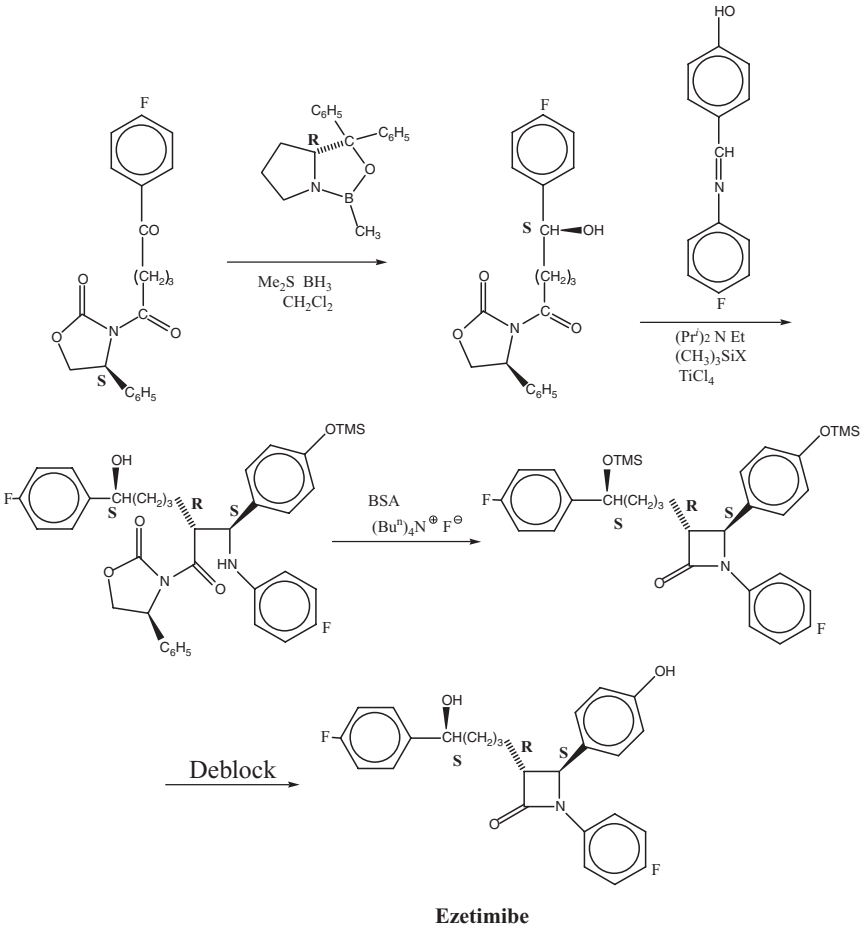
It was, and the ceftibuten produced using the electrochemical route proved to be of equivalent quality to that produced by Shionogi.

Despite the technical success, the process was a commercial failure in that it was never adopted by Shionogi.[33]

We went on to show that the electrochemical reduction process afforded an elegant route to a key cefaclor intermediate diphenylmethyl 7-amino-3-chloroceph-4-carboxylate (Scheme 12). (see footnote 31).

[32]Bywood, R., Gallagher, G., Sharma, G. K., and Walker, D. *J. Chem. Soc, Perkin Trans. I*, 1975, 2019.

[33]Despite requiring only approximately $1.5 million in capital investment in electrochemical reduction equipment, such expenditure was not considered worthwhile because the capacity of Shionogi's existing ceftibuten plant was considered adequate for future market projections, and the new process would require additional resources for registration with the FDA and other agencies. In addition, Shionogi was not convinced by our savings projections on the cost of goods. We discussed this matter many times over lunch in the Gas Building in Osaka. When I asked for a change of lunch venue to the Electricity Building (I did not know if one existed), Eichii Yamaguchi only smiled!



Ezetimibe

SCHEME 13. Schering–Plough synthesis[35] of the β-lactam Ezetimibe.

The project slowly died, a suitable analogy being the last passages of Haydn's Farewell Symphony.[34]

This excursion covers scientific "wanderings" through the mostly conventional β-lactam antibiotic field—we did not participate in the even more exotic adventures in the carbapenem field, which is undoubtedly worthy of historical review.

β-LACTAM ADDENDUM

The β-lactam antibiotics' field continues to employ thousands of scientists worldwide, if not the tens of thousands during its heyday in the 1960s through the 1980s.

[34] In which the musicians each snuff out the candle over their music stands when they complete their piece! By the time I finished, even the audience had left!!!!

Undoubtedly, further β-lactam antibiotics will be marketed to continue what is widely perceived as a historic 70-year contribution to the welfare of mankind.

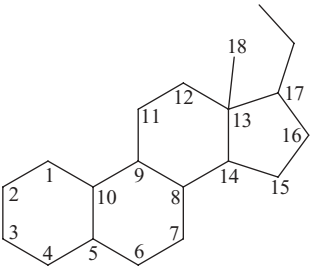
Nor are the contributions to be made by β-lactam structures to the pharmaceuticals field over. The extraordinary developments of recent years in cholesterol absorption inhibitors (CAIs) based on the β-lactam ring deserve some mention, especially since Dr. T. K. Thiruvengadam in our chemical process development organization in Schering–Plough is the brilliant architect of one of the patented syntheses of this novel class of CAIs. His synthesis[35] of Ezetimibe (Zetia), outlined in Scheme 13, serves to (a) introduce this new direction in the development of novel β-lactam medicinals and (b) end this excursion in the field of β-lactams.

PART II: EXCURSIONS IN THE STEROID FIELD

This section describes the early history leading to creation of the steroid industry, provides an account of key processes used in the manufacture of the oral contraceptives and anti-inflammatories currently marketed in the United States and highlights the creation of diverse biological activities by molecular manipulation of the steroid molecule. The section concludes with an outline of a few of the synthesis challenges faced and overcome in the manufacture of betamethasone anti-inflammatories.

Introduction

Over the course of history, the ancients discovered extraordinarily diverse medicinal and poison applications for extracts from the natural world. In the last hundred years, most of the active principles of these extracts have been isolated and identified and many shown to be structural variants of the steroid molecule **(I)**.

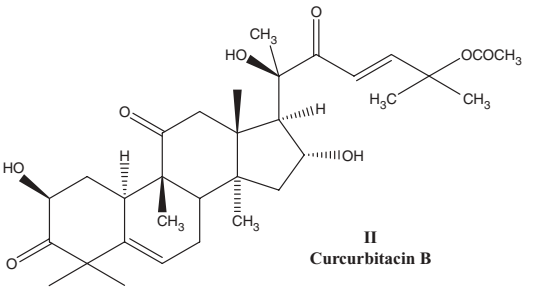


I

The cucurbitacins **(II)**, found in plants of the *Cucurbitaceae* family (gourds, cucumbers, etc.) and also in *Begoniaceae*, *Euphorbaceae*, and others, have been used

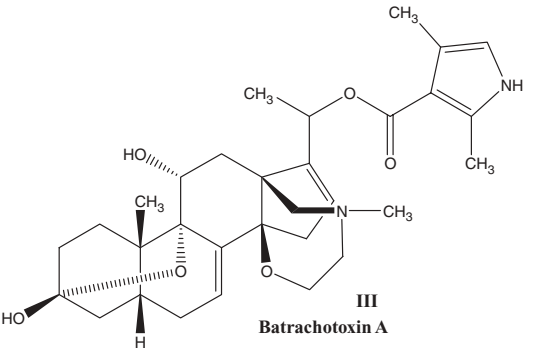
[35]Thiruvengadam, T. K., Fu, X., Tann, C.-H., McAllister, T. L., Chiu, J. S., and Colon, C. U.S. Patent 6,207,822, 2001 (to Schering Corp.).

as emetics, narcotics, antimalarials, and anthelmintics.



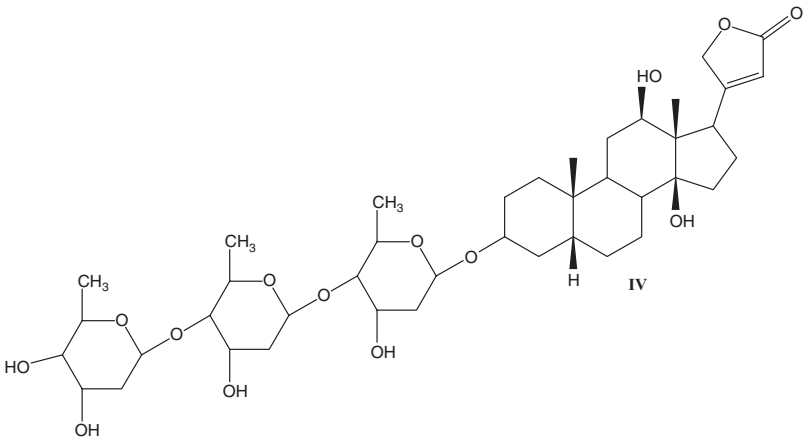
II
Curcurbitacin B

Batrachotoxin A **(III)**, just one of many steroidal alkaloids, is one of the most lethal substances known ($LD_{50} = 2\mu g/kg$ subcutaneously in mice). It is found in the skin secretions of the brightly colored tropical frog *Phyllobates aurotaenia* and is used by Colombian Indians to prepare poison darts.



III
Batrachotoxin A

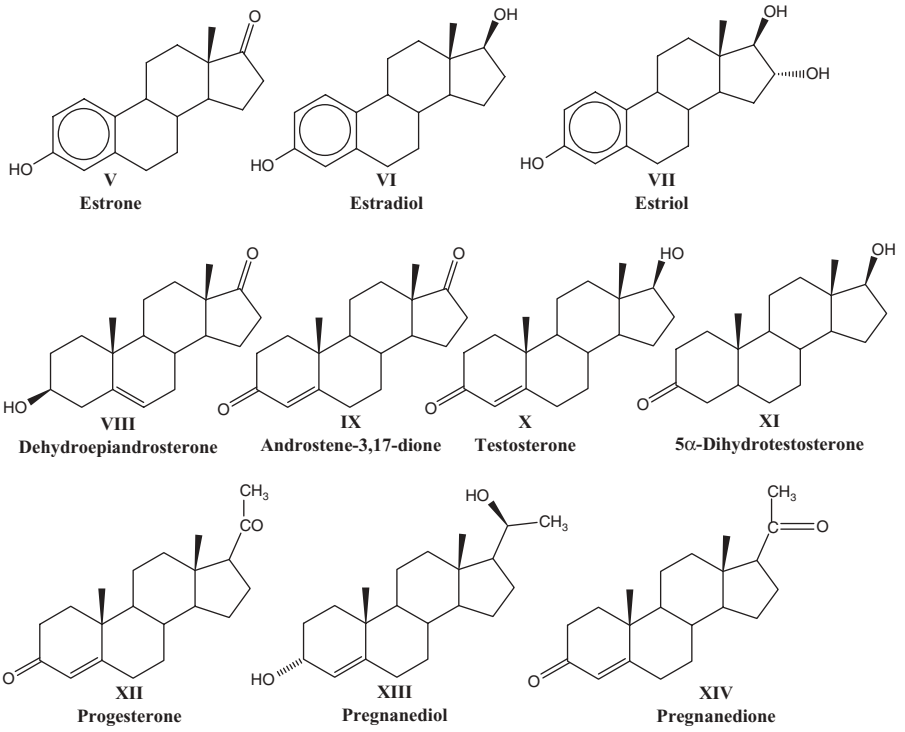
Digoxin **(IV)** is in widespread medical use today as a cardiotonic. It is extracted from the Foxglove, *Digitalis lanata*.



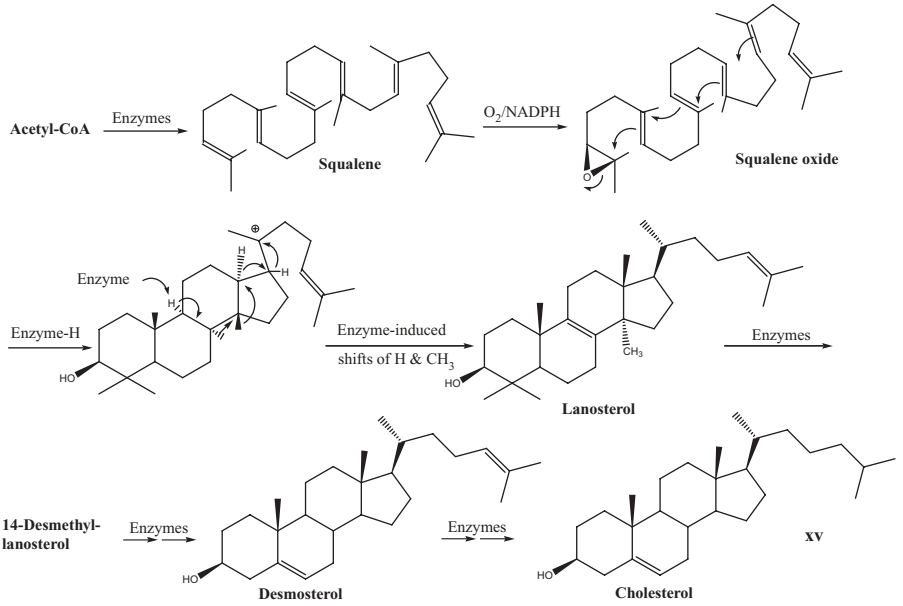
IV

The steroid molecules **II–IV** illustrate the diverse biological activity which nature has produced through biosynthetic processes. During the 20th century, man gained a greater appreciation of the biological activity associated with the steroid molecule and created an extraordinary range of new activities through structural manipulation (see later). It is pertinent to add here that scientific investigation of biological processes reached across many other fields including amino acids, peptides and proteins, carbohydrates, alkaloids, and so on.

As knowledge grew, earlier more empirical approaches to treating disease gave way to a more rational effort directed at understanding the biochemical processes taking place in the human body. The isolation and purification of biologically active molecules from human and other animal organs enabled scientists and physicians to undertake painstaking degradative studies to determine their structure and begin to piece together structure–activity relationships. In regard to steroids, in the 1920s and 1930s work on the sex hormones secreted by adrenal glands, gonads, and placenta identified the principal estrogens **(V–VII)** and androgens **(VIII–XI)**. Studies on the ovarian organs identified the gestagens, with the principal one being progesterone **(XII)** secreted during the menstrual cycle. Also, urine from pregnant animals was found to contain (in addition to the estrogens) several pregnanes, notably pregnanediol **(XIII)**, pregnanedione **(XIV)**, and related compounds.



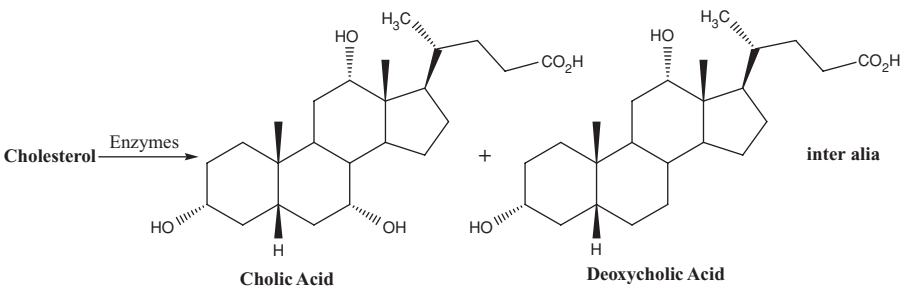
Early in the 20th century, and continuing today, exploration of the mechanisms of biochemical transformation occurring in man and other animals became an important



SCHEME 1. The biosynthesis of cholesterol.

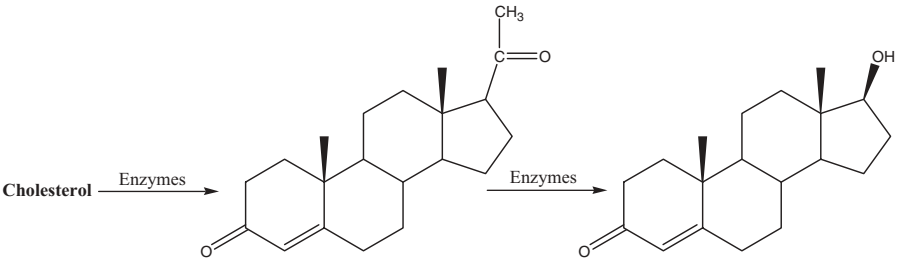
branch of academic work. Understanding the pathways by which the steroid molecule is assembled provided a humbling appreciation of nature's supreme elegance in molecular assembly (Scheme 1). The biosynthesis of lanosterol and cholesterol attracted the most attention. Many hypotheses proposed by major scientists (Robinson, Woodward, Cornforth, Eschenmoser, Arigoni, and Stork) stimulated work that culminated in a series of papers defining the steps occurring in cholesterol biosynthesis.[36]

The further degradation of cholesterol in the liver gives the bile acids:



[36](a) Stork, G., and Burgstahler, A. W. *J. Am.Chem.Soc*., 1955, **77**, 5068. (b) Eschenmoser, A., Ruzicka, L., Jeger, O., and Arigoni, D. *Helv. Chim. Acta*, 1955, **38**, 1890. (c) Van Tamelen, E. E., Willett, J. D., Clayton, R. B., and Lord, K. E. *J. Am. Chem. Soc*., 1966, **88**, 4572. (d) Van Tamelen, E. E., Leopold, E. J., Marson, S. A., and Waespe, H. R. *J. Am. Chem. Soc*., 1982, **104**, 6479. (e) Van Tamelen, E. E. *J. Am. Chem. Soc*., 1982, **104**, 6480.

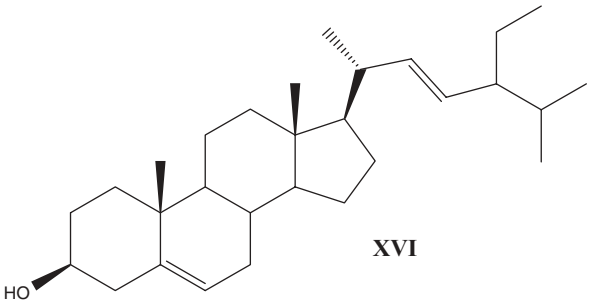
Ox bile, which contains cholic acid as its principal constituent, provided one of the earliest mammalian sources of steroid raw materials for the commercial manufacture of the androgens. In nature, cholesterol itself is the mammalian precursor of the androgens, the biosynthesis passing through progesterone **(XII).**



XII
Progesterone

X
Testosterone

In the 1930s, recognition of the role progesterone was playing in the development of a fetus and in inhibiting ovulation, thereby preventing pregnancy, stimulated only weak commercial interest. The main reason lay in the great difficulty and astronomical cost of producing progesterone. Early supplies were made from pregnanediol (ex mammalian pregnancy urine)[37] and stigmasterol (**XVI**, ex soy and calabar beans).[38]

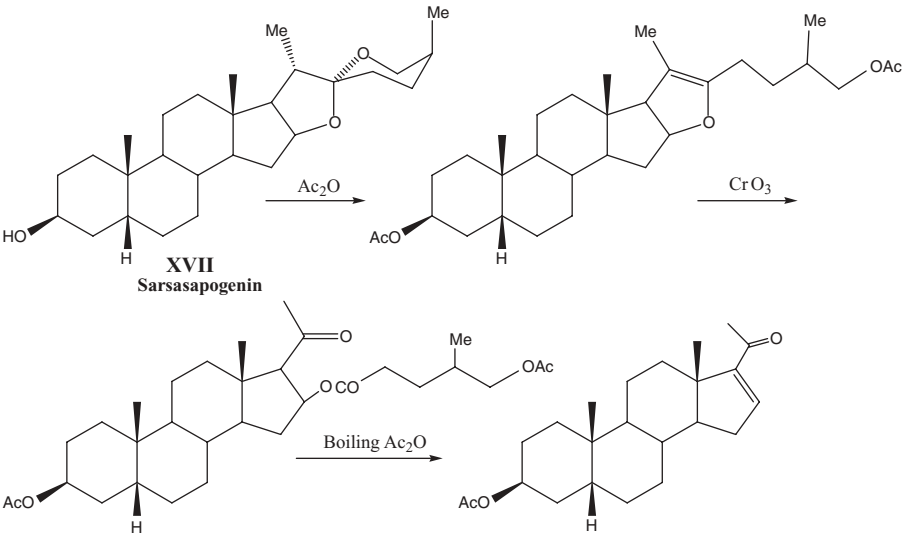


XVI

Some progesterone was also produced from cholic acid[39] and some from cholesterol, available from nonsaponifiable animal matter, including wool fat. However, at the time, nature's exquisite enzyme-mediated transformation of the C-17 side chain of cholesterol could not be reproduced or mimicked using chemical means. Oxidative techniques, including oxidative degradation, were widely employed in producing mixtures of steroids from which progesterone was recovered in low yield. The work needed can only be described as heroic. As a result, the cost of progesterone was commercially prohibitive.

It took several years and a maverick chemist with new ideas on other steroid sources, and a towering commitment to prove them, to achieve a breakthrough. In

[37] Butenandt, A., and Schmidt, J. *Berichte*, 1943, **67**, 1901.
[38] Butenandt, A., Westphal, U., and Cobler, H. *Berichte*, 1934, **67**, 1611, 1903, and 2085.
[39] Zondek, B., and Bergman, E. U.S. Patent 2,314,185 (1943).



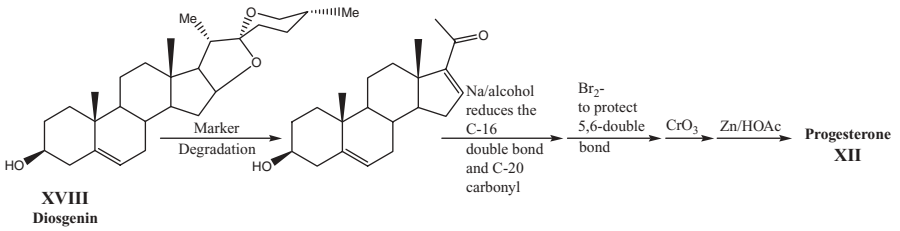
SCHEME 2. The Marker degradation[41a,b] of sarsasapogenin.

1938, Russell Marker, working at State College, Pennsylvania, with funding from the Parke Davis Co., proposed an alternative formula[40(a)] for the steroid sapogenin, sarsasapogenin (**XVII**, isolated from the Sarsaparilla root by hydrolysis of the C-3 glycosidic side chain), to the structures proposed by Power[40(b)] and Jacobs.[40(c,d)]

Based on his new structure, Marker reasoned that the C-17 side chain should be much more amenable to chemical degradation than that of cholesterol. He went on to prove his hypothesis creating the "Marker degradation," a process still in commercial use. The Marker degradation is outlined in Scheme 2. Unfortunately, at the time, obtaining sarsasapogenin proved an expensive proposition leading Marker to search for another plant source of steroids of the sapogenin class. This soon led him to identify a wild Mexican yam of the Dioscoreaceae family (known as cabeza de negro in Mexico), which proved to be a useful source of diosgenin **(XVIII)**. [Later (1949) a yam (barbasco) with a higher diosgenin content (up to 5% on a dried basis) was discovered and commercialized.] Marker collected cabeza de negro roots in Veracruz state which were "lost" in transport. One 50-pound root was recovered by dint of bribing a policeman and surreptitiously spirited back to Pennsylvania where he used his degradation process[41(c)] to access the intermediate needed to refine his synthesis of progesterone **(XII)** – (Scheme 3).

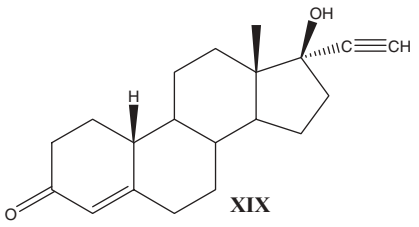
[40](a) Marker, R. E., and Rohrmann, E. *J. Am. Chem. Soc*., 1939, **61**, 846. (b) Power, F. B., and Salway, A. H. *J. Chem. Soc*., 1914, **105**, 201. (c) Jacobs, W. A., and Simpson, J. C. E. *J. Biol. Chem*. 1934, **105**, 501. (d) *idem ibid*, 1935, **109**, 573.

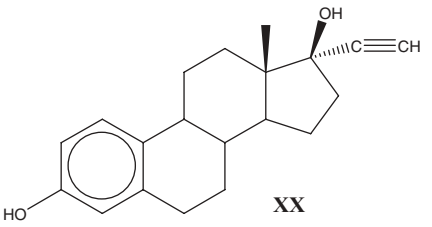
[41](a) Marker, R. E., and Rohrmann, E. *J. Am. Chem. Soc*., 1939, **61**, 3592. (b) *idem ibid*., 1940, **62**, 518, 521, **896**, and 898. (c) Marker, R. E., Tsukamoto, T., and Turner, D. L. *J. Am. Chem. Soc*., 1940, **62**, 2525.



SCHEME 3. Marker process for the manufacture of progesterone.

Although the sponsor of Marker's research at State College obtained U.S.-only patents on his work,[42] Marker was unable to get support from the pharmaceutical industry to undertake the commercialization of his process for the manufacture of progesterone. He eventually found backing in Mexico City, founded Syntex, and began production in 1944. Following a financial dispute with his backers in 1945, he quit, taking his process secrets with him. Syntex hired Dr. George Rosenkranz, who was able to rediscover the process and restart production in a few months. Rosenkranz subsequently was the driving force in building Syntex into a scientifically powerful steroid research company in Mexico City. Syntex was responsible for the discovery and development of some of the most important progestogens, which, when mixed with an estrogen, were marketed as oral contraceptives—for example, structures **XIX** and **XX**. The 3-methyl ether of estrogen **XX**, Mestranol, is also used in some formulations. Indeed a Mestranol and Norethinodrel [the 5(10) double-bond isomer of **XIX**] formulation was the first, albeit short-lived, oral contraceptive on the market (Enovid, G.D. Searle).

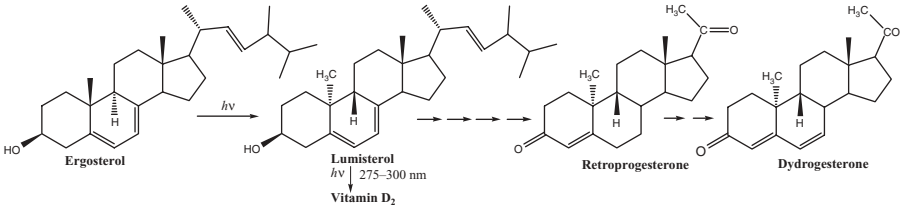




Several other companies were quickly attracted into the field, notably G. D. Searle, Roussel–UCLAF, Wyeth, Philips–Duphar, Organon, Upjohn, and Merck, each pursuing the synthesis of new molecules. The most important consideration was to find novel patentable structures derived from their positions in their chosen starting raw

[42](a) Marker, R. E. U. S. Patent 2,223,377, 1940 (to Parke Davis & Co.). (b) Marker, R. E. U. S. Patent 2,352,852, 1944 (to Parke Davis & Co.) Marker's failure was also despite his prescient observation that Mexican women had been eating yams of the *Dioscorea* genus for centuries for contraception.

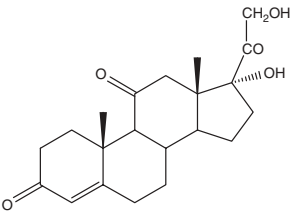
materials. Roussel–UCLAF and Merck founded their work on the bile acids. Ingeniously, Philips–Duphar found a niche based on lumisterol, a so-called retrosteroid prepared by UV irradiation of a benzene–alcohol solution of ergosterol, the most important of the provitamins D. Ergosterol was itself obtained from yeast. Ultraviolet irradiation of ergosterol inverts C-10 methyl and C-9H.[43]



Dydrogesterone[44] still has a small market today. Wyeth, being a later starter, founded its business on total synthesis (see later).

Other producers of steroid contraceptives started with diosgenin, tigogenin (a 5α, 6-dihydroderivative of diosgenin) or hecogenin (a 12-keto derivative of tigogenin). The last two compounds are both obtained from numerous species of the Agave plant. More recently, sitosterol (from the soy bean industry) and cholesterol have become attractive as starting raw materials, largely due to improvements in removing the C-17 side chain using methods that create a 17-carbonyl functionality.

The contraceptive field received the most attention in the 1940s and early 1950s. A second major development in the steroid field was triggered by the 1949 announcement by Hench et al.[45] at the Mayo Clinic that cortisone greatly relieved the ravages of rheumatoid arthritis.



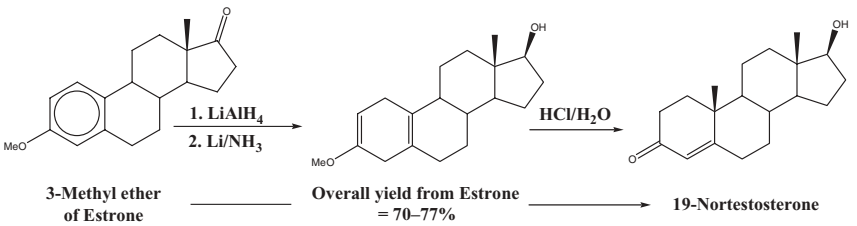
Cortisone

Merck and Co. had produced the cortisone used by Hench in research quantities using a 36-step synthesis from bile acids. Hench's revelation rapidly escalated interest in steroidal anti-inflammatories. A brief outline of ongoing developments in each of these fields follows.

[43] Askew, F. A., Bourdillon, R. B., Bruce, H. M., Callow, R. K., Philpot, J. St. L. and Webster, T. A. *Proc. Roy. Soc. (London)*, 1932, **B109**, 488.

[44] (a) Reerink, E. H., Westerhof, P., and Scholer, H. F. L., U.S. Patent 3,198,792,1962 (to North American Philips). (b) Westerhof, P. and Reerink, E. H., *Rec. Trav. Chem.*, 1960, **79**, 771.

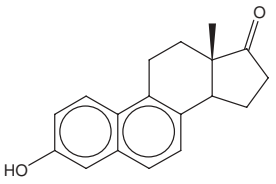
[45] Hench, P. H., Kendall, E. C., Slocumb, C. H., and Polley, H. F., *Ann. Rheum. Dis.*, 1949, **8**, 97.



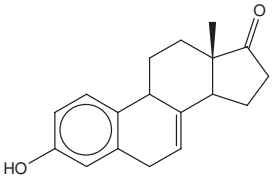
SCHEME 4. Conversion of the 3-methyl ether of estrone to 19-nortestosterone.

Contraceptives. The realization that progesterone was only weakly active when administered orally, stimulated vigorous programs both to overcome this disadvantage and also to find more active progestational steroids.[46] One of the earliest successes was the discovery[47] by the Syntex group that 19-norprogesterone was four to eight times more active than progesterone as a progestational hormone. Shortly thereafter, this observation led to the identification of 19-nor-17α-ethinyltestosterone (**XIX**, Norethindrone[48]).

The key chemical step in the creation of starting materials for the production of the 19-nor series of compounds resulted from the pioneering work of Birch and Mukherji[49(a)] who reduced the 3-glyceryl ether of estradiol to 19-nortestosterone with sodium or potassium. Wilds and Nelson[49(b)] improved the original procedure and created the basis of a commercial process by utilizing the 3-methyl ether of estrone and reducing the aromatic ring using lithium and liquid ammonia (Scheme 4).



XXI



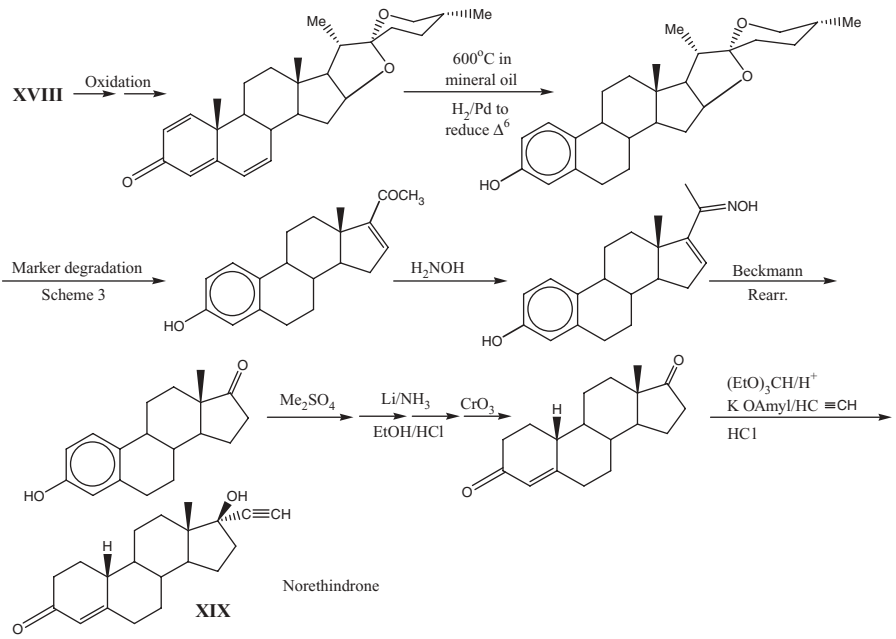
XXII

[46]However, progesterone, in a finely micronized form, is marketed (Prometrium) in large-dose capsules (100 mg and 200 mg) for the treatment of some menstrual conditions. Micronization increases the bioavailability of insoluble APIs (see Chemical Engineering).

[47](a) Miramontes, L., Rosenkrantz, G., and Djerassi, C. *J. Am. Chem. Soc*., 1951, **73**, 3540. (b) *idem ibid*., 1953, **75**, 4440. (c) Tullner, W. W., and Hertz, R., *J. Clin. Endocrinology Metab*., 1952, **12**, 916. (d) Interestingly, early work by Dirscherl et al. (Dirscherl, W., *Z. Physiol. Chem*., 1936, **239**, 53 and Dirscherl, W., Kraus, J., and Voss, H. E., *Z. Physiol. Chem*. 1936, **241**, 1) demonstrated that hydrogenated products of estrone (i.e.19-nor steroids) possessed some androgenic activity. Marker, R. E., and Rohrmann, E. *J. Am. Chem. Soc*., 1940, **62**, 73 also described the hydrogenation of estrone and the preparation of relatives of 19-nor-testosterone and 19-nor-androstenedione.

[48]Djerassi, C., Miramontes, L., Rosenkranz, G., and Sondheimer, F. *J. Am. Chem. Soc*., 1954, **76**, 4092. Almost simultaneously, the G. D. Searle group identified Norethynodrel [the 5(10) double-bond isomer of Norethindrone]: Colton, F. B. U.S. Patents, 2,691,028, 1954 and 2,725,389, 1955 (to G. D. Searle).

[49](a) Birch, A. J., and Mukherji, S. M. *J. Chem. Soc*., 1949, 2531. (b) Wilds, A. L., and Nelson, N. A. *J. Am. Chem. Soc*., 1953, **75**, 5366.



SCHEME 5. Outline of Syntex Process for the Manufacture of Norethindrone.

In the early days, estrone was recovered from the urine of pregnant mares, but this source proved unattractive because of the difficulty of separating it from related compounds, notably equilenin **(XXI)** and equilin **(XXII)**.

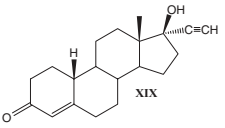
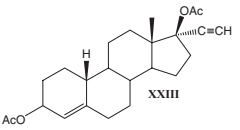
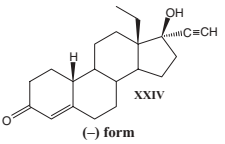
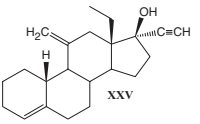
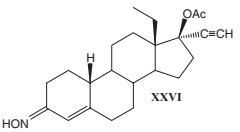
Later the estrone produced for commercial purposes was obtained from diosgenin. Diosgenin was first oxidized to its 1,4,6-triene-3-one derivative, which was aromatized by pyrolysis at 500–600°C,[50] subjected to the Marker degradation and the 17-acetyl group removed by Beckmann rearrangement of the 20-oxime. The overall Syntex process[51] for the manufacture of Norethindrone from diosgenin **(XVIII)** is outlined in Scheme 5.

Today, the major oral contraceptives on the market in the United States are mixtures of the estrogen, 17α-ethinylestradiol **(XX)** and one of the progestogens listed in Table 1. The first two progestogens have also been formulated with mestranol, the 3-methyl ether of **XX**.

[50]The aromatization reaction was first applied to steroids by Inhoffen, H. H., U.S. Patent 2,361,847, 1944 (to Schering Corp.) and later greatly improved by Hershberg, E. B., Rubin, M. and Schwenk, E. *J. Org. Chem.* 1950, **15**, 292. The Hershberg work provided the foundation for the industrial process.

[51]Sondheimer, F., Neumann, F., Ringold, H. J., and Rosenkranz, G. *J. Am. Chem. Soc*., 1954, **76**, 2230. (b) Rosenkranz, G., Mancera, O., Sondheimer, F., and Djerassi, C. *J. Org. Chem*., 1956, **21**, 520. (c) Djerassi, C., Miramontes, L., and Rosenkranz, G. U.S. Patent 2,744,122, 1956 (to Syntex).

TABLE 1. Progestogen Components of Most-Prescribed Oral Contraceptives in the United States

Compound	Name	Mixture Name[a]	Original Company
	19-Nor-17α-ethinyltestosterone (Norethindrone)	Brevicon	Syntex[13]
	Ethynodiol diacetate	Demulen	G. D. Searle[52]
	Norgestrel	Alesse	Wyeth[53]
	Desogestrel	Desogen	Organon[54]
	Norgestimate	Ortho Cyclen	Ortho[55]

Source: *Physicians Desk Reference*, 55th edition, Medical Economics Company, Inc. Montvale, New Jersey, 2001.

[a]Many other market names exist for the mixture, depending on the formulation, cross-licensing, and so on.

It is pertinent to note that market forces eventually favored the 19-nor progestogens of Table 1 over the 19-methylprogestogens, at least in the United States.[56]

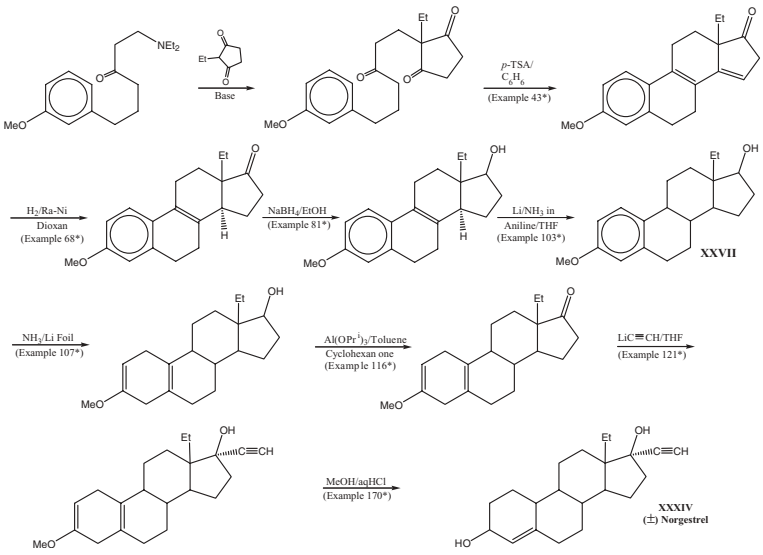
[52]Colton, F. B. U.S. Patent 2,843,609, 1958 (to G.D. Searle).

[53](a) Smith, H. Belgian Patent 623,844,1963 (*Chem. Abstr*., 1964, 61, 4427). (b) Smith, H., Hughes, G. H., Douglas, G. H., Wendt, G. R., Buzby, G. C., Edgren, R. A., Fisher, J., Foell, T., Gadsby, B., Hartley, D., Herbst, D., Jansen, A. B. A., Ledig, K., McLoughlin, B. J., McMenamin, J., Pattison, T. W., Phillips, P. C., Rees, R., Siddall, J., Siuda, J., Smith, L. L., Tokolics, J., and Watson, J. H. P. *J. Chem. Soc*., 1964, 4472. (c) Hughes, G. H., and Smith, H. U.S. Patent 3,959,322, 1976 (to Herchel Smith)—patent original priority date August 1964!

[54](a) van den Broek, A. J.; van Bokhoven, C., Hobbelen, P. M. J., and Leemhuis, J. *Rec. Trav. Chim*. 1975, **94**, 35. (b) van den Broek, A. J. U.S. Patent 3,927,046, 1975 (to Akzona, Inc.).

[55]Schroff, A. P. U.S. Patent 4,027,019, 1977 (to Ortho).

[56]Several 19-methyl compounds, derived from plant starting materials, were marketed in combination with an estrogen such as **XX**. Some of the best known were Provest (Medroxyprogesterone



*Example numbers are from U.S. Patent 3,959,322,1976 [see footnote 53 (c)].

SCHEME 6. Outline of Smith and Hughes' (Wyeth's) synthesis of Norgestrel (see footnote 53).

The early successes of the Syntex group in producing orally active contraceptives from the 19-nor steroids attracted several companies into the field. All the competing compounds introduced by the rival companies also carry the 17β-hydroxy-17α-ethinyl moiety and owe their marketing to their patented distinctions from the original Norethindrone. Probably the most heroic achievement in the 19-norsteroid field resulted from the work of Dr. Herchel Smith (University of Manchester and later Wyeth Laboratories, Inc.), who, with his co-workers and particularly Dr. Gordon Hughes, pioneered the commercialization of steroid manufacture by total synthesis. Dr. Smith was uniquely placed in Manchester being a protégé of Professor A. J. Birch, whose Birch reduction process[49(a)] instigated the work leading to the Syntex process for the manufacture of Norethindrone.

Total synthesis, although disadvantageous in requiring optical resolution to create the most biologically active compounds, has the advantage of enabling a wide range of structural changes to be made which could not be easily done starting with naturally occurring steroids. Total synthesis thus increased the opportunity to create enhanced biological activity and, very important, to create an essential patent portfolio. Dr. Smith brilliantly and opportunistically rose to the occasion with a synthesis of the progestogen, Norgestrel **(XXIV)**, marketed by Wyeth as Alesse. An outline of this synthesis is given in Scheme 6.

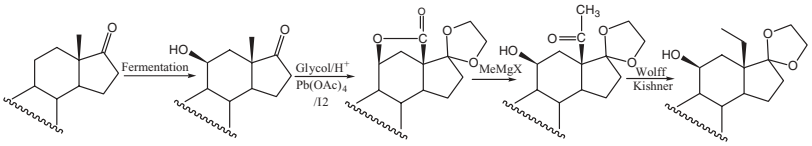
acetate, or 17α-acetoxy-6α-methyl-progesterone), Gestafortin (Chlormadinone acetate, or 17α-acetoxy-6-chloro-6,7-dehydroprogesterone), and Ervonum (Megestrol acetate, or 17α-acetoxy-6,7-dehydro-6-methyl-progesterone).

From the outset, Dr. Smith and his large team of co-workers[57] focused on alternatives to the C-13 methyl group in natural steroids and on introducing the acetylene moiety at C-17 following the leads of G. D. Searle and Syntex (see footnote 48).

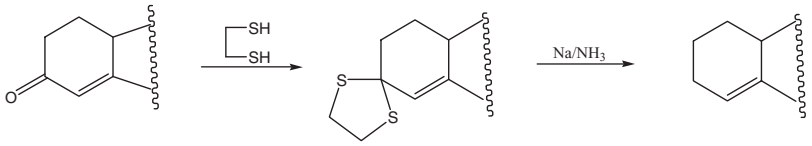
In producing the (−) form of Norgestrel optical resolutions were carried out as early in the synthesis as possible, with such as compound **XXVII** being a favored starting point. Both chemical resolution (of the hemisuccinate[58]) and dehydrogenation methods[59] were used for resolution.

A decade later, Organon workers discovered the 13β-ethyl compound, Desogestrel **XXV** (see footnote 54). This molecule is interesting in demonstrating that significant structural change can be made without affecting progestogen activity (**XXV** lacks a 3-oxo substituent and carries an 11-exomethylene group; however, the biologically active metabolite is the 3-oxo compound). Because of its unique structural features, the Desogestrel molecule is more costly to produce than others in Table 1. Starting materials are such as Birch's 19-nortestosterone or Smith and Hughes' 13-ethyl analogue of 3-0-methyl estradiol **(XXVII)**. In order to introduce Desogestrel's unique features, the Organon workers employed both standard and some novel chemistry.

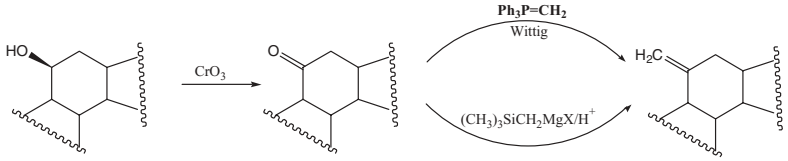
(a) Conversion of 10-methyl to 10-ethyl:



(b) Conversion of 3-keto to 3-CH_2:



(c) Conversion of 11β-HO to 3-exomethylene:



[57] Smith, H., Hughes, G. A., Douglas, G. H., Hartley, D., McLoughlin, B. J., Siddall, J. B., Wendt, G. R., Buzby, G. C., Herbst, D. R., Ledig, K. W., McMenamin, J. R., Pattison, T. W., Suida, J., Tokolics, J., Edgren, R. A., Jansen, A. B. A., Gadsby, B., Watson, D. H. R., and Phillips, P. C. *Experientia*, 1963, **19**, 394.

[58] Buzby, G. C., Hartley, D., Hughes, G. A., Smith, H., Gadsby, B. W., and Jansen, A. B. A. *J. Med. Chem.*, 1963, **10**, 199.

[59] Smith, L. L., Greenspan, G., Rees, R., Foell, T., and Alburn, H. E. *J. Org. Chem.* 1966, **31**, 2512.

Those seeking more depth on the total synthesis of steroids are referred to the very informative book by Blickenstaff et al.[60]

In concluding this section, it is pertinent to point out that improvements made in the total synthesis and optical resolution of steroids over the last three decades have greatly reduced the costs of manufacturing all the steroids in Table 1 made via the total synthesis route. Today, the cost of most steroids made by the total synthesis route are comparable with the costs of those produced from plant sources.

Anti-inflammatories. Identification of the field as worthy of commercial pursuit arose from findings in academia, beginning in the 1930s, that extracts from the adrenal glands possessed hormone activity. One of these, found by Kendall (Mayo Foundation), was known as Kendall's compound E (later cortisone). Several industrial organizations, notably Organon, Upjohn, Schering A.G., and Merck, sensed commercial potential and were helpful to academia in producing extracts from animal organs using their large-scale equipment. In 1942, the National Research Council (NRC) in the United States sponsored a research program with the visionary objective of finding a method for the synthesis of enough cortisone to evaluate its possible application to medicine. Although the war hampered European collaboration, a corresponding program was also going on in the ETH in Zurich under the guidance of Professor Tadeus Reichstein. The NRC program led to the finding by Hench and co-workers that cortisone was effective in relieving the symptoms of arthritis (see footnote 45). As already indicated, the bile acids were the major source of raw materials for the cortisone supplied to Hench by Merck. Immediately following Hench's revelations, Roussel in Paris and Schering in New Jersey[61] took out licenses from the Research Corporation (set up to manage the intellectual property generated during NRC studies) to utilize cholic acids in their own programs for the production of cortisone.

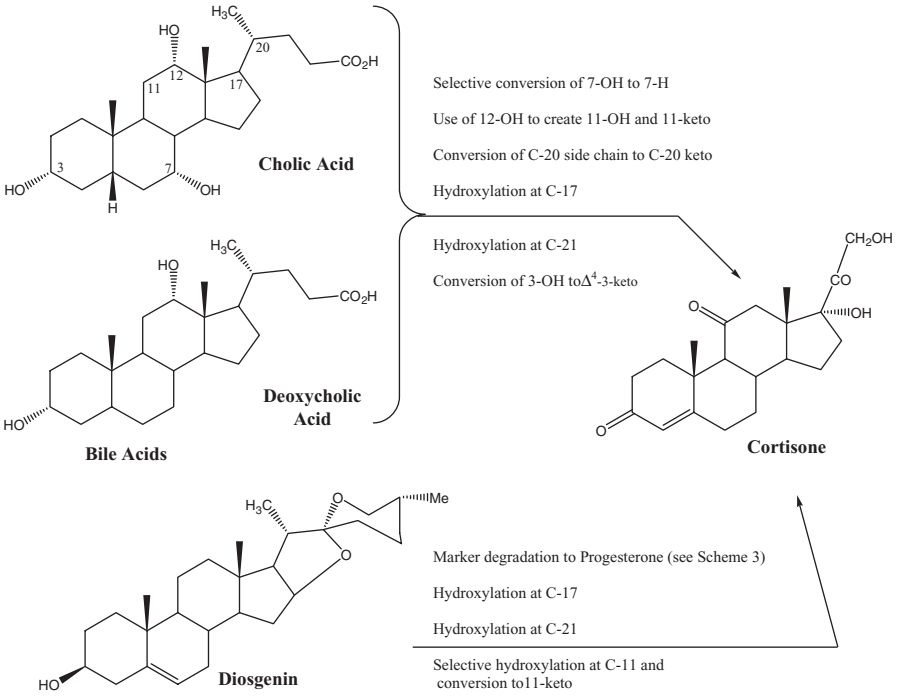
Bile acids were the logical starting point for the manufacture of cortisone in the late 1940s, but steroids from plant sources, and particularly diosgenin ex yams, were gaining credibility as time passed. The chemical synthesis challenges associated with each of these raw materials are outlined in Scheme 7.

From a commercial point of view, one of the most important breakthroughs favoring the route from diosgenin resulted from the work of Durey Peterson in Upjohn. Peterson and co-workers (following the precedent set by Alexander Fleming?) collected a culture of *Rhizopus arrhizus* on an agar plate left out on a window sill in Kalamazoo and found that it would hydroxylate progesterone in the 11α position.[62] This led them to *Rhizopus nigricans* which hydroxylated the 11α position of progesterone in over 80% yield.[62(b)] Other companies found 11α –hydroxylating

[60] Blickenstaff, R. T., Ghosh, A. C., and Wolf, G. C. *Total Synthesis of Steroids* (*Organic Chemistry*, Vol. 30), Academic Press, New York, 1974.

[61] Schering (U.S.) became a separate U.S. Company resulting from American seizure of Schering A.G. assets during World War II.

[62] (a) Peterson, D. H., and Murray, H. C. *J. Am. Chem. Soc*., 1952, **74**, 1871. (b) Peterson, D. H., Murray, H. C., Eppstein, S. H., Reineke, L. M., Weintraub, A., Meister, P. D., and Leigh, H. M. *J. Am. Chem. Soc*. 1952, **74**, 5933. (c) Eppstein, S. H., Meister, P. D., Peterson, D. H., Murray, H. C., Leigh, H. M; Lyttle, D. A., Reineke, L. M., and Weintraub, A. *J. Am. Chem Soc*., 1953, **75**, 408.



SCHEME 7. Structural manipulations for the conversion of bile acids and diosgenin.[63]

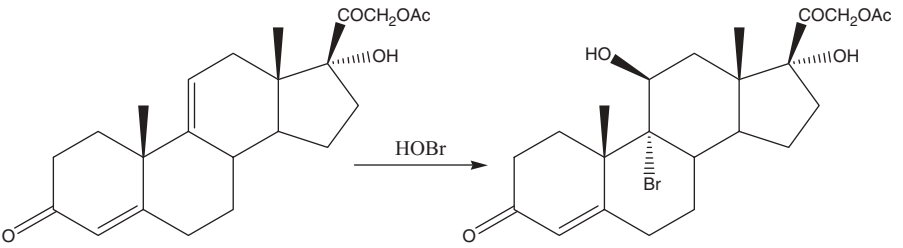
microorganisms of their own (Searle discovered *Aspergillus* strains and Schering discovered *Metarrhizium*). New technology, as well as increased plant capacity and competition, drove the cost of cortisone down by a factor of almost 100 in the next decade.

Vigorous R&D programs were initiated by many companies in Europe and the United States with the objective of finding and patenting compounds with greater activity and fewer side effects than cortisone or its acetate. Oral administration of these two compounds was found to cause undesirable side effects such as salt retention. Ointment and other topical dosage forms looked to be preferred ways of delivering these drugs, but considerable variability in activity was observed: Cortisone acetate, for example, was inactive in topical dosage whereas hydrocortisone acetate (carrying an 11β-carbinol group in place of cortisone's 11-keto group and the same 21-acetate) was active in both topical and oral forms.

Further evaluation of minor compounds in the extracts of animal organs did not provide any leads to suggest that structural variants with greater activity or fewer side effects than observed with cortisone might be found. It appeared that conformation

[63]For a detailed account of the many years of work taken to achieve a working process to produce cortisone from bile acids, see Fieser, L. F., and Fieser, M. *Steroids*, Reinhold Publishing Co., New York, 1959, Chapter 19.

of the cortisone and hydrocortisone molecules was vital to their activity. However, more active compounds did emerge as a result of peripheral observations.[64] Fried, working in Squibb, in the course of studies on the conversion of epicortisol (the 11α-hydroxy analogue of hydrocortisone) into hydrocortisone, prepared the 9α-bromo 11β-hydroxy compound, **XXVIII**, by the addition of hypobromous acid to the $\Delta^{9,11}$ olefine, **XXIX.** Fried speculated that the addition reaction should have given the 9α-bromo-11β-hydroxy compound and thought that if the orientation of the hydroxyl group was indeed 11β, as in hydrocortisone acetate, then compound **XXVIII** might show some weak antiarthritic activity.[65]



XXIX **XXVIII**

To the Squibb group's surprise, **XXVIII** proved to have almost one-third of the activity of cortisone acetate. This revelation set off an examination of other halohydrins. The 9α-fluoro analogue of **XXVIII** proved to be almost 11 times as active as cortisone acetate, and the 9α-chloro analogue was almost five times as active.

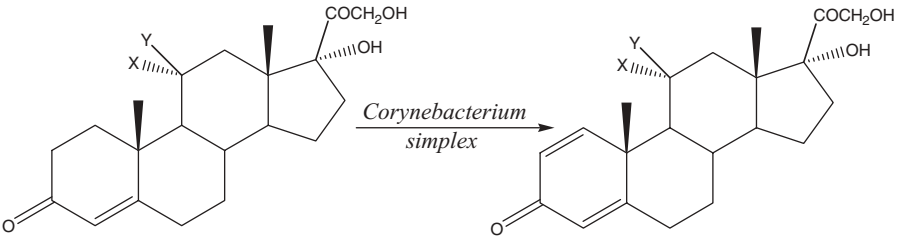
However, the new compounds still possessed salt retention disadvantages. Nevertheless, the Squibb groups findings, coupled with other beneficial discoveries (see below), set off an enthusiastic stampede for superior anti-inflammatory steroids.

One of the other major contributions leading to improved biological properties emerged from work carried out by Hershberg and co-workers in Schering Corporation, New Jersey. They were interested in finding microorganisms that would selectively hydrolyze the diacetate ester of hydrocortisone. Attempts to achieve this using *Corynebacteria* led to a new compound proven to be the Δ^1 dehydro derivative of hydrocortisone diacetate. Insignificant degradation of the C-17 side chain was observed. The Schering workers promptly subjected cortisone and hydrocortisone to the new microbial technique, creating prednisone **(XXX)** and prednisolone **(XXXI)** (Scheme 8).[66] Prednisone and prednisolone proved to be superior to cortisone and

[64] "Chance," Pasteur once said, "only visits the prepared mind."

[65] (a) Fried, J. and Sabo, E. F., *J. Am. Chem. Soc* 1953, **75**, 2273. (b) *idem ibid*., 1954, **76**, 1455. (c) Fried, J., Thoma, R. W., Perlman, D., Herz, J. E., and Borman, A. *Recent Progress in Hormone Research*, 1955, **11**, 149.

[66] (a) Herzog, H. L., Nobile, A., Tolksdorf, S, Charney, W., Hershberg, E. B., and Perlman, P. L., *Science*, 1955, **121**, 176. (b) Nobile, A., Charney, W., Perlman, P. L., Herzog, H. L., Payne, C. C., Tully, M. E., Jevnik, M. A., and Hershberg, E. B. *J. Am. Chem. Soc*., 1955, **77**, 4184. (c) Nobile, A. U.S. Patent 2,837,464, 1958 (to Schering Corporation). (d) Nobile, A. U.S. Patent 3,134,718, 1964 (to Schering Corporation). It should be noted that Schering's publications and patents were delayed because of the time required



Cortisone X, Y = O
Hydrocortisone X = H, Y = OH

Prednisone (XXX) X, Y = O
Prednisolone(XXXI)X = H, Y = OH

SCHEME 8. Microbiological dehydrogenation of cortisone and hydrocortisone.

hydrocortisone in both antiarthritic activity and particularly in greatly minimizing salt retention (mineralocorticoid activity).[67]

Many other structural variants were pursued, the most beneficial being the introduction of fluorine or methyl at the 6α position and, later, methyl at the 16α or 16β position. Considerable improvements in biological activity were also created by esterification of hydroxyl substituents at C-17 and C-21. Some aspects of the synthesis of the 16-methyl glucococorticoids are detailed later in a summary of some of the work undertaken by my colleagues in Schering.

Table 2 lists the most-prescribed anti-inflammatory steroids on the U.S. market today. Table 2 shows that some of the first compounds to be marketed still have a place in the treatment of inflammatory disease 50 years and more after their discovery. Table 2 also illustrates that continued effort to improve potency, to increase safety and to find better drug delivery systems (e.g., inhalers) succeeded in creating marketable products into the 1990s. Today very little, if any, research is going on to find improved steroid anti-inflammatory drugs. Some work continues in the pharmaceutical development area mostly to improve the formulation of existing molecules and to find better delivery systems.

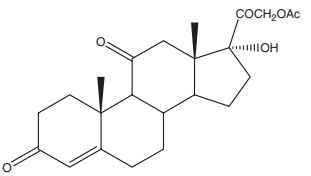
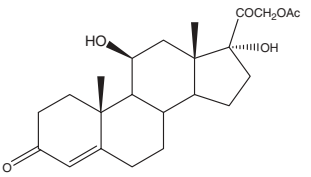
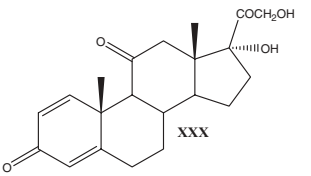
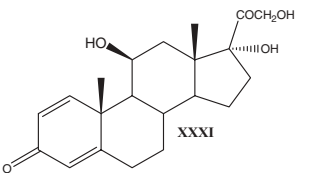
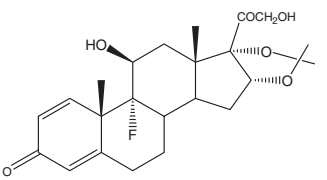
It should be noted that many market names are used for all of the anti-inflammatories listed in Table 2, depending on market liaisons, generic competition, derivatives such as esters, and the form of the drug product (e.g., topical, inhaler, nasal spray, etc.). For example, Schering's betamethasone 17,21-dipropionate is marketed as Diprosone, and Glaxo's betamethasone-17-valerate was marketed as Betnovate.

With a few exceptions the main structural features needed for anti inflammatory activity are the $\Delta^{1,4}$-3-ketone structure, hydroxyl at C-11β and C-17α and hydroxyacetyl at C-17β. Esterification of either or both C-17 and C-21 hydroxyl groups is a common feature of all the anti-inflammatories produced after the mid-1960s. Discovery of the importance of esterification was largely due to work at Glaxo. This work is worth highlighting since it provides an early example of the importance of

to establish that Schering had the priority in invention over competing claims by others, notably Merck, Upjohn, Syntex, Squibb, and Pfizer.

[67] Prednisone and prednisolone are some four times more active at glucocorticoid than at mineralocorticoid receptors.

TABLE 2. Most-prescribed Anti-inflammatories on the U.S. Market

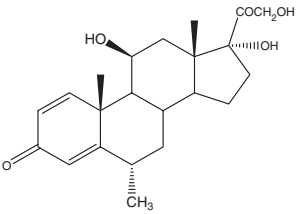
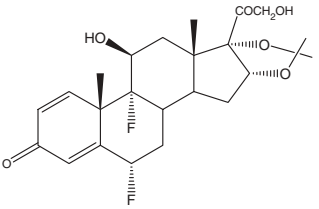
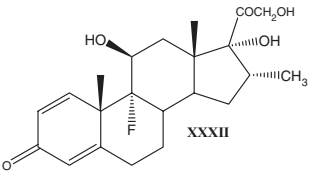
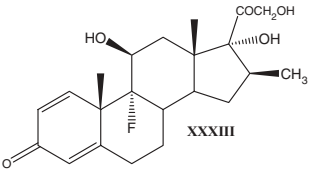
Compound	Name	Market Name	Original Company
	Cortisone acetate	Cortone acetate	Merck[68]
	Hydrocortisone acetate	Hydrocortone acetate	Merck[69]
	Prednisone	Prednisone	Schering[66]
	Prednisolone	Prednisolone	Schering[66]
	Triamcinolone Acetonide	Azmacort Nasacort	Lederle/Squibb[70]

[68] Sarett, L. H. *J. Biol. Chem.*, 1946, **162**, 601.

[69] Wendler, N. L., Graber, R. P., Jones, R. E., and Tishler, M. *J. Am. Chem. Soc.* 1950, **72**, 5793.

[70] (a) Bernstein, S., Lenhard, R. H., Allen, W. S., Heller, M., Littell, R., Stolar, S. M., Feldman, L. I., and Blank, R. H. (American Cyanamid/Lederle). *J. Am. Chem. Soc.*, 1956, **78**, 5693. (b) Fried, J., Borman, A., Kessler, W. B., Grabowich, B., and Sabo, E. F. (Squibb). *J. Am. Chem. Soc.*, 1958, **80**, 2338. (c) Lederle (American Cyanamid) became the patent holder for the joint marketing venture through its U.S. Patents, as follows: Bernstein, S., Lenhard, R. H., and Allen, W. S. U.S. Patent 2,789,118, 1957; Bernstein, S., and Allen, G. R., Jr., U.S. Patent 2,990,401,1961 and Allen, G. R. Jr., Marx, M., and Weiss, H. J. U.S. Patent 3,021,347,1962.

TABLE 2. (*Continued*)

Compound	Name	Market Name	Original Company
	Methylprednisolone	Medrol	Upjohn[71]
	Fluocinolone acetonide	Synalar	Syntex[72]
 XXXII	Dexamethasone	Decadron (Merck)	Merck/Schering[73]
 XXXIII	Betamethasone	Celestone (Schering)	Schering/Merck[74]

(*Continued*)

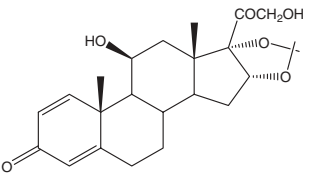
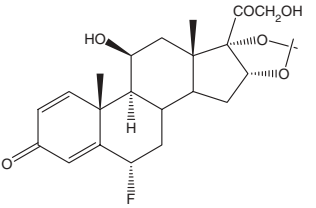
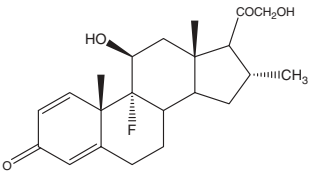
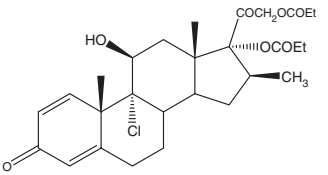
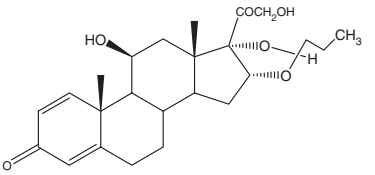
[71](a) Spero, G. B., Thompson, J. L., Magerlein, B. J., Hanze, A. R., Murray, H. C., Sebek, O. K., and Hogg, J. A. *J. Am. Chem. Soc*., 1956, **78**, 6213. (b) Sebek, O. K., and Spero, G. B. U.S. Patent 2,897,218, 1959 (to Upjohn).

[72]Mills, J. S., Bowers, A., Djerassi, C., and Ringold, H. J. *J. Am. Chem. Soc*. 1960, **82**, 3399. Bowers, A., and Mills, J. S. U.S. Patent 3,014,938, 1961 (to Syntex).

[73](a) Arth, G. E., Fried, J., Johnston, D. B. R.; Hoff, D. R., Sarett, L. H., Silber, R. H., Stoerk, H. C., and Winter, C. A. (Merck). *J. Am. Chem. Soc*. 1958, **80**, 3161. (b) Oliveto, E. P., Rausser, R., Nussbaum, A. L., Gebert, W., Hershberg, E. B., Tolksdorf, S., Eisler, M., Perlman, P. L., and Pechet, M. M. (Schering). *J. Am. Chem. Soc*., 1958, **80**, 4428. (c) Oliveto, E. P., Rausser, R., Weber, L., Nussbaum, A. L., Gebert, W., Coniglio, C. T., Hershberg, E. B., Tolksdorf, S., Eisler, M., Perlman, P. L., and Pechet, M. M. *J. Am. Chem. Soc*., 1958, **80**, 4431.

[74](a) Taub, D., Hoffsommer, R. D., Slates, H. L., and Wendler, N. L. (Merck). *J. Am. Chem. Soc*., 1958, **80**, 4435. (b) Oliveto, E. P., Rausser, R., Herzog, H. L., Hershberg, E. B., Tolksdorf, S., Eisler, M., Perlman, P. L., and Pechet, M. M. (Schering). *J. Am. Chem. Soc*., 1958, **80**, 6688.

TABLE 2. (*Continued*)

Compound	Name	Market Name	Original Company
	Desonide	Locapred Desowen	Lederle[75]
	Flunisolide	Nasalide	Syntex[76]
	Desoximetasone	Topicort	Roussel[77]
	Beclomethasone dipropionate	Beconase	Glaxo[78]
	Budesonide	Rhinocort	Bofors[79]

(*Continued*)

[75](a) Bernstein, S., Littel, R., Brown, J. J., and Ringler, I. *J. Am. Chem. Soc*., 1959, **81**, 4573. (b) Bernstein, S., and Allen, G. R., Jr. U.S. Patent 2,990,401, 1961 (to American Cyanamid/Lederle).

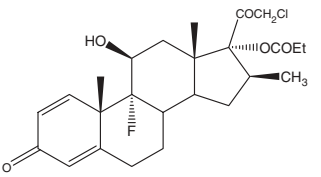
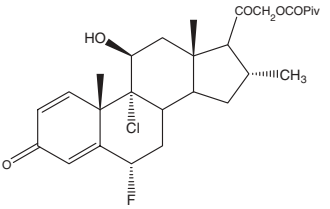
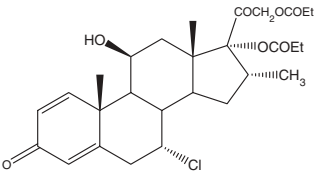
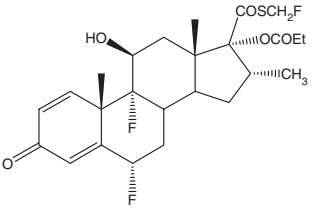
[76]Ringold, H. J., and Rosenkranz, G. U.S. Patent 3,124,571, 1964 (to Syntex).

[77]Jolly, R., Warnant, J. and Goffinet, B. U.S. Patent 3,099,654 (to Roussel—UCLAF).

[78]Elks, J., May, P. J., and Weir, N. G. U.S. Patent 3,312,590, 1967 (to Glaxo).

[79](a) Thalen, B. A., and Brattsand, R. L. *Arzneimittel-Forsch*, 1979, **29**, 1787. (b) Brattsand, R. L., Thuresson, B., Claeson, K. G., and Thalen, B. A. U.S. Patent 3,929,768, 1975 (to Bofors).

TABLE 2. (*Continued*)

Compound	Name	Market Name	Original Company
	Clobetasol propionate	Temovate	Glaxo[80]
	Clocortolone pivalate	Cloderm	Schering A. G.[81]
	Alclomethasone dipropionate	Aclovate	Schering[82]
	Fluticasone propionate	Cutivate Flonase	Glaxo[83]

(*Continued*)

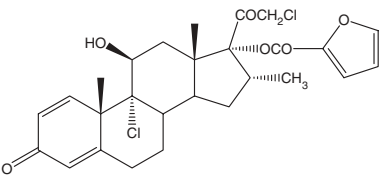
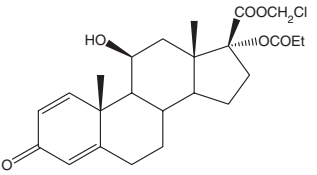
[80]Elks, J., May, P. J., and Weir, N. G. U.S. Patent 3,312,590, 1967 (to Glaxo).

[81]Kasper, E., and Phillipson, R. U.S. Patent 3,729,495, 1973 (to Schering A.G.).

[82](a) Green, M. J., Berkenkopf, J., Fernandez, X., Monahan, M., Shue, H-J., Tiberi, R. L., and Lutsky, B. N. *J. Steroid Biochem.*, 1979, **11**, 61. (b) Green, M. J., Shue, H.-J.; Shapiro, E., and Gentles, M. A. U.S. Patent 4,076,708, 1978 (to Schering).

[83](a) Phillipps, G. H., Bailey, E. J., Bain, B. M., Borella, R. A., Buckton, J. B., Clark, J. C., Doherty, A. E., English, A. F., Fazakerley, H., Laing, S. B., Lane-Allman, E., Robinson, J. D., Sandford, P. E., Sharratt, P. J., Staples, I. P., Stonehouse, R. D., and Williamson, C. *J. Med. Chem.*, 1994, **37**, 3717. (b) Phillipps. G. H.; Bain, B. M., Steeples, I. P., and Williamson, C. U.S. Patent 4,335,121, 1982 (to Glaxo).

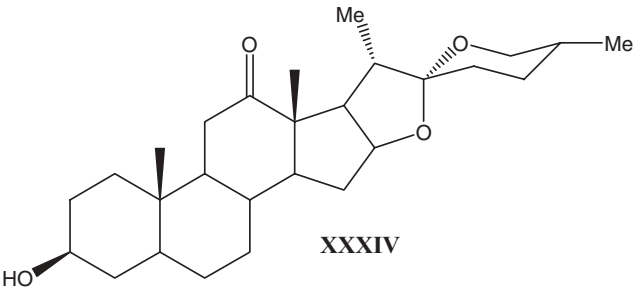
TABLE 2. (*Continued*)

Compound	Name	Market Name	Original Company
	Mometasone furoate	Elecon Nasonex	Schering[84]
	Loteprednol etabonate	Alrex	Otsuka[85]

Source: *Physicians Desk Reference*, 55th edition, Medical Economics Company, Inc., Montvale, New Jersey, 2001.

finding an assay to identify the effects of structural change on biological activity—but first a little background on Glaxo's steroid interests.

Glaxo was one of several European companies involved in finding a route to cortisone. Initially, Glaxo worked with ergosterol as a starting material but soon switched to hecogenin **(XXXIV)** found in juices discarded by the manufacturers of sisal fiber in East Africa.



XXXIV

Hecogenin, like the cholic acids, possesses a C-12 oxygen function and was regarded as the best available prospect for the preparation of cortisone. Glaxo's relationship with Schering[86] and its position in hecogenin encouraged Schering to arrange a

[84](a) Shapiro, E. L., Gentles, M. J., Tiberi, R. L., Popper, T. L., Berkenkopf, J., Lutsky, B., and Watnick, A. S. *J. Med. Chem.*, 1987, **30**, 1581. (b) Shapiro, E. L. U.S. Patent 4,472,393, 1984 (to Schering).

[85]Bodor, N. S. U.S. Patent 4,996,335,1991 (to Otsuka).

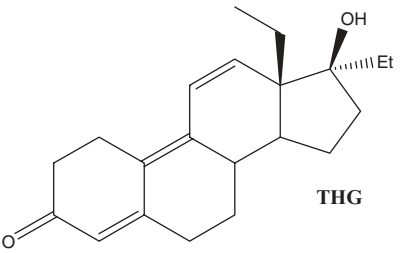
[86]Glaxo was already a licensee of Schering's prednisone-prednisolone patents.

working relationship with Glaxo in which Glaxo agreed to develop a process for the manufacture and supply of betamethasone to Schering in exchange for marketing rights to betamethasone and derivatives. A growing interest in topical dosage forms and the knowledge that betamethasone was not particularly active topically against eczema led Glaxo to the hypothesis that a less polar form of betamethasone such as an ester might penetrate the skin better. To test this hypothesis, an assay was needed which would evaluate the relative potency of betamethasone derivatives in topical situations. Glaxo heard of the work of a Dr. A. W. McKenzie, a dermatologist in St. John's Hospital, London, who claimed that the relative potency of topical steroids could be measured by their ability to create vasoconstriction and skin "bleaching" after overnight contact with the skin under a protective dressing. The McKenzie test proved crucial[87] in the rapid evaluation of a variety of esters and the selection of the valerate (Betnovate)[88] as the best. Betnovate was found to be three times as active as Synalar (Table 2), the best compound on the market at the time. Schering later developed the 17,21-dipropionate of betamethasone (Diprolene/Diprosone) which proved to be even more potent than Betnovate.

Today, the markets for anti-inflammatory and contraceptive steroids amount to billions of dollars a year. Although these two markets are by far the major ones for steroids, it is worth closing this historical review with an indication of other biological activities based on the steroid molecule.

Arguably, no other molecule has had more biological diversity built into its basic four-ring structure than the steroid molecule. By way of illustration, Table 3 provides an incomplete list of several steroid structures and their very different biological activities. Most of the compounds in Table 3 are still on the market.

The diversity of biological activities identified in Table 3 and the known role of steroids in the biochemical processes taking place in the human body suggest to the optimist that additional useful steroid products might emerge in the future. However, no one anticipates that another blockbuster industry to rival the anti-inflammatory and oral contraceptives fields will arise. The illegal use of anabolic steroids such as stanozolol (Table 3) to enhance "sporting" performance has spawned a small "underground" industry to design "undetectable" anabolic steroids. One example is tetrahydrogestrinone (THG).



THG

[87]It was reported by Sir David Jack and Dr. Tom Walker, in their tribute to Dr. B. A. Hems (1912–1995), *Royal Society Biographical Memoirs*, 1997, 228, that Dr. McKenzie was given a radiogram (a combination radio and record player) for his invaluable contribution.

[88]Elks, J., and Bailey, E. J. U.S. Patent 3,376,193, 1968 (to Glaxo).

TABLE 3. A Selection of Steroids with Diverse Biological Activity

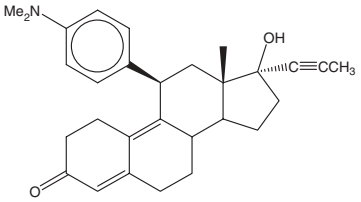
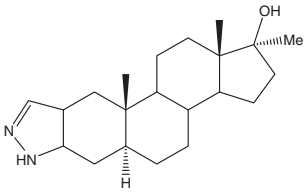
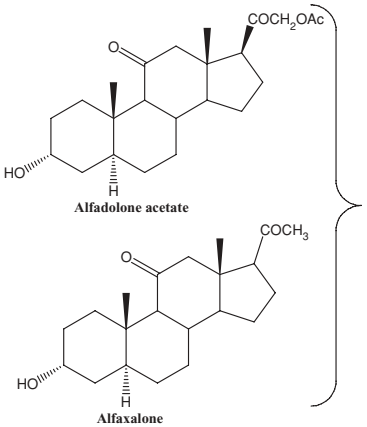
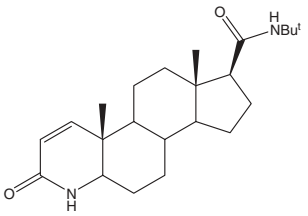
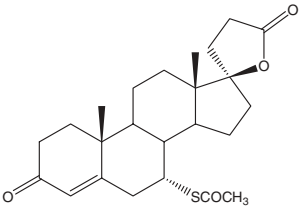
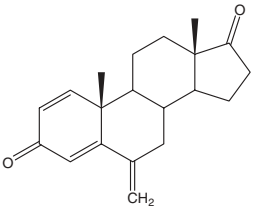
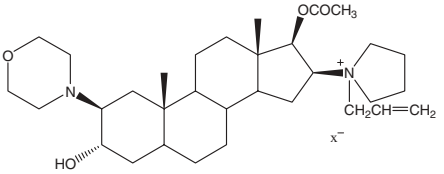
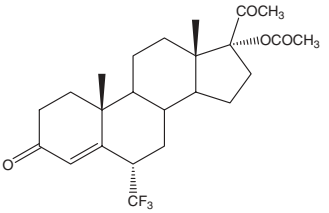
Compound	Name	Biological Activity and Original Company
	Mifepristone RU-486	Abortifacient, Roussel–UCLAF, 1982 (often in combination with a prostaglandin—Misoprostol)
	Stanozolol	Anabolic agent, Sterling Drug, 1962, Controlled substance
 Alfadolone acetate Alfaxalone	Combination is Althesin	Anesthetic, Glaxo, 1971 Structure IV
Structure IV	Digoxin	Cardiotonic, Ancient origins
	Finasteride Proscar	Treatment of benign prostatic hypertrophy, Merck, 1985; also marketed to treat male hair loss

TABLE 3. (*Continued*)

Compound	Name	Biological Activity and Original Company
	Spironolactone	Diuretic/Antihypertensive, G. D. Searle, 1961
	Exemestane Aromasin	Treatment of advanced breast cancer. Pharmacia/Upjohn
	Rocuronium Zemuron (also Vecuronium, Pancuronium, and Pipecuronium)	Marketed as a family of similar structures for muscle relaxation in surgeries, Organon, 1990
	Flumedroxone Demigran	Antimigraine, Lövens Komiske Fabrik, 1962

This compound, accessible from commercial intermediates such as **XXVII**, was added to the list of banned substances following its identification in a spent syringe sent anonymously to the Olympic Analytical Laboratory in Los Angeles in June 2003. Despite the risks, clandestine efforts continue. A second designer steroid, desoxymethyltestosterone, carrying a 17β-methyl-17α-hydroxy functionality, 3-desoxy, and the A-ring double bond at $\Delta^{2,3}$ was identified in 2005. Perversely, it seems likely that the ethical medical community will benefit from knowledge gained on the adverse health effects arising from the illegal use of banned substances.

In conclusion, negative aspects aside, one can only look back with amazement and marvel at the astounding achievements of the many thousands of people who created the steroid industry.

Adventures in Steroid Chemistry

Schering Chemical Development's intense involvement in the business end of the company's steroid manufacturing operations proved to be an adventure because of its broad open-ended scope. We were invited, and funded, by the Manufacturing Division to help its offshore manufacturing operations improve their technical performance (process safety, process yields, and plant throughput) so as to reduce manufacturing costs and, in addition, to enable them to avoid the need to make capital investments in offshore plants, notably in Puerto Rico and Mexico City. To this end, they added vigorous support to the efforts being promoted by the Research Division to upgrade the Chemical Development operation. This comprised reorganization, investment in modern facilities, the addition of highly qualified scientists and engineers, and the introduction of modern instrumentation. The family of people in Chemical Development who were mostly concerned with Manufacturing Division's technical problems came from Taiwan, China, India, the United States, Ireland, Italy, Poland, Romania, and the United Kingdom.

We established a close rapport with colleagues in the offshore operations. Through exchanges of people, frequent meetings, a focus on science, enthusiasm, and management support, much was achieved. In local vernacular, "we had a ball."[89]

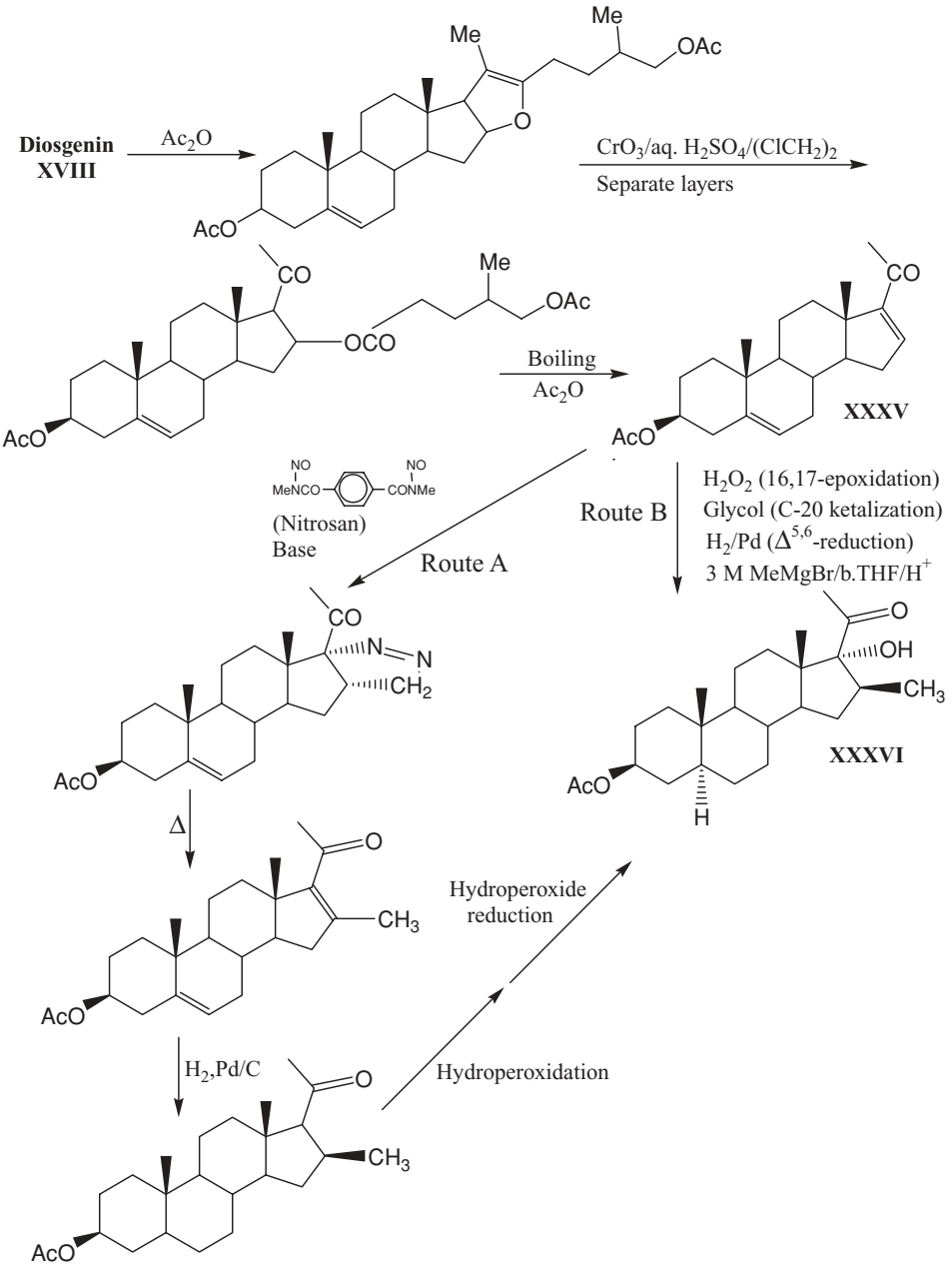
I will close this section with a description of a couple of general projects, one each with our colleagues in Mexico City and Puerto Rico. These were:

- Overcoming a Health/Safety issue in the manufacture of a betamethasone intermediate from Diosgenin in Mexico City, and the evaluation of newer raw materials derived from plants.
- The early steps for converting the 11α-hydroxylated betamethasone intermediate into betamethasone alcohol precursors in Manati, Puerto Rico.

From Plant Saponins to 16β-Methyl Intermediates. With the Bhopal disaster in India in mind, the initial program of work with our colleagues in Mexico City was directed at reexamining an alternative process to the existing process using diazomethane as a reagent for the introduction of the 16β-methyl group (Scheme 9, Routes B and A, respectively).

Perversely, our earliest work was to determine what could be done to ensure continuation of the diazomethane-based operation in light of DuPont's decision to terminate nitrosan production. Production of nitrosan in Mexico City was established using DuPont's process. Understandably, the perceived carcinogenic nature of nitrosan and the continuing, albeit relatively rare, occurrence of minor diazomethane

[89]Our consultant, Professor Ronald Breslow, once famously remarked "I cannot believe you people get paid so much money for having so much fun!"



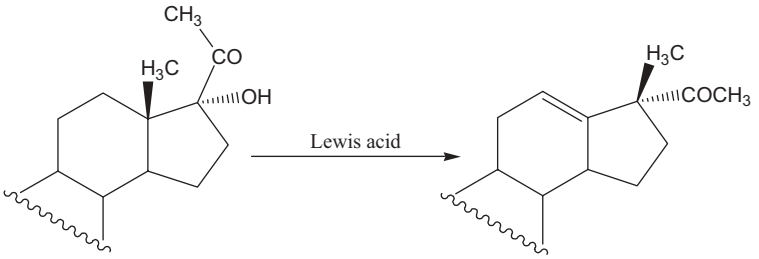
SCHEME 9. Conversion of Diosgenin to 16β-methyl intermediates.

explosions only added to the anxiety and prompted questions on what might be done to enhance safety in the short term.[90]

Ing. Miguel Escobar, General Manager of our Mexico City facility, suggested that one way around using diazomethane would be to reexamine the possibility of starting with the 16α, 17α-epoxide of **XXXV**. He had saved approximately 100 kg of this compound from a failed earlier program of work. He reported that the epoxide was easy to product. In adopting this suggestion, we engaged Professor Eugene Braetoff, University of Mexico City, to investigate the sequence of reactions outlined in Route B, Scheme 9. Professor Bratoeff demonstrated that the sequence of reactions was feasible, but found that process yields at both the ketalization and Grignard reaction steps were poor. In particular, substantial byproduct formation was observed during the ketalization step.

Dr. Donal Maloney, temporarily based in our Mexico City plant, was given responsibility for understanding and developing a process for the ketalization step and Dr. David Tsai (Union, New Jersey) was assigned corresponding responsibility for the Grignard reaction step.

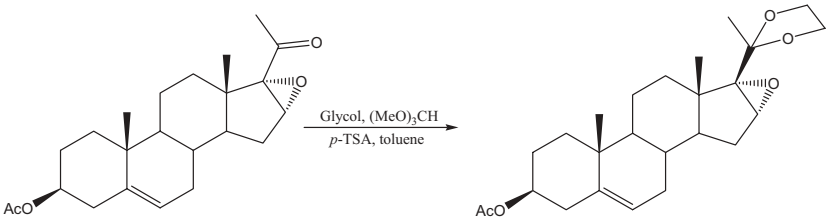
Dr. Maloney, in collaboration with Professor Bratoeff and Dr. Richard Draper (visiting from Union, New Jersey), quickly found, using NMR, that the BF_3 catalyst being used to promote the ketalization at high temperature was causing a Meerwein–Wagner rearrangement along the lines of the reaction reported by Schering's Dr. H. Herzog years earlier.[91]



[90]The Mexico City diazomethane plant suffered minor damage with each explosion. Fortunately, the plant was set up in the open and no personnel injuries were sustained. Glaxo kindly invited us to visit their own diazomethane plant in Montrose, Scotland. This facility was sited in a bunker in a remote on-site location. One of several reasons for Glaxo's excellent safety record in operating this plant was due to their plant design, with polished internal surfaces—rough surfaces are known to trigger detonations. In today's world, those needing to use diazomethane would seek the services of custom manufacturers skilled in producing and using this compound in situ— for example, Phoenix Chemicals Ltd. (see Proctor, L. D., and Warr, A. J. *J. Org. Proc. Res. Dev.*, 2002, **6**, 884) and Aerojet General Corporation (see Archibald, T. G., Huang, D.-S., Pratton, M. H., and Harlan, R. F. U.S. Patent 5,817,778, 1998; and Archibald, T. G., Barnard, J. C., and Harlan, R. F. U.S. Patent 5,854,405, 1998).

[91]Herzog, H., Joyner, C. C., Gentles, M. J., Hughes, M. T., Oliveto, E. P., Hershberg, E. B., and Barton, D. H. R *J. Org. Chem.*, 1957, **22**, 1413.

Rearrangement was avoided by ketalization at lower temperature with a mixture of ethylene glycol, trimethylorthoformate and *p*-toluenesulfonic acid as a catalyst.

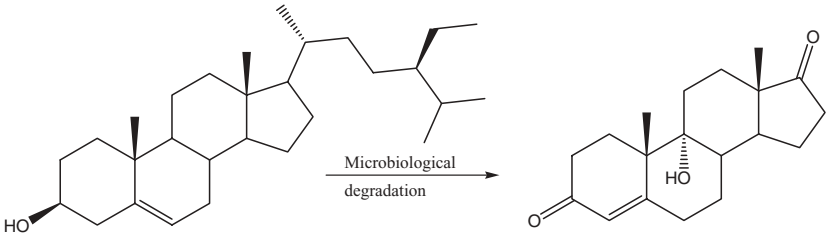


Catalytic hydrogenation of the $\Delta^{5,6}$ double bond proved straightforward. Reaction with an excess of Grignard reagent at high temperature followed by work-up gave **XXXVI** (free 3-hydroxy form). Key factors in forcing the Grignard reaction to completion were reaction temperature, the molar excess of methyl magnesium bromide, and the reaction concentration. An important consideration in operating in Mexico City (elevation approximately 7000 feet) was the boiling point of reaction solvents. In our case, the THF (used as a Grignard reaction solvent) had to be substantially replaced by toluene to enable us to increase the reaction temperature to a practical figure.

The replacement of Route A (Scheme 9) by Route B was a triumph of collaboration and the application of science.

Shortly thereafter, we were visited by Marketing/Technical people from Gistbrocades in Delft offering us 9α-hydroxyandrost-4-ene-3,17-dione (9α-OH AD, **XXXVIII**) as a new steroid raw material.

Gist had succeeded in building on the pioneering work of others[92] by finding their own, industrially attractive, microbiological system for the efficient degradation of sitosterol, available in large quantities from soya bean byproducts to **XXXVIII.**[93]



Sitosterol
XXXVII

9α -OH AD
XXXVIII

[92](a) Sih, C. J., and Weisenborn, F. L. U.S. Patent 3,065,146, 1962 (to Olin Mathieson Chemical Corporation) set the stage with their finding that C-9 unsubstituted steroids can be microbiologically hydroxylated to C-9α-hydroxysteroids. (b) Later, Upjohn workers pioneered the use of a mutant of *Mycobacterium fortuitum* to degrade sitosterol to **XXXVIII** (Wovcha, M. G., Antosz, F. J., Knight, J. C., Kominek, L. A., and Pyke, T. R. *Biochim. Biophys. Acta*, 1978, **539**, 308.)

[93]The beauty of the microbiological method lies in its ability to oxidize the structurally similar C-17 side chains of other steroids which contaminate sitosterol (e.g., campesterol, dihydrobrassicasterol, and stigmasterol—all of which carry the 3β-hydroxy-5-ene structure) at both C-17 and 9α sites to compound **XXXVIII.**

The quality of the **XXXVIII** obtained by the microbiological degradation process was surprisingly good.

The main reasons for interest in a totally different starting material were the likelihood of greater process efficiency, lower costs, and freedom from dependence on diosgenin from the Barbasco root. Cost projections using the Gist-brocades price idea for **XXXVIII**, our own cost calculations based on the literature, the downstream process simplifications we envisaged, and the demonstrated elimination of a major source of impurities in the Schering synthesis of a key $\Delta^{9,11}$-olefine[94] (see also later section entitled "Conversion of 11α-Hydroxylated Betamethasone Intermediate into Betamethasone Alcohol in Puerto Rico") were major driving forces in the Schering decision to evaluate the Gist-brocades starting material. This decision recognized that considerable changes in the Schering manufacturing plant would be needed to accommodate the new chemistry, that much of the existing plant (e.g., the fermentation unit for introducing the 11α-hydroxy substituent) would be idled, and that there would be a significant involvement of Quality Assurance and Regulatory Affairs personnel if Schering made the decision to adopt the Gist-brocades starting material.

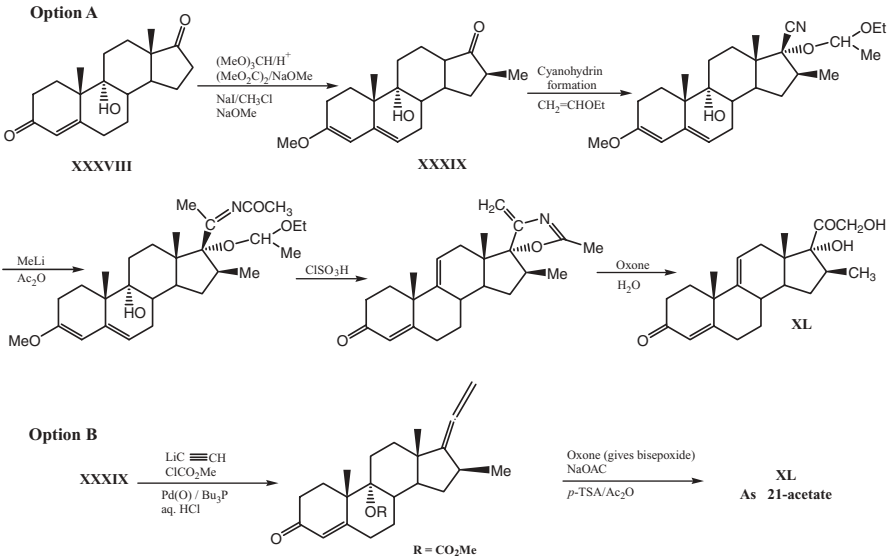
Given a supply of **XXXVIII** from Gist-brocades, the main thrust of our work became finding ways of introducing the dihydroxy acetone side chain at C-17. The elegant work published by Upjohn chemists Van Rheenen and Shephard[94] provided a foundation for our own work. Over the next three years, our Dr. David Andrews, Dr. Nick Carruthers, and Dr. Anantha Sudhakar identified two promising options for further development (Options A&B, respectively, in Scheme 10).

By the beginning of 1990, the reactions in Scheme 10 had mostly reached the *Method* stage of development (see Chapter 8 for the definition of *Method*). In short, considerable process development and scale-up work, in collaboration with manufacturing and others, was still needed to create a process.

The year 1990 proved to be a turbulent one in which many uncertainties needed to be resolved, not least of which was the Gist-brocades announcement that they were in negotiation with several companies to sell their 9α-hydroxyandrost-4-ene-3,17-dione **(XXXVIII)** technology. We subsequently learned that Roussel–UCLAF had bought the Gist-brocades technology and would be abandoning their long-standing position using bile acids as a starting material. Roussel also expressed interest in continuing to supply **XXXVIII** to Schering. A few in Schering manufacturing were unnerved by the thought of relying on a competitor to supply starting material, but it was other considerations that dictated the decision not to develop the route via **XXXVIII.**

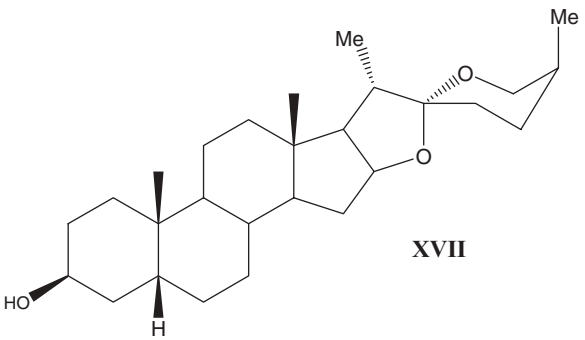
Schering's New Drug Application for Mometasone Furoate (see Table 2) was nearing approval by the FDA, and plant capacity projections were such as to require that we increase plant capacity more rapidly than could be achieved by developing

[94]The Schering synthesis of a $\Delta^{9,11}$-intermediate, essentially by dehydration of an 11α-hydroxy intermediate, always resulted in the formation of approximately 10% (frequently more) of an unwanted $\Delta^{11,12}$-olefine. Formation of this impurity not only diverted valuable starting steroid into useless product, but also caused purification problems in later process steps. Although "dehydration" of 9α-hydroxysteroids can lead to formation of a $\Delta^{8,9}$-olefine impurity (see (footnote 92(a)), this unwanted reaction has been shown to be avoidable [see Beaton, J. M., Huber, J. E., Padilla, A. G., and Breuer, M. E. U.S. Patent 4,127,596, 1978 (to Upjohn); and VanRheenen, V., and Shephard, K. P. *J. Org. Chem.*, 1979, **44**, 1582.]



SCHEME 10. Potential routes to betamethasone intermediates from 9α-hydroxyandrost-4-ene-3,17-dione.

one of the options in Scheme 10. Essentially this amounted to directing efforts into increasing the yield of existing plant processes and to developing a long-standing idea, promoted by our Mexico City General Manager, Ing. Miguel Escobar, to develop Sarsasapogenin **(XVII)** as the starting material.



XVII

The Sarsasapogenin idea did not come out of the blue. As often happens, thinking scientists and engineers often quietly pursue ideas in a low-key way, outside the mainstream of work, and launch them when they feel they have a workable prospect. Indeed, just as Ing. Escobar had been quietly evaluating opportunities to develop sarsasapogenin as a starting material, we in Chemical Process development had been working for years on ideas for improving the yield of the current manufacturing process (see later section entitled "Conversion of 11α-Hydroxylated Betamethasone

TABLE 4. Principal Commercial Sources of Steroid Raw Materials from Plants

Plant	Main Countries of Origin	Main Steroid Component
Barbasco (yam)	Mexico, China	Diosgenin (XVIII)
Agave	East Africa, Mexico, China	Hecogenin/Tigogenin (XXXIV,[95])
Soyabean	Numerous	Sitosterol/Stigmasterol (XXXVII/XVI)
Yucca	Mexico, United States	Sarsasapogenin (XVII)

Intermediate into Betamethasone Alcohol in Puerto Rico"). These low-key efforts later coalesced into the lead process (see later).

The principal issues in promoting the idea of a new starting material in the steroid field are the cost, practicality, quantity, reliability, and quality of the source and, in this case, what the chemical plant requirements would have to be to process it. Ing. Escobar had been aware for some time of the decline in the collection of Barbasco roots for his diosgenin production. For the most part, this was a consequence of a movement started by President Echeverria years earlier. This movement led to government efforts to maintain the Barbasco natural resource for the country rather than allow the multinational pharmaceutical companies to harvest at will. This only resulted in most multinationals seeking alternative steroid sources. Reduction of the supply of roots led Ing. Escobar to develop sources of diosgenin **(XVIII)** and tigogenin[95] in China to guard against possible disruption of the domestic supply of roots. At this point, it is worth summarizing the principal commercial plant sources of steroid raw materials (Table 4).

The success of the multinationals in exploiting alternative steroid sources exposed the limitations of the wild yam. Yams were laboriously dug from the ground exclusively for those involved in the manufacture of steroids. In contrast, all the other plant sources of steroids identified in Table 4 were harvested for other industries; these industries generally regarded the steroid-containing waste as worthless to them.

Thus, hecogenin and tigogenin are byproducts of the sisal (hemp fiber) industry, sitosterol and stigmasterol are byproducts of the large soyabean industry, and, in the late 1980s, Sarsasapogenin appeared, to Ing. Escobar, likely to become a byproduct of a fledgling Northern Mexico industry in cattle feed, Yucca oil, and other minor products.

The possible use of sarsasapogenin, originally suggested by the redoubtable Russell Marker (see footnote 41), had been explored by Schering in the late 1970s following the Mexican government's efforts to create a steroid starting material business.[96] Schering's Hershel Herzog, working with a botanist (P. Simpson), surveyed large stands of *Yucca brevifolia* plants in the American southwest and in 1978 publicized his findings that the fruits of this plant could yield viable quantities of sarsasapogenin. The initiative was not followed up because the Mexican government did not pursue its diosgenin business venture and there was later indication that the U.S. government

[95] Structurally this is hecogenin **(XXXIV)** with the 12-keto group reduced to CH_2.

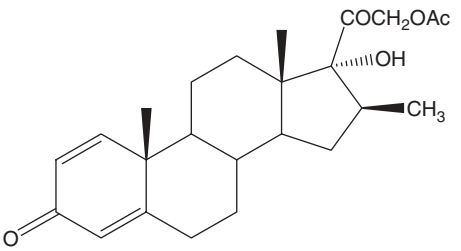
[96] Herzog, H., and Oliveto, E. P. *Steroids*, 1992, **57**, 617.

had expressed some concern about exploiting the fruits of the plant in the American southwest in case it became endangered in the wild.

Ing. Escobar quietly followed up the Herzog initiative and explored potential sources of sarsasapogenin from Yucca plants in Mexico. He found that there was already an established business in northern Mexico built around utilizing the fruits of *Yucca filifera* in the cattle feed business. The sweet fruits that develop from a panicle of white flowers 10–15 ft above the ground were snipped off the plant with long-handled clippers by Mexican farmers in their winter season, enabling them to greatly supplement their income or simply just work to meet their needs! The fruits were chopped and the black seeds, comprising almost 25% by weight of the total fruit, were separated. The sweet chopped fruit was mixed with dried chicken manure (still rich in protein since chickens do not process all the protein present in their feed) and supplements and the product sold as cattle feed. The seeds contain a useful oil that is extracted for domestic purposes. The de-oiled milled seeds cannot be fed to animals because of their steroid content. Analysis of de-oiled seeds showed them to contain approximately 6% sarsasapogenin (versus only approximately 4–5% diosgenin in dried Barbasco root).

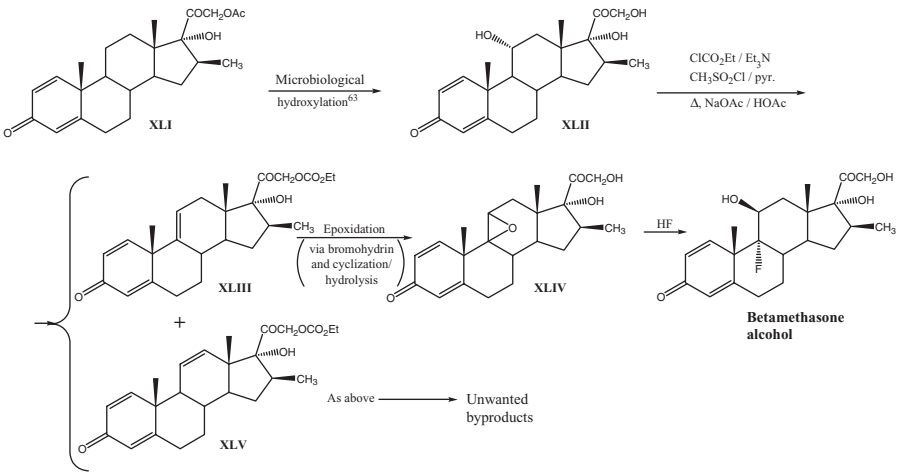
Though there are many thick stands of Yucca filifera, the distribution of the plant is mainly sparse, spread across approximately 800,000 hectares (2 million acres) in four states (Durango, Coahuila, Nuevo Leon and San Luis Potosi). However, judging by this author's experience gardening in New Jersey, the seed germinates readily and could undoubtedly be grown commercially in a warm climate.[97] The only downside would be a 12 to 15-year wait for the Yucca to commence flowering and setting fruit! There is also a need to ensure proper pollination—apparently this is achieved naturally in the arid areas west of Saltillo by a small flying beetle.

The production of sarsasapogenin from de-oiled seeds in our Mexico City plant proved straightforward using essentially the same equipment as previously used in the production of diosgenin from dried Barbasco roots. Indeed, virtually all of the subsequent chemical processing steps leading to the final intermediate produced in Mexico (viz. compound **XLI**) were implemented in the same plant as was used starting with diosgenin.



XLI

[97]In New Jersey, it is necessary to bring the potted plant into a warm building and place it under lights for the winter. After 10 years, this is becoming a serious challenge: One needs to dress in body armor to prevent impalement on its formidable array of bayonets, and that's just to get your arms round the pot!



SCHEME 11. Conversion of Mexican intermediate XLI into betamethasone alcohol.

Although there is an advantage (versus diosgenin) in starting with sarsasapogenin, since no hydrogenation step is needed to reduce the $\Delta^{5,6}$ double bond as in Scheme 9, (compounds **XXXV** to **XXXVI**), there proved to be some small disadvantage in utilizing the sarsasapogenin-derived compound equivalent to **XXXVI**, which carried a 5β-hydrogen. Further work was needed to optimize the chemistry for introducing the $\Delta^{1,4}$ -3-ketone into the 5β-hydrogen equivalent of **XXXVI.**

All the work needed to switch from diosgenin to sarsasapogenin as the starting material was carried out much faster than the program seen as needed if we were to adopt 9α-hydroxyandrost-4-ene-3,17-dione **(XXXVIII)** as the starting steroid. A major factor in the decision making was the time projected for all the plant modifications that would have been necessary starting with **XXXVIII**. In short, all the process selection and development work, and particularly all the engineering design, plant installation, and process testing in a new or adapted plant, was eliminated by deciding to use sarsasapogenin in the existing plant.

The success of the Mexico City program, largely inspired by Ing. Escobar, imaginatively and enthusiastically established by chemists and engineers in Union, New Jersey, and Mexico, and unswervingly supported by senior management, provided an excellent example of what can be achieved when groups with different objectives and skills are teamed to work together toward a common goal.

Conversion of 11α-Hydroxylated Betamethasone Intermediate into Betamethasone Alcohol in Puerto Rico. As indicated in the section entitled "From Plant Saponins to 16β-Methyl Intermediates," the most inefficient steps in processing the final intermediate from Mexico (i.e., **XLI**) into betamethasone alcohol were the steps to introduce the $\Delta^{9,11}$ double bond into **XLI**. The process sequence is outline in Scheme 11.

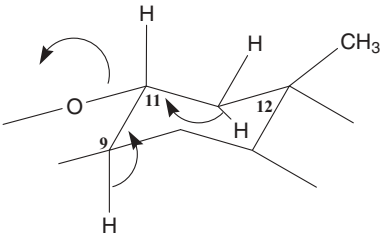
The formation of >10% of the $\Delta^{11,12}$-olefine byproduct **(XLV)** not only represented a significant loss of desired steroid, but introduced a further loss by requiring wasteful purifications of both the epoxide **XLIV** and betamethasone

alcohol. Formation of **XLV** occurred because the 11α-hydroxy group (as its mesylate) in **XLII** is not anti-coplanar with the 9α-H—elimination from a position of true anti-coplanarity would be expected to greatly favor formation of the desired $\Delta^{9,11}$ olefine **(XLIII)**. Indeed, it is known that 11β-hydroxy steroids corresponding to **XLII**, which possess favorable anti-coplanarity with 9α-H, can be "dehydrated" to the $\Delta^{9,11}$ olefine in 90% yield.

The problem of improving the yield of the $\Delta^{9,11}$ olefine had been tackled, with little success, by several of our scientists over many years.[98] The Schering fermentation scientists, several with past experience in trying to find a practical biological system for introducing the 11β-hydroxy group into **XLI**, did not encourage us to try to reopen this project—they thought that it would be more productive to put resources into improving the existing strain, which produced the 11α-hydroxy steroid **(XLII)** in Puerto Rico.

Not surprisingly, given the long history of failure, few of our chemists seemed willing to take on the $\Delta^{9,11}$-olefine project. One who asked was Dr. Chou Tann, who had already established a record of success on other projects. He was given the task at a time of increased awareness that there was an urgent need to improve process yield, product quality, and plant throughput in the manufacture of betamethasone alcohol. Dr. Tann's proposals, to investigate the use of reactive phosphorus compounds to form $(Cl)_x(O)_y$ P–O bonds with the 11α-hydroxy group and to find ways of "arranging" a cis elimination with the 9α-H, were greeted with skepticism. The skeptics thought that compounds such as $POCl_3$ and PCl_5, suggested by Dr. Tann as worthy of investigation, would give high levels of the 11β-chloro compound through an S_Ni type of reaction. However, Dr. Tann pointed to old literature which showed that 11α-hydroxysteroids would react at room temperature with $POCl_3$ to give $\Delta^{9,11}$ steroids, albeit in only 15% yield,[99] and with PCl_5 to give $\Delta^{9,11}$ steroids in 65% yield.[100] The ratio of $\Delta^{9,11}$ to $\Delta^{11,12}$ olefines was 98:2 in the $POCl_3$ case and not reported in the PCl_5 case. The skeptics pointed out that the PCl_5 reaction[100] gave 9α, 11β-dichloride as a major byproduct and that the very low yield using $POCl_3$ did not augur well.

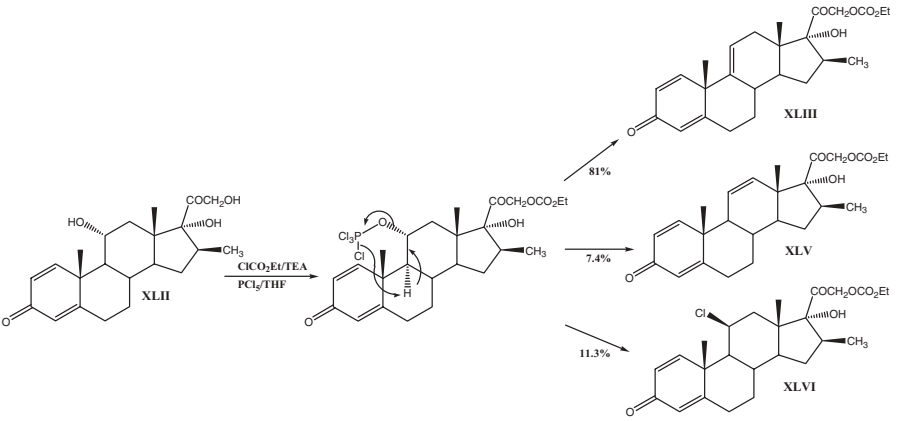
Examination of the molecular mechanics energies of elimination to $\Delta^{9,11}$ versus $\Delta^{11,12}$ by Dr. B. E. Bauer of the Schering Research computational chemistry group revealed an energy difference between the two eliminations of only 1.51 kcal/mol in favor of the $\Delta^{9,11}$-elimination.



[98]From time to time, I assigned the "dehydration" problem, for a few months, to incoming scientists, as well as a few of our experienced ones who were "between projects."

[99]Bernstein, S., Lenhard, R. H., and Williams, J. H., J. Org. Chem., 1954, **19**, 41.

[100]Shoppee, C. W., and Nemorin, J. *J. Chem. Soc., Perkin Trans*., 1973, 542.



SCHEME 12. PCl_5-mediated "dehydration" of 11α-hydroxysteroids.

In spite of all the negatives, and in keeping with the principle that one should never use theory to abort an experiment, Dr. Tann took on the project.

In exploring the 11α-chlorophosphate idea further, Dr. Tann's group concentrated on solvent choice and temperature effects, with PCl_5 as the reactant. Tetrahydrofuran was selected as the solvent following comparison of reactions carried out in this solvent versus pyridine and methylene chloride. A reaction at room temperature in THF gave an encouraging result. Three products were produced, with the desired $\Delta^{9,11}$ olefine being the major one (Scheme 12 summarizes the findings and outlines the speculative mechanism for the main reaction). An alternative mechanism could be via dehydrochlorination of an initially formed 11β-chlorosteroid (XLVI). Against this it was observed that when pyridine was used as the solvent at room temperature, the PCl_5 "dehydration" actually produced 44% of **XLVI**!

Interestingly, no 9α,11β-dichloride was produced under the conditions employed.

In developing the chemistry further, it was reasoned that the small energy difference between the $\Delta^{9,11}$- and $\Delta^{11,12}$-eliminations would be enhanced in favor of the $\Delta^{9,11}$ olefine at low temperatures. This led to a study of the effects of temperature with the results summarized in Table 5.

Despite the very low levels of 11β-chlorosteroid impurity **(XLVI)** produced in the low-temperature reactions, it was thought prudent to find a process for reducing the level of the 11β-chloro compound or eliminating it altogether. This was because the betamethasone alcohol produced from PCl_5-derived $\Delta^{9,11}$ olefine could contain up to 0.1% of a new impurity, found to be the 21-alcohol corresponding to **XLVI**. Since we preferred to avoid dealing with the potential regulatory issues associated with introducing a new impurity into an API, we sought a simple method for eliminating the 11β-chloro compound. Based on observations that **XLVI** gave predominantly the $\Delta^{9,11}$ olefine **(XLIII)** when heated at 80°C in aqueous acetonitrile, Dr. Tann's group experimented with other polar solvents and found that simply heating **XLVI** in dimethyl sulfoxide at 90°C until the dehydrochlorination was complete gave >97%

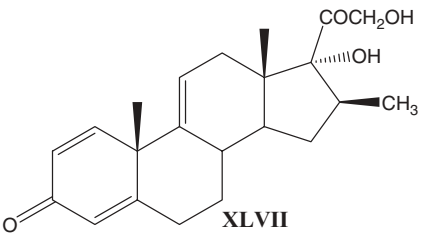
TABLE 5. Influence of Temperature on the "Dehydration" of XLII (as its 21-Cathylate) by PCl_5 in THF[a]

Temperature	% $\Delta^{9,11}$	% $\Delta^{11,12}$	% 11β-Chloro (XLVI)
Room temperature	81	7.4	11.3
−20°C	92.3	4.9	2.8
−45°C	95.5	3.3	1.2
−78°C	97.5	1.8	0.7
−85°C	98.4	1.3	0.3

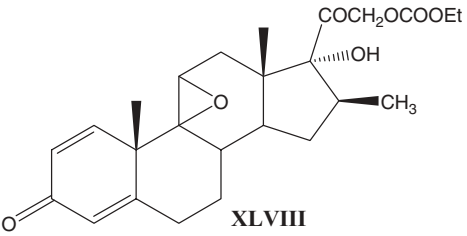
[a] All figures are HPLC area %.

of **XLIII**. In practice, this evolved into heating in DMSO for 1 hr at approximately 100°C. The PCl_5-mediated "dehydration" process was patented and published.[101]

Dr. Tann's group went on to study the subsequent reactions for converting **XLIII** into **XLIV** (Scheme 11). The first step was to isolate, identify, and quantify the impurities and then determine how best to avoid their formation. The main impurities, generally produced in low amounts in the manufacturing plant, were compounds **XLVII** and **XLVIII**.



XLVII

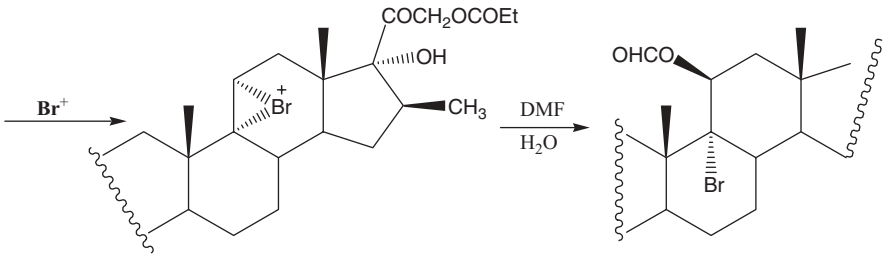


XLVIII

XLVII was speculated as being formed by the debromination of a 9α,11β-dibromo derivative of **XLIII** during the epoxidation process, whereas the 21-cathylate **XLVIII** was believed to have arisen due to occlusion in the relatively insoluble crystals of desired epoxide **(XLIV)** formed during the hydrolysis of this 21-cathylate in methanol/tetrahydrofuran.

Formation of **XLVII** was avoided by carrying out the epoxide formation step in DMF (as solvent) with a low level of 70% $HClO_4$. It was reasoned, correctly, that a bromoformate would be the preferred intermediate over a bromohydrin or dibromo intermediate and that this would cyclize to the β-epoxide more cleanly. This proved to be the case, eliminating 9α,11β-dibromo intermediate formation and with it the impurity **XLVII.**

[101] (a) Fu, X., Thiruvengadam, T. K., Tann, C.-H., Lee, J., and Colon, C. U.S. Patent 5,502,222, 1996 (to Schering Corp.). (b) Fu, X., Tann, C.-H., Thiruvengadam, T. K., Lee, J., and Colon, C. *Tetrahedron Lett*, 2001, **42**, 2639.



Formation of **XLVIII** was avoided by utilizing a solvent mixture (methanol/methylene chloride versus methanol/tetrahydrofuran) in which the epoxide **(XLIV)** was more soluble, thus avoiding the occlusion problem. This work was published.[102]

The new PCl_5-mediated "dehydration" reaction coupled with the improved epoxidation reaction created major benefits for the manufacturing division. The overall yield in taking the a 11α-hydroxy compound **(XLII)** to the epoxide **(XLIV)** (Scheme 11) increased from 60% to 85% and the quality of the epoxide improved to 99% purity from 92% previously. Although capital investment in low-temperature plants was necessary, wasteful purifications were eliminated, plant throughput was increased substantially, and regulatory concerns were greatly diminished. As a result, the cost of goods for betamethasone alcohol dropped dramatically.

STEROIDS ADDENDUM

The historical development of the steroid industry summarized, albeit briefly, in this excursion provides perspective both on the medical importance of steroids and on the astonishing contributions made by scientists and engineers of many disciplines, from many countries, which led to today's industry worth many billions of dollars a year. Tragically, World War II prevented German and Swiss chemists from making greater contributions to this industry.

The relatively high cost of steroids, along with the small scale of operations, allowed chemists working in the steroids field the luxury of taking an unconfined approach to developing chemical syntheses and processes. Thus, it has been possible to consider the use of many avant garde chemical reactions and chemical reagents, biological transformations, and process conditions that the larger chemical industry generally does not consider because of cost or hazards. Such contributions have in many cases brought relatively exotic chemistry of all types into the mainstream of chemical process development.

The development of process chemistry in the steroid field has played an important role in challenging chemists to find ways of dealing with specific transformations in polyfunctional molecules. This has enhanced appreciation of the role of protecting groups, reaction selectivity, chiral chemistry, and the need for high-yielding chemical reactions. Chemical engineers have also played a vital role in translating new chem-

[102] Fu, X., Tann, C.-H., and Thiruvengadam, T. K. *J. Org. Proc. Res. Dev.*, 2001, **5**, 376.

istry into plant practice; without their ingenuity, much of the new chemistry would not have reached plant operations. All the new chemistry has challenged process analysts to find and apply analytical techniques, enabling them to quantify chemical reactions and identify and quantify impurities. Inevitably, in the highly regulated world of today, everyone needs to be conscious of the needs in meeting the requirements of Regulatory Affairs (e.g., API impurities), Safety (e.g., finding alternatives to hazardous reagents, etc.), and the Environment (e.g., tracking and dealing with the disposition of such as oral contraceptives).

As indicated by Table 3 in this presentation, there is still life left in the steroid industry, now more than 70 years old. Ongoing research to understand the biological workings of the human body will undoubtedly uncover more opportunities for creating steroidal drugs.

For those of us who have worked in the steroid field for some time, the progress made, looking back, can only be regarded with a deep sense of satisfaction, humility, and awe. Looking forward, there is still much to be learned and done.

10

CASE STUDIES

Development work is always rewarding, even when bittersweet.

INTRODUCTION

A long and demanding program of work is needed to take a potential API from the identification stage to the market. Process development chemists and engineers working in the pharmaceutical industry initially reproduce or adopt research chemists' *Recipes* to supply the small quantities of APIs that enable research colleagues to progress their biological evaluations. Later, when a final candidate structure is selected for further work, they engage both in further improving the research recipe and/or quickly searching for and developing a synthesis *Method* suitable for safe scale-up. Scale-up of this *Method* provides large quantities of the API for further development. Chemical *Process* development follows as part of the enormous comprehensive effort that a company undertakes to harness all of the many disciplines and resources (in chemical and biological research, toxicology, clinical, chemical, and pharmaceutical development, etc.) needed to create an NDA submission and gain FDA approval.

In reality, almost all of the molecules identified in the torrent of enthusiasm attending the discovery phase will fail to become commercial APIs. Most are "weeded out" during the preliminary evaluation phase. Even then, very few of the survivor molecules will succeed in becoming commercial APIs. The development climate, like the weather, is unpredictable—becoming more certain only as information from many

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sources coalesces. Nevertheless, candidate API molecules selected for development are all progressed as though they will all succeed.

Chemists are fortunate in that the discipline of the chemistry profession enables them to rise above the uncertainties. As a group, they are easily "transported" above the fray by the intellectual challenges, the flow of ideas, and the molecular manipulations they see as needed for a practical synthesis. Successful management of such wonderful professionalism is an important requirement in pursuing a development program. It is not easy to be "carried away" and yet keep your feet on the ground. It is not easy to accommodate all the disciplines needed to succeed and adjust to broader points of view. It is not easy to handle project failure even though failure is often for reasons that are outside one's control—for example, a toxicity issue. Although mourning losses is difficult (mourning is harder the longer one has spent on a project), the chemist and engineer can frequently salvage considerable scientific satisfaction from the technical successes within the chemistry of the project. Publication, if possible, also helps to bring closure.

Under the heading of "Case Studies," I am providing two examples of chemical process development projects. One of these, the development of a commercial process for the manufacture of the cardiovascular drug, Dilevalol hydrochloride, reached the manufacturing and marketing stage, albeit briefly. The second case summarizes the early process research work carried out to identify a safe, low-cost process for the manufacture of the brain cancer drug, Temozolomide. This work never got beyond the laboratory phase of identifying a better process option for the manufacture of an intermediate—our avant-garde proposals for building the Temozolomide molecule itself were never tested. Despite the unfinished state of the project, it is worth recounting the ideas and their progression. Sad to say, many projects end like this—in a suspended state, perhaps one day to be resurrected!

CASE 1: DILEVALOL HYDROCHLORIDE—DEVELOPMENT OF A COMMERCIAL PROCESS

Background

The turbulent nature of active pharmaceutical ingredient (API) development is widely recognized. Only I in 10 or so new entities identified for development will reach the marketplace.[1] Pharmacological, Toxicological and Clinical findings can halt development at any time. The rate of progression of a new entity can be greatly changed by toxicology issues, by metabolic findings, formulation difficulties, the availability of bulk supplies, readouts from both clinical studies and the FDA, changing market conditions and so on. In short, priorities are constantly shifting. The process of

[1] DiMasi, J. A. Success rates for new drugs entering clinical testing in the United States, *Pharmacology and Therapeutics*, July 1995, **58**, 1. See also Scrip, 1995, August 18, p. 18. Overall, the significance of prior testing of an API outside the United States is apparent: For licensed-in compounds the success rate was 29.4%; for compounds first tested abroad, 14.6%; for those originated and first tested in the United States, 10.4%.

API development also runs so fast that, from a chemical development standpoint, conflicts between keeping the IND synthesis and improving or changing to a better synthesis provide endless challenge and, frequently, much frustration. In an API development respect, Chemical Development organizations act mostly in a service role, providing high-quality APIs for toxicology, clinical, pharmaceutical development, and analytical programs in a timely manner. Beyond the service role, chemical development's contribution to the identification and development of a commercial process is generally crucial. In this area, involvement with manufacturing organizations is essential—indeed the most successful chemical development organizations have a close link with manufacturing.

In achieving its mission, a Chemical Development organization relies upon chemists, engineers, and analysts as the primary professionals and works to forge important collaborations with other groups. Above all, Chemical Development ensures the safety of its chemical processes from the beginning and increasingly concerns itself with creating as environmentally sound a process as possible. Beyond Safety, the groups of most importance, especially at the start of a project, are Quality Control and Regulatory Affairs—a continuous dialogue addresses issues and expedites the filing of IND's, IND updates, and NDAs.

The development of a commercial process for the manufacture of dilevalol hydrochloride was not much affected by toxicology, pharmacology, or formulation considerations since experience with labetalol hydrochloride had provided a knowledge base on which to build. The greatest challenges were provided by the need to produce large quantities very quickly, by the cost-of-goods (COG) target and by chiral synthesis requirements—we assumed that a chiral synthesis would lead to the lowest COG.

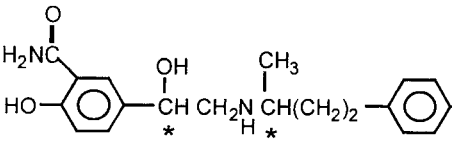
Introduction

The development of dilevalol hydrochloride[2] for use as a vasodilator and competitive antagonist at β-adrenergic receptor sites was an outgrowth of efforts in Schering–Plough, initiated in the late 1970s, to determine whether a single enantiomer of the racemic α- and β-antagonist labetalol would offer an advantageous marketing situation. It was speculated that one of the four enantiomers which comprise labetalol would carry enhanced β-adrenergic receptor blocking activity and fewer side effects.

Testing the concept required the preparation of pure samples of each of the four enantiomers. These were prepared by Gold et al.[3] and Chemical Development using classical resolution and chiral synthesis methods. It was quickly found that the RR enantiomer, later named dilevalol, was virtually free of α-adrenergic receptor blocking activity and also possessed superior vasodilator properties versus labetalol.

[2]U.S. Patent 4,619,919 to Schering Corporation, Nov. 14, 1986; U.S. Patent 4,950,783 to Schering Corporation, Aug. 21, 1990.

[3]Gold, E. H., Chang, W., Cohen, M., Baum, T., Ehrreich, S., Johnson, G., Prioli, N., and Sybertz, E. J. *J. Med. Chem.*, 1982, **25**, 1363.



The receptor blocking properties of the four enantiomers were published by Gold et al.[3] and Hartley.[4] A summary of Gold's figures is presented in Table 1.

TABLE 1. Summary of Comparative Cardiovascular Effects of Labetalol and Its Stereoisomers Relative Potencies[a]

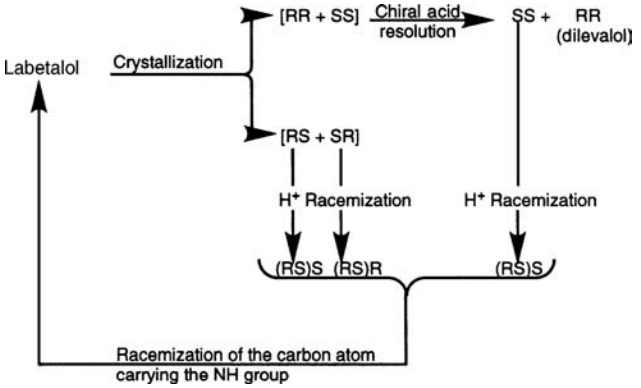
Compound	β_1-Receptor Blockade	α-Receptor Blockade	Vasodilation
Labetalol	1	1	1
RR isomer	3.5	<0.2	7
RS isomer	<0.06	0	–
SR isomer	<0.05	5.1	–
SS isomer	0	1.5	–

[a]Potencies normalized to labetalol = 1. β_1-Blockade and α-blockade are on different absolute scales (see Gold et al.[3] for detail and qualifications).

These results demonstrate that the RR and SR enantiomers are most responsible for the β- and α-blocking activities, respectively. Hartley[4] also showed that a 1:1 mixture of RR and SR enantiomers was twice as active a β-blocker as labetalol and about 1.3 times as potent an α-blocker.

Based on knowledge of the activity of the RR enantiomer and other marketing considerations, the Schering Cardiovascular Therapy Team decided to pursue the development of a 100- to 200-mg maintenance dose twice daily. This situation raised cost-of-goods (COG) questions which were addressed to Chemical Development through the marketing representative in the Cardiovascular Therapy Team. By the time of the COG request, Chemical Development had taken over the implementation and development of the chiral synthesis of dilevalol outlined by the Schering–Plough Research organization. Although this chiral synthesis was improved and shown to be workable from an initial supply standpoint (indeed it was scaled up to meet urgent bulk drug supply needs), it was not considered a good candidate for commercial operation. Nevertheless, in the spirit of reaching to achieve the lowest COG, we in Chemical Development projected that considerable simplification of the Research chiral synthesis should be possible (see later). Since both the Research chiral synthesis and the projected simplified synthesis of dilevalol were based on the original labetalol synthesis, we "guesstimated"—following discussion with Schering Manufacturing, who produced labetalol—that a fully absorbed manufacturing cost (raw materials,

[4]Hartley, D., *Chem. Ind.*, 1981, 551.



SCHEME 1.

labor and overhead) at a 50-tonne/annum scale (a figure provided by Marketing for 3 years after launch) should be in a range as follows:

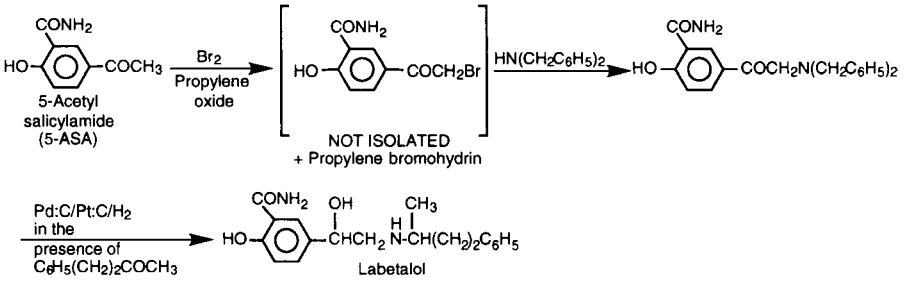
$$\text{Cost of dilevalol} = [3 \times \text{cost of labetalol}] \pm 25\%$$

Not surprisingly, given these figures, Marketing promptly set the COG target at [3 $\times$ cost of labetalol] **minus** 25%!

It is worth adding a cautionary note in regard to COG projections. In the early phases of a project, such as was the case with dilevalol, there is a danger that COG projections might be used to justify termination of a project, rather than serve to challenge the creativity of process R&D Chemists to invent a better synthesis. Fortunately, in the dilevalol case, the Cardiovascular Therapy Team and particularly Marketing and Manufacturing aggressively supported the development chemists and engineers in their efforts to create a simpler synthesis. COG projections were used, as the project developed, to validate that the core simpler, lower-cost synthesis strategy was viable and to identify those features and components of the synthesis most in need of improvement.

Early Considerations in Selecting a Synthesis Route for Further Development

The possibility of separating dilevalol from labetalol was considered as an option at the commencement of the dilevalol project. However, it quickly became clear, from work carried out in both Research and Development, that this approach might not be a viable option. Although the racemic pairs (RR + SS and RS + SR) were separable by crystallization, and although the optical resolution of the RR and SS enantiomers could be achieved through salt formation with a chiral acid, the direct yield of dilevalol was less than 20%. Nevertheless, it was recognized that if the recovery and recycling of the waste streams from the physical and optical resolutions could be carried out efficiently, considerable economies would be obtained (Scheme 1).



SCHEME 2.

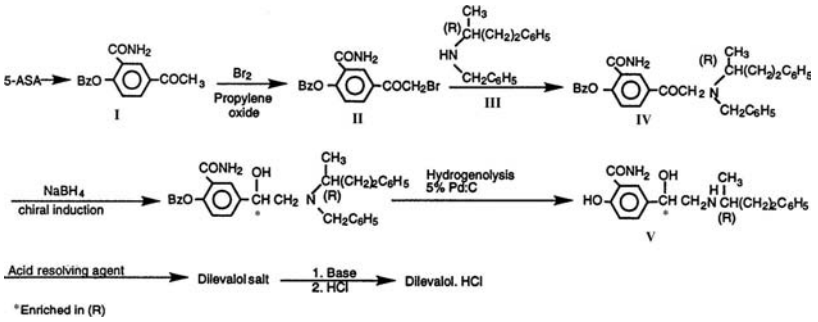
Acid-catalyzed racemization of the benzylic alcohol in the waste was shown to be quite straightforward. However, racemization of the carbon carrying the amino group appeared likely, from probing experiments, to prove difficult especially on a manufacturing scale. Moreover, COG concerns haunted the prospects of creating an efficient separation and recycling process, especially one starting with the most expensive molecule in the labetalol synthesis, labetalol itself. In summary, labetalol was considered unsatisfactory as a starting material on account of the logistics of the initial separations, the low one-pass yield of dilevalol, the need for two steps to racemize the very large quantity of waste, and the excessive solids handling requirements. Simple calculations showed that the Marketing COG target for dilevalol would not be attainable starting with labetalol. Furthermore, it was quickly evident that a large labor-intensive manufacturing plant would be needed to develop a dilevalol process based on labetalol.

The above realities, along with the realization that large quantities of dilevalol would be needed quickly for the Toxicology, Clinical, and Pharmaceutical Development programs, led Research to propose a chiral synthesis for the initial supplies. The process identified was based on the use of a labetalol intermediate and analogous chemistry to that used in the subsequent manufacturing steps for labetalol.

Synthesis of Initial Supplies of Dilevalol for Cardiovascular Therapy Team Programs

The process for the manufacture of labetalol is outlined in Scheme 2.

It was clear that a dilevalol synthesis strategy based on Scheme 2 would be advantageous. Use of the same intermediates and synthesis scheme as used for labetalol introduces operating economies. In addition, faster implementation and lower costs were anticipated by building on existing operations. Furthermore, although it was recognized that dibenzylamine in the labetalol synthesis was an expensive way of introducing the NH_2 group needed in labetalol, it was reasoned that use of a secondary amine, with the desired chirality already built in, may lead to induction of chirality in the subsequent reduction step. The Research synthesis was based on the *O*-benzyl derivative of 5-ASA (**I**) and is outlined in Scheme 3.



SCHEME 3.

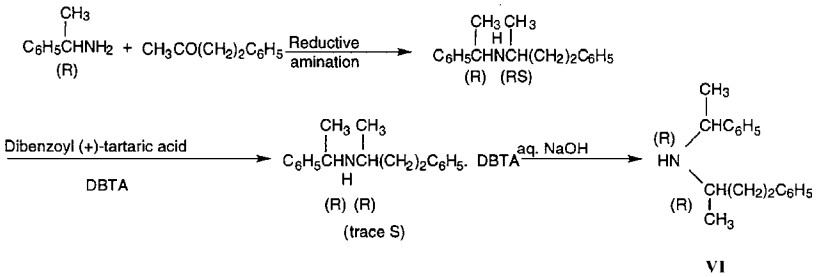
In this approach the R-amine moiety in **III** was considered likely, in view of the work of Yamada and Koga[5] and later Kametani et al.,[6] to provide some inductive control in the sodium borohydride reduction of **IV**. Moreover, the R-amine moiety is a necessary component of dilevalol. Desired inductive control was quickly demonstrated by Gold et al. (internal communication, October 25, 1979). However, a broad study of process conditions, particularly of solvent and temperature effects, only gave, at best, a ratio of RR to SR of

RR	SR
75%	25%

A later publication by Hartley (see footnote 4) validated these figures.

The above result provided a basis for the idea that if both alkyl substituents on the amine moiety were R-configuration inductive control in the sodium borohydride reduction of the keto group might be greatly increased. Since α-methylbenzylamines are known to hydrogenolyze relatively easily (cf. benzylamine itself), α-methylbenzyl substitution was considered a good choice. The ready availability of both RS- and R-α-methylbenzylamine prompted investigation of this proposal.

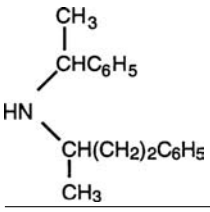
The RR-secondary amine (**VI**) was synthesized as follows:



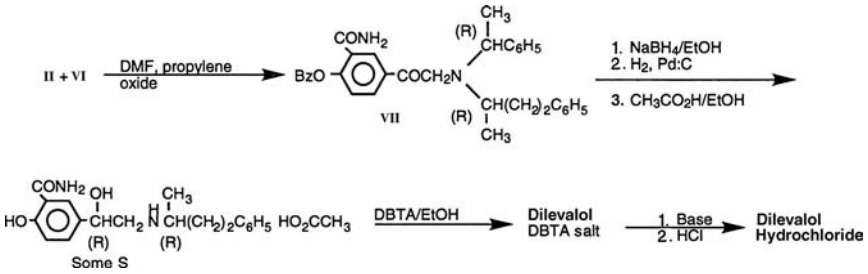
[5]Yamada, S., and Koga, K. *Tetrahedron Lett*. 1967, No. 18, 1711; Koga, K., and Yamada, S. *Chem. Pharm. Bull*., 1972, **20**, 526.

[6]Kametani, T., Kigasawa, K., Hiiragi, M., Wagatsuma, N., Kohagizawa, T., and Inoue, H. *J. Pharm. Soc. Japan*, 1980, **100**, 839.

TABLE 2.

Conformation of 	Stereoisomer Analysis of Crude Dilevalol Acetate				Stereoisomer Analysis of Dilevalol DBTA Salt				Yield of Dilevalol DBTA Salt Based on Starting RR Secondary Amine
	RS	SR	RR	SS	RS	SR	RR	SS	
RR:RS* = 52:48	—	21.3	77.5	1.2	—	4.3	94.6	1.2	50.5%
RR > 98%	0.7	10.2	86.9	2.1	0.2	2.3	96.2	1.3	59.0%

* S component derives from RS-α-methylbenzylamine.



SCHEME 4.

Reaction of **VI** with **II** gave a high yield of aminoketone **VII**, which when reduced first with sodium borohydride and then with hydrogen Pd/C gave crude dilevalol isolated as its acetate (Scheme 4). The acetate salt was purified by dissolution and crystallization as its DBTA salt.

In order to determine whether or not added steric effects in using α-methylbenzyl contributed to the induction of R configuration in the sodium borohydride reduction, the same sequence of reactions was carried out employing RS-α-methylbenzylamine. Analysis of the products from both reaction sequences gave the results summarized in Table 2.

Table 2 indicates that there is little difference between benzyl and RS-α-methyl benzyl in terms of inductive effect in the ketone reduction. Furthermore, as expected, the use of the secondary amine **VI**, in which both amine substituents were R in conformation did give a desirable increase in the yield of dilevalol. As an aside it is known that hydrogenation of the keto group in compound **IV** gives a 1:1 mixture of the RR and SR enantiomers (see footnote 4). From this it is clear that the most important factors in the induction of maximum chirality in the ketone reduction step

are the complexation of borohydride with the amine function (see footnote 5) and the like chirality of the *N*-alkyl substituents.

The above Scheme 4 process utilizing RR-amine (**VI**), referred to as the "RR-amine process," became the IND process for producing hundreds of kilos of dilevalol hydrochloride needed for the early clinical, toxicological, and pharmaceutical sciences work. The Scheme 4 process was patented.[7] It should be noted that, despite a great deal of work on process conditions, solvents and reducing agents the ratio of RR to SR could not be improved. Thus, in a practical sense, it proved impossible to eliminate the DBTA resolution as a step for creating desired chiral purity. Minor changes in the process and improving the optical purity of **VI** gave an acceptable-quality dilevalol with an RR assay of generally greater than 97%. Process changes were filed, as IND updates, with the FDA as they were validated. The full analytical specification set for dilevalol, as its hydrochloride salt, was

- Description: White to off-white powder.
- Identification:
  A. I.R.—Agrees with reference standard specification.
  B. Chloride—Responds to test.
  C. TLC—Sample spot migrates at the same rate (R_f) as the reference standard spot.
- Related Compounds: Maximum 1% total with not more than 0.5% of any one substance.
- Stereoisomer Content: Maximum 3% total of other stereoisomers (SS + RS + SR).
- Specific Rotation $[\propto]_D^{26} = -26.5^\circ$ to -30.5°
- Loss on Drying: Maximum 0.5%.
- Residue on Ignition: Maximum 0.1%.
- Heavy Metals: Maximum 0.002%.
- Assay (HPLC): 97–102% (calc. on dry basis).

The impurity profile (synthesis related impurities) was actually better for dilevalol than for the parent compound, labetalol, reflecting the benefits of further purification during the DBTA resolution step. Thus, although dilevalol hydrochloride contained traces of DBTA itself, no tertiary amine impurities or brominated dilevalol could be detected—both types of impurity are present at very low levels in labetalol.

Selecting the NDA Process and Reducing the Cost-of-Goods

The above "RR-amine process," based on RR-amine (**VI**), was used for the first approximately two-year production program supplying most of the early requirements of bulk drug for the Clinical, Toxicology, and Pharmaceutical Development

[7]U.S. Patent 4,658,060 to Schering Corporation, Apr. 26, 1982.

programs. During this time, efforts were undertaken to improve the process and to assess its commercial potential. At the same time, process research was going on in Chemical Development to evaluate the simpler synthesis, referenced earlier, which was projected as likely, if successfully developed, to meet the Marketing COG targets. Other ideas for improving the simpler synthesis, as well as ideas for radically different synthesis, were "championed" during this period.

Initially, only a small effort was disposed to assess the feasibility of the simpler synthesis. This grew at the expense of the "RR-amine process" because it became evident that this process was, like its forerunner (the separation of labetalol isomers), unlikely to achieve the Marketing COG target. Ideas for radically different syntheses were given an even lower priority and were often left to "bootleg efforts" by the originators.

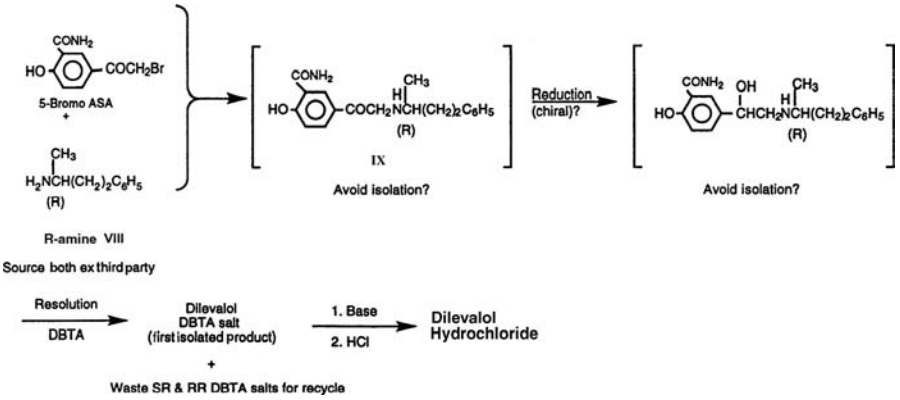
The simpler synthesis was built on the same premise as the "RR-amine process", namely that it should be based on the existing labetalol process, particularly in terms of using the same or similar raw materials and intermediates, wherever possible, and also using similar plant equipment. The simpler synthesis grew out of a critique of the disadvantages of the "RR-amine process" (Scheme 4).

Main Disadvantages of Scheme 4	Improvements
1. Too many steps.	Avoid steps or combine them.
• Is benzylation of the phenol necessary.	Test elimination of Bz protection.
• RR-Amine is a new compound—low-cost source needed.	Go to third party—minimize investment.
• Chiral reduction not 100%—DBTA resolution unavoidable.	Minimum is to recycle DBTA.
• Two reductions necessary ($BH_4^{\ominus}$ and H_2/Pd:C)	One reduction if Bz eliminated
• High solvent and reagent usage.	Increase reaction concentration/Recycle.
2. Costs are high.	
• Expensive chiral α-methylbenzylamine is lost as $C_2H_5C_6H_5$.	Since DBTA resolution is unavoidable, eliminate enhancement of chiral induction.
• Recovering/recycling wastes adds costs.	Minimize wastes.
• Considerable capital investment needed—high depreciation	} Simplify process to reduce/avoid these costs.
• Labor-intensive	

Based on the above critique the simpler process was defined as follows (Scheme 5).

The simplified process concept was itself the subject of criticism and doubt:

- Could R-1-methyl-3-phenylpropylamine (R-amine, **VIII**) be sourced at low enough cost?



SCHEME 5.

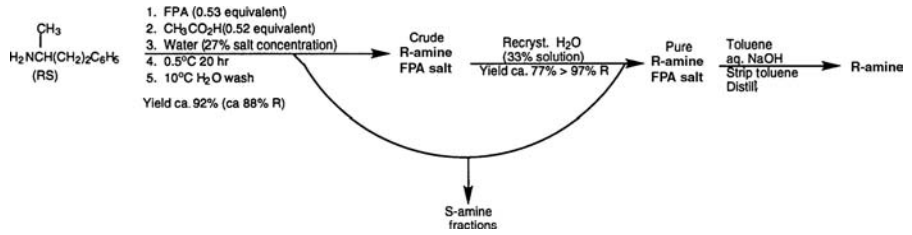
- Would the likely dialkylation of R-amine (**VIII**) introduce new impurities which are difficult to remove?
- Would R-amino ketone (**IX**) be isolable relatively free of dialkylated impurities, thereby serving as a purification step if needed?
- Would the DBTA resolution of an expected 1:1 SR: RR mixture be efficient?
- Would the dilevalol hydrochloride obtained by this Scheme contain any new impurities which would complicate the Regulatory registration process?
- Could the work needed to demonstrate and prove that the simplified process gives dilevalol hydrochloride acceptable to Regulatory Affairs and the FDA be done in the time frame needed to update the IND prior to NDA filing?

Raw Materials Sourcing. There was relatively little problem in sourcing 5-bromoacetylsalicylamide (in-house) or dibenzoyl-(+)-tartaric acid (large tonnage Italian source). Although RS-1-methyl-3-phenylpropylamine was available at low cost ($10–12/kg) in tonnage quantities (Germany and Holland) no supplier of the R-amine **VIII** was known.

R-1-Methyl-3-phenylpropylamine. Many chiral acids were evaluated, with water as the solvent, before *N*-formyl-*L*-phenylalanine (FPA) was selected as the best acid for resolving RS-1-methyl-3-phenylpropylamine. The resolving acid and process were patented.[8] An outline of the commercial process implemented in Germany is given in Scheme 6.

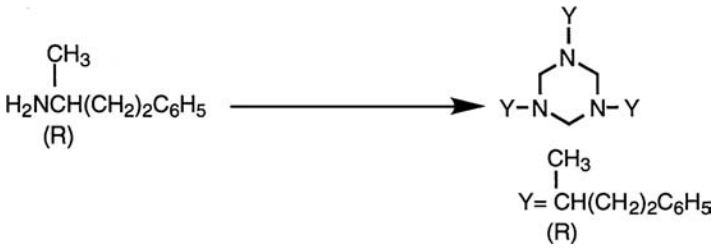
The resolution process step worked very well on a commercial scale. In an early version, the R-amine was obtained as a methylene chloride solution. This had not posed a problem in the Chemical Development plant. Methylene chloride was rapidly distilled using a condenser system which efficiently liquefied the distilled methylene chloride. when this process was transferred to Germany, the rate of distillation of the

[8]European Patent 320898 to Schering Corporation, June 21, 1989.



SCHEME 6.

methylene chloride in the equipment available was greatly extended (from 3–4 hours to >30 hours) to enable the German plant to stay within its environmental emission permit for methylene chloride. Under these conditions the R-amine was alkylated



In hindsight, the effects of using methylene chloride as a solvent for a primary amine should have been predictable. The reality is that the possibility of adverse reactions occurring was lost with repeated successful use of methylene chloride under the rapid distillation conditions prevailing in the Chemical Development plant.

Various solvents were evaluated as methylene chloride replacements. Toluene was selected as best meeting all the needs. Thus, the R-amine was sufficiently soluble, water phases were readily separable at 25°C, and toluene contamination was of no consequence since the reaction of R-amine and 5-bromoacetylsalicylamide was already conducted in the presence of traces of toluene.

The chemical resolution process of Scheme 6 was developed into an economically favorable one by the ready recycle of both the FPA resolving agent and the combined (mostly S) amine fractions. FPA, which was prepared by methyl formate reaction with L-phenylalanine, was shown to be stable (no racemization and no hydrolysis) when the resolution and work-up processes were conducted within the pH range of 2–12 at temperatures below 25°C (higher temperatures were not studied). FPA meeting specification was isolated in yields of ca. 95% by simple acidification of its aqueous salt solutions and filtration.

The 1-methyl-3-phenylpropylamine containing fractions of largely S conformation were found to be readily racemized without degradation by heating at 150°C and 150 psi hydrogen in the presence of Raney nickel.[9] Thus the manufacturers of

[9]Finding by Dr. N. Carruthers and R. DeVelde in our laboratories.

RS-1-methyl-3-phenylpropylamine, who produced this compound by the reductive amination of benzylacetone, were well able to racemize the byproduct S-containing fractions, thereby providing some additional cost reduction and also avoiding a waste disposal problem.

Although the above commercial process succeeded in providing R-1-methyl-3-phenylpropylamine (VIII) for significantly less than $100/kg several other companies carried out research to find even lower cost processes based on the RS raw material. A few of these processes will be described later.

Development of the New NDA Process to a Commercial Scale

Early Considerations. A degree of nervousness developed in the early stages of evaluation and promotion of the simpler synthesis. Many were concerned by the risks associated with process change. In particular QC and Regulatory Affairs raised questions on quality, especially the impurity profile and the equivalence of dilevalol hydrochloride from the simpler process. By this time the 'biobatch' had already been produced via the "RR amine process" for toxicological and pharmacological work. Understandably Pharmaceutical Development, in harmony with QC and Regulatory Affairs, wanted assurance that such parameters as crystal size, bulk density, particle size distribution and tablet dissolution rates would not change and that tablets from the simpler synthesis would be bioequivalent to the dilevalol hydrochloride from the "RR-amine process" already registered in the IND application. In short, urgent evaluations of the product of the simpler synthesis were needed in order to gather the data required for an IND update. Regulatory Affairs proposed that, since the NDA filing was only about 2 years away, the data needed to validate the simpler synthesis should be obtained as quickly as possible and presented to the FDA Cardiovascular Division reviewer, as much in advance of the NDA filing as we could manage.

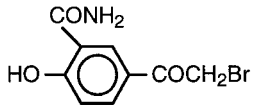
In defense of the process change, it was pointed out that the R-amine and RR-amine processes were based on the same chemistry. Nevertheless, we still needed to accommodate the views of those who queried whether the hydrogenolysis step in the "RR-amine process" was somehow also introducing a purge of "something" during the debenzylatoin step in Scheme 4! Those with concerns did, however, concede that by intersecting the "RR amine process" before the DBTA resolution and purification steps, the simpler R-amine process did maintain considerable "clean-up" capability.

The Schering Manufacture Division was, at the same time, also looking to the future by initiating outside evaluation of the "RR-amine process." This effort was intended to determine whether others, with under-used manufacturing plant capacity, could take on the production of dilevalol hydrochloride, or a late intermediate, and generate cost projections, at a 50-metric tonne/annum production rate, which would be advantageous versus in-house projections. The primary objective was to source a late intermediate, thereby allowing Schering Manufacturing to undertake the final steps itself under the strictest GMP control. Another scenario was also initiated, with both Chemical Development and Manufacturing determining the capital investments which would be required to manufacture dilevalol hydrochloride in-house. The figure for a 50 tonne/annum manufacturing plant on the Schering manufacturing site in

Ireland via the "RR-amine process", assuming raw material outsourcing, was estimated at $48–50 million. Chemical Development proposed that since it had much unused plant equipment in Union, New Jersey (bequeathed by Manufacturing when it moved operations to Puerto Rico), that an alternative would be to carry out early launch manufacture of a late stage intermediate in Union by using the simpler synthesis. Ireland would then take on the manufacture of the dilevalol hydrochloride in mostly existing plant. The reasoning was that it would be advantageous to limit capital spending and delay major investment in manufacturing plant until the process was better defined and the market needs were better known. Since the Union capital investment was projected at only $5–6 million, this strategy was adopted. This approach also made best use of Chemical Development's chemical engineers who were closely involved in the design of the process as well as in the testing and selection of process equipment.

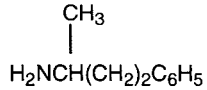
Process Development Leading to FDA Review. One of the core premises in the simpler process as outlined in Scheme 5 was that it would be highly desirable, especially from a cost reduction standpoint, to avoid isolating solids. In this way all the equipment and labor needs associated with solids handling would be avoided, thereby reducing the product cost by minimizing labor and overhead costs and also by boosting the process throughput and plant capacity. The main disadvantage of such a strategy is that the process loses an outlet for byproducts (impurities) and generally requires that high reaction yields are obtained to minimize the need for purging reaction byproducts. The following describes the successful efforts to combine process steps such that the first isolated product from the reaction sequence is dilevalol as its DBTA salt.

From Raw Materials to Dilevalol DBTA Salt. In order to provide the best chance of success in the Scheme 5 sequence, great emphasis was placed on starting with the highest-quality raw materials.



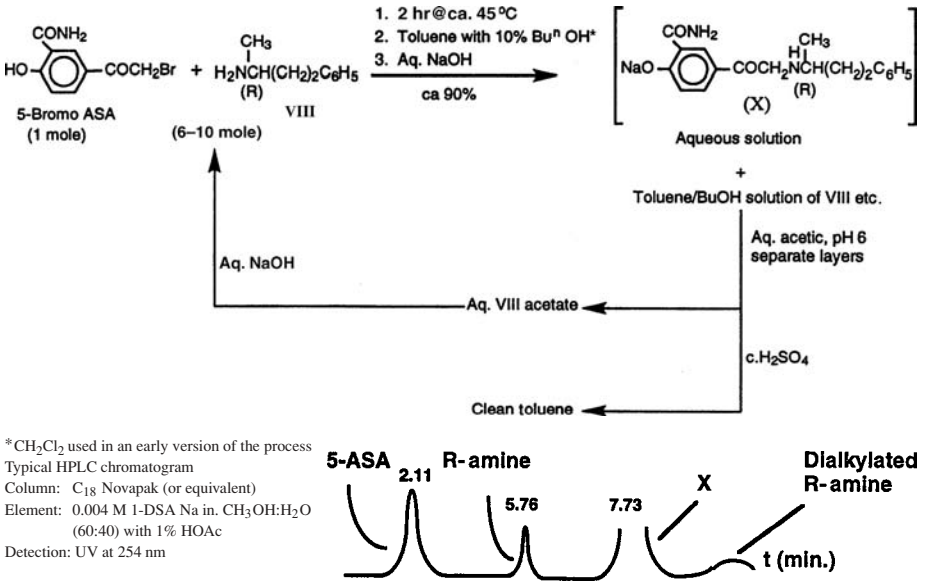
5-Bromoacetyl salicylamide
(5-Br ASA)

Appearance: White to cream solid.
Identity: IR agrees with standard.
Purity (HPLC): $> 95\%$
The major impurity is 5-acetylsalicylamide (5-ASA).
Small amounts ($< 0.3\%$) of ring brominated impurity are also present.



R-1-Methyl-3-phenylpropylamine

Appearance: Clear, colorless to light yellow liquid.
Identification: IR agrees with standard.
Specific Rotation: $[\alpha]_D^{20} = -19.0 \pm 1.5^\circ$ (c= 5 in cyclohexane).
Enantiomeric Purity: Minimum 98% R (Moshers acid method)
Residual Solvent: $\leq 0.5\%$ (gc).
Related Compounds: $\leq 1\%$ (gc).
Assay: 98–102% ($HClO_4$ titration)



*CH_2Cl_2 used in an early version of the process
Typical HPLC chromatogram
Column: C_{18} Novapak (or equivalent)
Element: 0.004 M 1-DSA Na in. CH_3OH:H_2O (60:40) with 1% HOAc
Detection: UV at 254 nm

SCHEME 7.

Quality criteria and analytical release specifications were set for all the solvents and reagents used in the process. Operating conditions for the process were established to ensure the minimum decomposition of intermediates and reagents, such as DBTA, at the same time as maximizing product yield.

In order to minimize dialkylation of the amino group, 5-BrASA was added to a large excess of the R-amine. This necessitated the engineering of a simple countercurrent toluene extraction system for recycle of the excess R-amine. This first reaction step was studied at a variety of temperatures, concentrations, excesses of R-amine and extraction conditions. The process was monitored by HPLC. In summary, the following outlines the optimum process to the sodium salt of R-aminoketone (**X**)—Scheme 7. The plant equipment layout is shown in Figure 1.

Although R-amine (**VIII**) forms a phenolate salt with phenols, no evidence of phenolate reaction with the bromoketone was found. As expected the only byproduct of consequence was the dialkylated R-amine (up to ca. 2%). The toluene solution containing the unreacted R-amine was extracted with aqueous acetic acid and the aqueous layer treated with aqueous sodium hydroxide to give neat R-amine for recycle. The color of the R-amine did increase with multiple recycles but this did not appear to affect the quality or yield of **IX**. As a precaution however, the R-amine was distilled after about every tenth batch. Although toluene could be recovered for re-use by distillation it was found that simple washing with c. sulfuric acid, separating the layers and washing with water gave toluene suitable for re-use.

In a further investigation, it was found that the aqueous solution of the sodium salt of R-aminoketone (X) could be acidified, the R-aminoketone extracted into a solvent

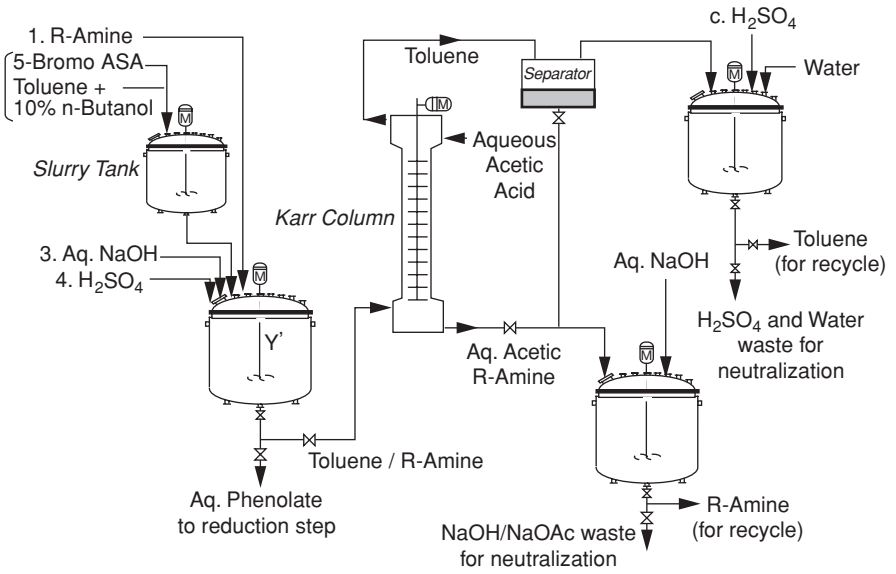


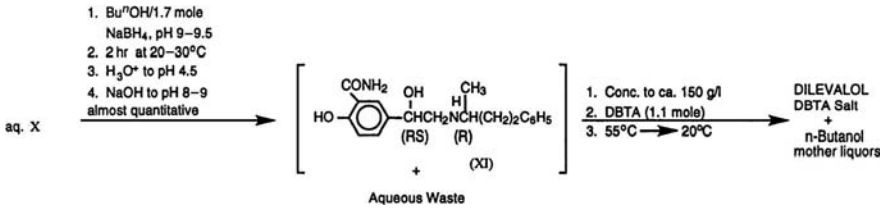
FIGURE 1. Plant Equipment for R-Amine reaction with 5-Bromo ASA (Scheme 7).

and precipitated as a pure hydrochloride. Although this step never proved necessary in commercial operation substantial quantities of the hydrochloride of R-aminoketone **IX** were produced for work on alternative routes to dilevalol (qv).

The optimum process for converting aqueous solutions of the sodium salt of R-aminoketone (**X**) to dilevalol DBTA salt resulted from a study of such parameters as reaction solvent, temperature, mole equivalents of sodium borohydride, mole equivalents of DBTA and crystallization conditions. The reduction process, which essentially yielded a 1:1 mixture of RR and SR compounds, was monitored by HPLC (Scheme 8). The plant equipment layout is shown in Figure 2. The process containment equipment (Krauss Maffei Titus system) used for the filtration, washing and drying steps is shown in Figure 3.

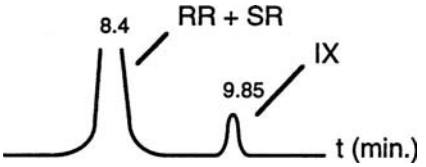
The purpose of the acidification step (to pH 4.5 with sulfuric acid) was to destroy the borate esters and complexes which compromised the distribution of the RR/SR mixture (XI) into the *n*-butanol layer. Considerable work was carried out on the crystallization of the dilevalol DBTA salt in an effort to avoid oiling and to crystallize a salt with an RR content of ca. 97%. This could be achieved by dissolution with DBTA at ca. 55°C and crystallizing at ca. 45°C. Higher yields of lower purity proudct (ca. 95% RR to 5% SR) were obtained by cooling to 0°C.

For day-to-day process monitoring and assay of the synthesis related impurity levels it proved more convenient to use a thin layer chromatographic assay [with an elution system comprising ethyl acetate (100), isopropanol (60), water (32), and ammonia (8)] than to use HPLC.



Overall yield 5-bromo ASA to dilevalol DBTA salt = 30–40%

Typical HPLC chromatogram
Column: C_{18} Novapak (or equivalent)
Element: 0.004 M 1-DSA Na in. CH_3OH:H_2O (60:40) with 1% HOAc
Detection: UV at 254 nm



SCHEME 8.

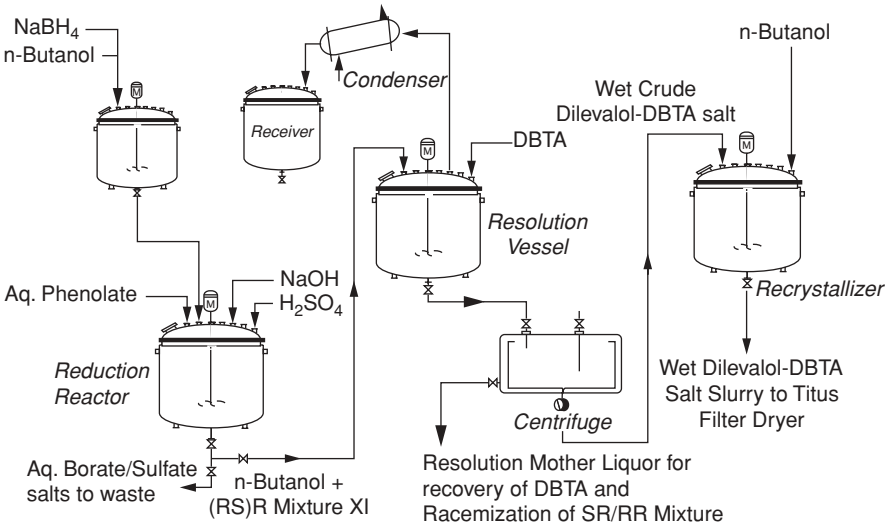
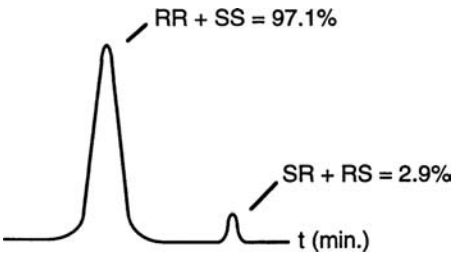


FIGURE 2. Plant equipment for reduction/resolution step (Scheme 8).

For assaying the enantiomeric purity of dilevalol in the DBTA salt, the Schering Research Analytical Department worked out an efficient glc procedure, utilizing methylboronic acid. Although the method did not separate RR and SS enantiomers or RS and SR enantiomers, it served to quickly indicate the efficiency of the resolution process since no racemization of the R-amine moiety was ever found. A typical glc trace was as follows:



The specification set for the dilevalol DBTA salt was

Appearance: White to off-white solid
Chemical Purity (tlc): <3% related substances
Enantiomeric Purity: RR + SS > 97%, SR + RS < 3%

As indicated by the above enantiomeric purity assay, the quality of the DBTA salt prepared according to Scheme 8 was often borderline (ca. 97%). A process was registered (as an IND update) for occasional use in which the salt was split back to the base (in *n*-butanol) and the DBTA salt formation step repeated. As time passed, it became apparent that it would be better, from an operations and economics standpoint, to seek a higher first crop yield (by cooling to ca. 0°C) and to recrystallize the wet first crop routinely. This position became the subject of criticism during the FDA's pre-approval inspection (q.v.).

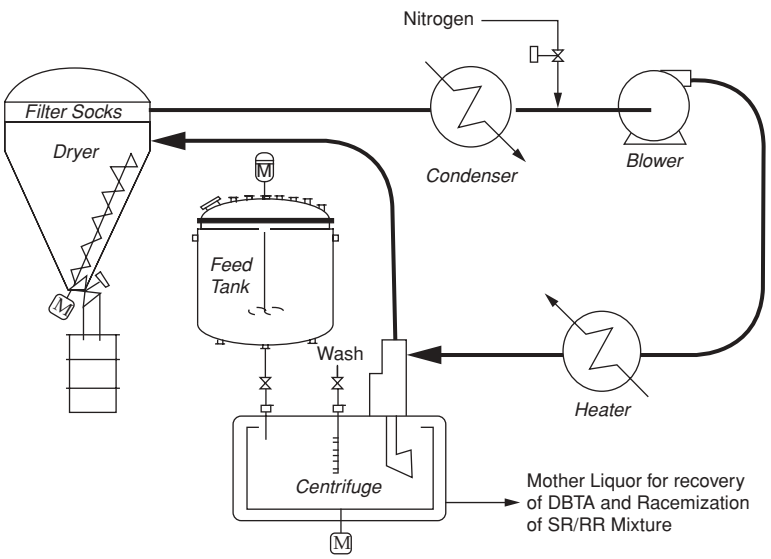


FIGURE 3. Plant equipment for filtration, washing, and drying of dilevalol DBTA salt.

Racemization and Recycle of the n*-Butanol Mother Liquors from the DBTA Resolution*. The aqueous base extraction of DBTA followed by acidification of the aqueous layer and filtration of the DBTA proved relatively straight forward. On the other hand, much work was needed to identify and develop the most cost-effective system for racemizing the SR/RR mixture (approximately 70:30 respectively in composition) and to recycle the racemate produced.

Initially the SR/RR mixture was precipitated as an oxalate salt, with azeotropic drying of the *n*-butanol to enhance the yield. This oxalate salt was filtered and the washed crystals racemized by heating with aqueous sulfuric acid at 40–60°C. The racemate was extracted into *n*-butanol at pH 8.3 to 8.8 for recycle to the resolution step. This process, although workable, proved cumbersome, necessitating the handling of large quantities of the oxalate salt, adding to equipment and labor requirements and also waste disposal problems. An elegant solution to the problem was generated by the finding that water wet *n*-butanol solutions of the 70:30/SR:RR mixture, as obtained after extracting the DBTA from the resolution mother liquors, could be racemized utilizing a strong cation exchange resin—Dowex XFS 43279 (H^+) was particularly effective. This operation was conducted in a batch fashion using a 2000-gallon jacketed glass-lined vessel equipped with a filter in the bottom valve for drawing off liquids. After loading the SR/RR mixture, the *n*-butanol was sucked away; the loaded resign was washed successively with one bed volume of *n*-butanol, followed by water, aq 5% sulfuric acid, and water. The racemization was carried out by heating the water resin slurry at ca. 90°C for 2 hours. The racemized SR/RR mixture was removed from the resin by treatment with aq. sodium hydroxide/*n*-butanol.

The pH was adjusted to 8.5 to retain carboxylic acid (ca. 7% hydrolysis of the amide) in the aqueous layer. The *n*-butanol layer containing the 1:1/SR:RR mixture (88–90% recovery) was recycled to the resolution step. The resin was regenerated via sulfuric acid treatment. This process was patented.[10] The equipment layout for this step is shown in Figure 4.

Dilevalol DBTA Salt to Dilevalol Hydrochloride. Very little improvement in the RR composition results from the transformation of dilevalol DBTA salt to dilevalol hydrochloride. Ethyl acetate was used as the solvent vehicle in early work. In a search for a more stable solvent methyl isobutyl ketone (MIBK) was selected as the best alternative. DBTA was removed by extraction into water with sodium hydroxide (DBTA of excellent quality was recovered from the aqueous phase in high yield >90%). The MIBK solution of dilevalol was then treated with hydrochloride acid to precipitate dilevalol hydrochloride (Scheme 9). The pH needed for maximum efficiency in the crystallization of dilevalol hydrochloride was 0.5 (this is in sharp contrast to the pH required for maximum efficiency in the crystallization of labetalol hydrochloride—pH 3.0). It should also be noted that dilevalol hydrochloride could not be handled in stainless steel equipment. Hastelloy, plastic or ceramic equipment was employed to eliminate the risk of coloration of dilevalol hydrochloride by traces of iron compounds. The plant equipment layout for this step is shown in Figure 5.

[10]International Patent Application, WO 91/08196 to Schering Corporation, June 13, 1991.

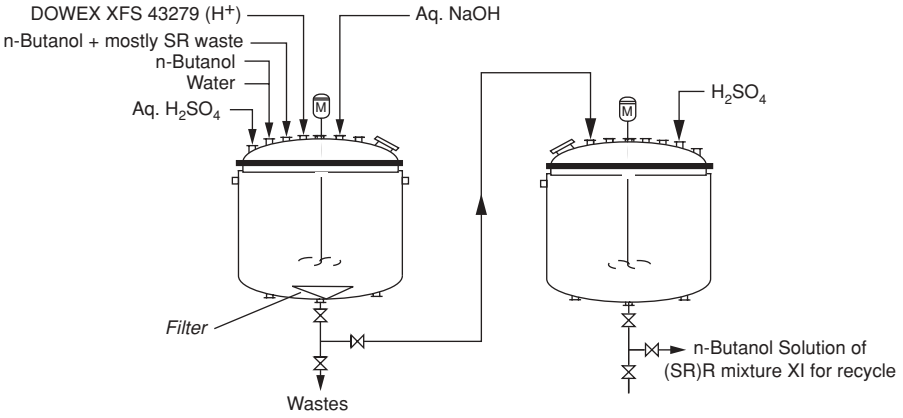
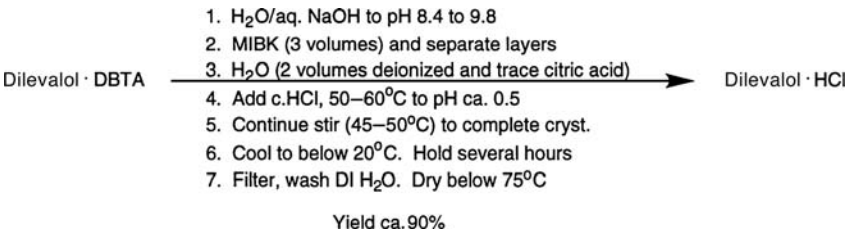


FIGURE 4. Equipment for Racemization of n-Butanol Solution of Mostly SR Waste.



SCHEME 9.

The conditions used in the hydrochloride formation/crystallization step were somewhat different when MIBK/water was used in place of ethyl acetate. In particular, hydrochloride formation needed to be carried out by adding concentrated hydrochloric acid to the MIBK solution of dilevalol base at ca. 55°C (versus ca. 25°C for ethyl acetate). In this way, oiling out of the hydrochloride salt was avoided. A small amount of citric acid was included in the crystallization system to chelate any traces of iron which may be introduced. The amount of water in the system is more than sufficient to dissolve the small amount of citric acid—in early versions of the process, using much less water, precipitation of some citric acid caused a slight discoloration of the dilevalol hydrochloride. The crystallization conditions were carefully chosen to produce a crystal which filtered and washed well, which dried well (to MIBK $<0.5\%$) and which gave a bulk density (ca. 0.3 g/ml) which met Pharmaceutical Development's criteria for operation of their tabletting process.

The work carried out on the dilevalol hydrochloride step was undertaken in close collaboration with Schering Manufacturing in Ireland, who contributed greatly to the establishment of the IND/NDA process conditions for final API preparation. The more aggressive process conditions of temperature, coupled with the use of a pH $<$ 1, as employed in the MIBK-based production process, were examined in depth. It

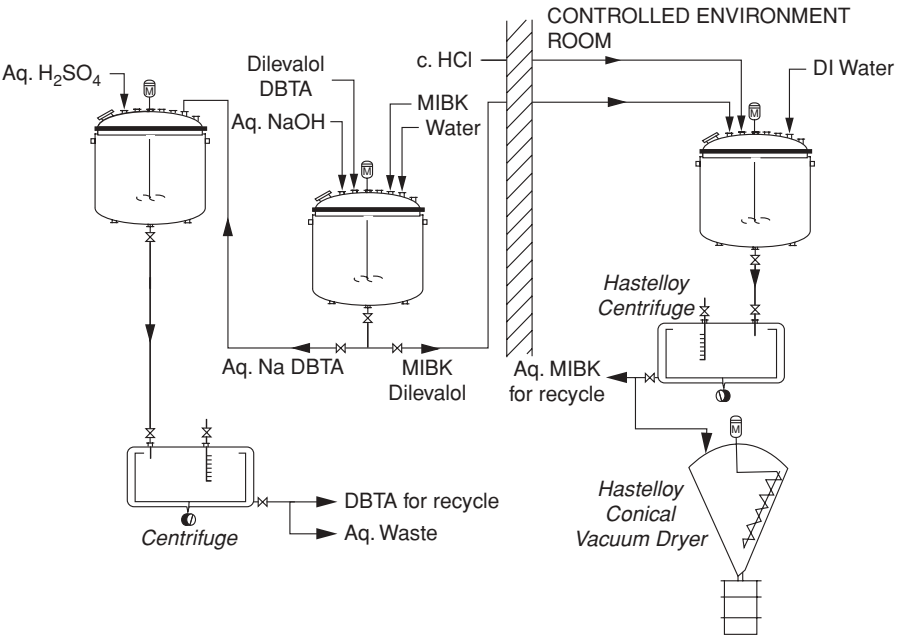


FIGURE 5. Equipment for conversion of dilevalol DBTA salt to dilevalol hydrochloride (Scheme 9).

was shown that the 50–60°C process condition in the crystallization step at low pH did not lead to detectable recemization at the carbinol center.

The product of the simpler synthesis was compared in detail with the product of the "RR-amine process." In particular, the Research Quality Control Unit searched for the presence of different polymorphs and new impurities (e.g., the dialkylation byproduct from the first step). They compared the stabilities of both products and also compared the hardness and dissolution rates of tablets made from both products. Since the DBTA resolution, crystallization, and product isolation steps, as wll as the final dilevalol hydrochloride preparation step, were the same for both the "RR-amine process" and the simpler synthesis, it was anticipated that these steps should protect against the introduction of new impurities or changed physical parameters in the final crystalline product. Such proved to be the case.

Process Engineering. Chemical Development's chemical engineers worked closely with the chemists and analysts in the internal team created to progress the dilevalol hydrochloride project. The engineering input and sharing of points of view contributed greatly to the speedy simplification of the process and the early focus on cost reduction through minimizing isolations and recycling solvents, as well as utilizing waste streams. Safety issues were identified and overcome. Emissions control needs were met. An existing plant was adapted to the requirements of the simpler synthesis.

Additional needed process equipment was evaluated, selected, purchased, and set up. Automation opportunities were defined, and process control instruments were tested, purchased, and installed. An existing clean (HEPA-filtered) area was upgraded for the final isolation of the dilevalol hydrochloride made in New Jersey—this was needed to serve the requirements for the parenteral dosage form.

The equipment flow sheets (Figures 1–5) outline vessel needs for the process. Equipment is mostly conventional. The only equipment purchases were a 2000-gallon glass-lined vessel for the racemization of fractions containing S-carbinol, a countercurrent extraction column (Karr column), and the automated Krauss Maffei Titus system. This latter piece of equipment (Figure 3) is designed for closed system crystallization, filtration, washing, and drying. It provides nitrogen blanketing, solvent capture, and drying capabilities under totally contained conditions. The only exposure of operators to the hypotensive dilevalol DBTA salt is during the step of offloading the dry powder; protective clothing is worn during this procedure. It is pertinent to add that process containment equipment of the type of the Titus system is invaluable in the processing of solids where dusts have explosion potential—dilevalol hydrochloride dust, for example, was found to be more explosive than coal dust.

FDA Review and Compliance Activities. A package of information detailing the above simpler synthesis and the definitive work carried out in Chemical Development, Research QC and Pharmaceutical Development to show equivalence versus the original "RR-amine process" was approved by the Review Branch of the FDA's Cardiovascular Division at a meeting in Rockville. This package provided the basis for the NDA filing.

Approval of several additional process changes was sought post the NDA filing. Although it is considered risky to request FDA approval of process changes after NDA filing (because of the potential that changes may set back the NDA review), Schering–Plough Regulatory Affairs was able to review additional changes, and all the supporting data, with the Cardiovascular Division and gain agreement that the changes were of a noncritical nature such that there was no risk of compromising the quality of dilevalol hydrochloride. The NDA chemistry section was updated without penalty and the changes adopted. The changes were:

1. The registration of toluene or *n*-butanol as the slurry solvent for adding 5-bromo ASA to the R-amine in the first step—minimizes solids handling.
2. The substitution of sulfuric acid for hydrochloric acid to reduce the pH to 4.5 after the borohydride reduction step—reduces the risk of plant corrosion and product contamination by iron.
3. The use of 55–60°C in the DBTA crystallization step with cooling to 25–45°C to replace the 50°C and cooling to 0–5°C—gave more consistent enantiomeric purity results (and slightly lower yields). It should be noted that we later reverted to 55–60°C in the crystallization steps with cooling to 0–5°C, followed by routine recrystallization.

4. The use of a wet *n*-butanol recrystallization for reprocessing out-of-specification DBTA salt to replace the original split back to the base and repeating the DBTA salt formation. The recrystallization process gave a product with higher enantiomeric purity.
5. Detail of the 50–60°C crystallization of dilevalol hydrochloride from MIBK/water. A comprehensive comparison report with the earlier process using 25°C hydrochloride crystallization temperatures was provided.

In today's more formalized review climate, it seems unlikely that such initiatives would be attempted. As a result, many companies in the Pharmaceutical Industry have taken on the challenge of accelerating definition of the NDA process, and today they essentially freeze the process by the start of the Phase III program.

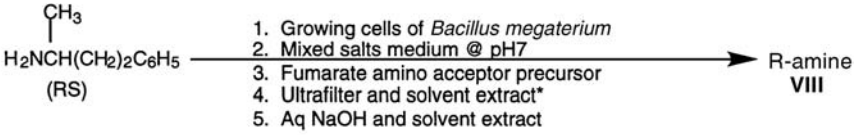
In regard to compliance with FDA Regulations for bulk drug substance manufacture, the Pharmaceutical Industry has, over the years, built a strong formalized program to meet GMP requirements. The industry continues an energetic dialogue with Regulatory Administrations around the world, primarily with United States, European, and Japanese Agencies. Harmonization of Regulatory guidelines is a major interest at this time.

For the manufacture of dilevalol hydrochloride (and other APIs), Schering created needed process and control documentation and set up formal compliance programs to ensure GMP guidelines were met. Major programs for ensuring GMP compliance include:

Operator and Management Training
Batch Sheet Preparation and Change Control
Materials Management and Control
Process Operation and Control
Equipment and Instrument Calibration
Equipment Monitoring and Maintenance
Validation (process chemistry, plant operation, and cleaning)
Facility and Equipment Cleaning Program
Quality Assurance Auditing and Continued Monitoring

These programs are also matched in the areas of Safety and Industrial Hygiene as well as Environmental Compliance.

At the time of the FDA's pre-approval inspection (our first) of the Chemical Development dilevalol DBTA manufacturing operation (dilevalol hydrochloride itself was manufactured in Schering's Ireland facility), Chemical Development received an FDA 483 notification stating that the full-time use of the butanol/water recrystallization process for dilevalol DBTA salt was in violation of the NDA. The NDA stated that the recrystallization process was registered for use only when the first crystallization of the DBTA salt gave a product outside specification; the FDA interpreted this to mean no more than about 10% of the time. Since the process had evolved



* Removes benzylacetone produced

SCHEME 10.

to taking a higher first crop yield of lower enantiomeric purity, followed by routine recrystallization, the FDA criticism was justified. The fact that higher-purity dilevalol DBTA was being produced by the change was subordinate to the wording of the NDA for which approval was given. An NDA supplement providing detail of the reasoning for the change, along with analytical comparison of batches made before and after the change, was filed with the FDA and approved.

Ongoing Process Development and Alternative Routes to dilevalol

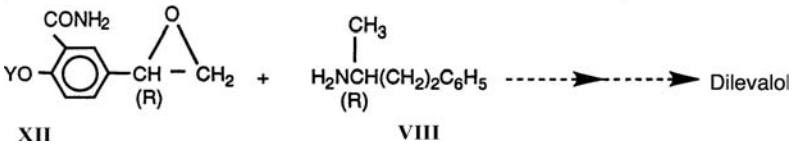
Once the recycle operations for R-amine, for DBTA, for the racemization of SR byproduct, and for solvent recovery were in place, the simpler synthesis as described above met the Marketing COG targets [3× cost of Labetalol minus 25%). Several additional cost reduction programs were in hand at the time of the NDA filing. The ones which were significant in terms of laboratory and pilot plant effort are worthy of brief reviews. Efforts on these programs illustrate the diversity of ideas and individual endeavor which flourished in the challenging climate created to solve the cost of goods problem.

Cost reduction efforts were undertaken both inside and outside the company. They covered the preparation of the raw materials, particularly R-1-methyl-3-phenylpropylamine and derivatives, and also several exciting programs for the direct preparation of dilevalol from chiral intermediates.

Raw Materials. The Celgene Company, Warren, New Jersey, building on the knowledge that RS-1-methyl-3-phenylpropylamine costs only $12/kg, proposed an enantiomeric enrichment process. This process, utilizing Celgene technology, is based on the ability of omega-amino acid transaminases to preferentially convert one of the two chiral forms of the racemic amine, in our case the S-enantiomer, to a ketone.[11] In this approach the S-enantiomer acts as the preferred nitrogen source (Scheme 10).

The process evolved to one in which the converting enzyme was isolated and used in a batch process with a small amount of pyridoxal 5-phosphate as co-factor and pyruvate as the amine acceptor.[12] This process was in a pilot plant phase when dilevalol hydrochloride was withdrawn from the market.

[11]U.S. Patent 4,950,606 to Celgene Corporation, Aug. 21, 1990.
[12]U.S. Patent 5,300,437 to Celgene Corporation, Apr. 5, 1994.



SCHEME 11.

Another initiative in the Schering Manufacturing Division was based on the idea the *N*-benzylated RS-1-methyl-3-phenylpropylamine may be readily resolved, and used advantageously in a process analogous to Scheme 3 without the phenol blocking group. This process did indeed work well giving a high RR enantiomer yield (ca. 80–85%) in the borohydride reduction step. The cost of the benzylation/debenzylation steps was not worked out (for comparison with the NDA process costs) by the time dilevalol hydrochloride was withdrawn.

Alternative Routes to Dilevalol Hydrochloride. The major disadvantage of the NDA process lies in the need for the classical resolution of the RS-carbinols **XI** using DBTA. Although the recycle of DBTA and the waste SR/RR mixture (ca. 70:30) did enable the COG target to be met, it would be far more elegant and potentially lower in cost if a more direct process could be found which would eliminate the classical resolution and recycling operations. The following proposals were evaluated.

Scheme 11 Option. A great deal of work was carried out on the preparation of R-epoxides (**XII**) and their reaction with R-amine (**VIII**). It has long been known that styrene oxides react with primary amines at either of the epoxide carbons, and also that neat amines appear to favor the desired reaction, attack at the methylene carbon atom of **XII**.[13]

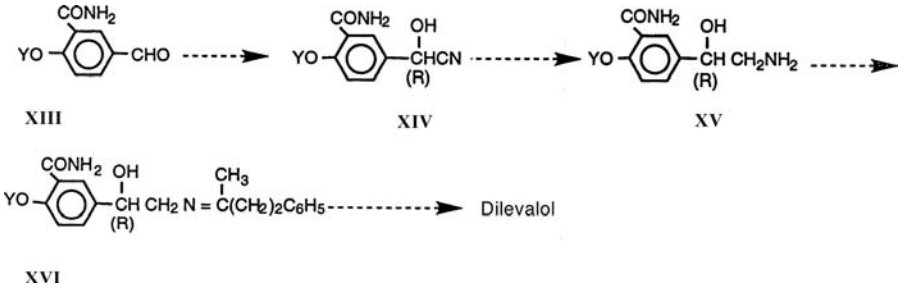
The epoxide (**XII**, Y = $C_6H_5CH_2$) was prepared in high yield and high ee(>98%) by the enantioselective reduction of bromoketone (**II**), using Itsuno chemistry[14] [with R-diphenylvalinol borane complex], followed by cyclization of the bromohydrin. Epoxide **XII** readily formed the desired aminocarbinol **XVIII** (Y = $C_6H_5CH_2$) with R-amine **VIII** which yielded dilevalol after hydrogenolysis of the benzyl group.

The corresponding series with the free phenol (**XII**, Y = H) gave a poor result.

The greatest problem with the epoxide sequence, apart from the extra blocking and deblocking steps, lies in the need for a large excess of the expensive R-diphenylvalinol

[13]Parker, R. E., and Isaacs, N. S. *Chem. Rev.*, 1959, **59**, 737.

[14]Itsuno, S., Hirao, A., Nakahama, S., and Yamazaki, N. *J. Chem. Soc., Perkin Trans. I*, 1983, (8), 1673. Itsuno, S., Ito, K., Hirao, A., and Nakahama, S. *J. Chem. Soc. Chem. Commun.*, 1983 (8), 469. Itsuno, S., Ito, K., Hirao, A., and Nakahama, S. *J. Org. Chem.* 1984, **49**, 555.



SCHEME 12.

borane complex. The Corey modification[15] of Itsuno's method, in which only catalytic amounts of a chiral auxiliary are needed, failed probably owing to complexation of borane with the ring amide and phenol (or protected phenol) groups, leading to chirally uncontrolled reduction of the keto group. Several other routes for preparing the chiral epoxide were pursued without success. These included biological approaches to the reduction of bromoketone (**II**) as well enzyme mediated selective hydrolysis of RS halohydrin esters.

The epoxide route was eventually abandoned on the grounds that cost reduction versus the NDA process did not appear to be attainable.

Scheme 12 Option. The oxynitrilase-catalyzed HCN addition to the aldehyde **XIII** appeared to offer an attractive prospect presuming that the R-cyanohydrin (**XIV**) could be formed, and this then converted to dilevalol via intermediates **XV** and **XVI**. Although the oxynitrilase-catalyzed formation of chiral aromatic and aliphatic cyanohydrins and their reduction to chiral aminoalcohols has been known for some time,[16] the selective reduction of **XIV** to **XV** and the likelihood of 100% induction in the reduction of the Schiff base **XVI** raised many questions.

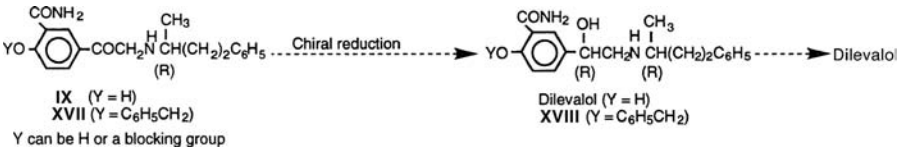
Work by our Swiss Chemical Development group demonstrated that when the hydroxyl group of the racemic form of **XV** ($Y = C_6H_5CH_2$) was blocked by *t*-butyldimethylsilyl, selective reduction of the nitrile to CH_2NH_2 could be achieved ($NaBH_4/CoCl_2/CH_3OH$). However, when the free cyanohydrin was reduced with the same reagent, only the hydroxymethyl compound could be obtained, presumably owing to cyanohydrin conversion to the aldehyde prior to the reduction step.

In addition, our Swiss group found, in probing experiments, that the racemic form of XV ($Y = C_6H_5CH_2$) did not give the Schiff base corresponding to **XVI**.

Since the Scheme 12 option appeared likely to require the extensive use of blocking groups, it lost its simple appeal and was abandoned.

[15]Corey, E. J., Bakshi, R. K., and Shibata, S. *J. Am. Chem. Soc*., 1987, **109**, 5551. In this paper, Corey et al. used S-diphenylprolinol as the chiral auxiliary.

[16]Becker, W., Freund, H., and Pfeil, E., *Angew. Chem. Int. Ed*., 1965, **4**, 1079.



SCHEME 13.

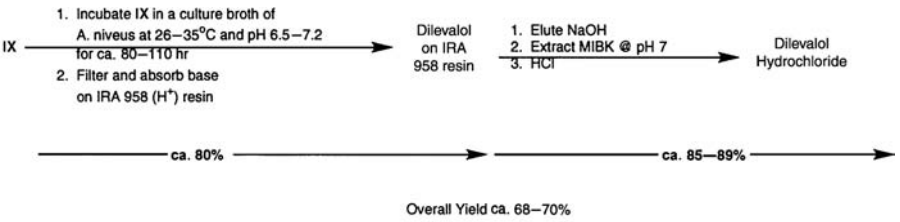
Scheme 13 Option. A great deal of work was carried out to find a reduction procedure for the chiral reduction of the readily available R-aminoketone (**IX**). In addition, despite the benzyl blocking group, the R-aminoketone (**XVII**) was also the subject of chiral reduction work.

It quickly became clear that the use of Itsuno chemistry for reducing the carbonyl group of XVII [with R-diphenylvalinol borane complex] would not be economic, again owing to the need for excesses of the borane complex. The catalytic elaborations of Itsuno's chemistry also failed.

Biotransformations have attracted increasing attention as more chiral APIs are being created by pharmaceutical companies. The use of microorganisms and enzymes is particularly attractive in that systems can often be "engineered" to achieve desirable goals. Moreover, biotransformations are generally carried out in water. It was logical therefore to screen the microorganisms in ATCC banks which are known to reduce ketones to carbinols. Some 50 microorganisms were screened, including bacteria (such as Schizomycetes) and fungi (such as Ascomycetes, Basidiomycetes, and Phycomycetes). Unfortunately, none of these was active in reducing the keto group of R-aminoketone (**IX**) to the desired R-carbinol, dilevalol. A major breakthrough occurred when Dr. William Charney of Schering's Biotechnology Development group observed a large underground oil storage tank being removed near his laboratory. Dr. Charney, who was about 70 years old at the time, clambered to the bottom of the approximately 15-foot deep pit for a soil sample. He isolated a novel fungus from this sample which rapidly carried out the desired transformation of **IX** to dilevalol. The organism was separated by the soil enrichment method, wherein the soil sample is mixed with a compound which restricts the growth to those organisms which can use that compound. In this case the compound was 5-methoxyacetyl-2-hydroxybenzamide. Incubation was carried out for several days and the mixture sampled using standard microbiological techniques and plated out. The active pure culture was a white mold, characterized as belonging to the genus *Aspergillus* and was further identified as *Aspergillus niveus*. An investigation of other members of the family, *Aspergillus niger* (ATCC 11488) *Aspergillus orxyae* (ATCC 1454), and *Aspergillus oryzae* (ATCC 11488), failed to provide chiral reduction of the keto group of R-aminoketone (**IX**). *Aspergillus niveus*, ATCC 20922, was the subject of patent claims.[17]

An outline of the process for the biotransformation of R-aminoketone (**IX**) to dilevalol at the point the project was canceled is as follows:

[17]U.S. Patent 4,948,732 to Schering Corporation, Nov. 7, 1989.



Since this process involved an *Aspergillus* fermentation as the last chemical transformation step, considerable concern was expressed concerning possible contamination of the dilevalol hydrochloride with such as citrinin or allergenic proteins. All test carried out by the time dilevalol hydrochloride was withdrawn were negative. However, a full testing program had not been completed.

It is clear from the conversion yield that the biological process was worthy of further development for potential use in the longer term. Work was especially needed to improve the concentration (8 g/liter at the time) and to deal with the slightly different impurity profile (total 0.3% with 0.1% identified as the R-amine **VIII**). Also, technologies (e.g. ultrafiltration) needed to be evaluated to ensure that proteinaceous material did not contaminate the product.

Withdrawal of Dilevalol Hydrochloride from the Market

Dilevalol hydrochloride was on the market in Japan and Portugal when it was withdrawn. Approximately 34 hepatic events were recorded in a population of 176,000 patients taking dilevalol hydrochloride. Most of the hepatic events were reversible, but there were two deaths. During an extensive clinical research and development program (ca. 10,000 patients), there had been no significant evidence to indicate that hepatotoxicity would become a problem once the drug was marketed. Since labetalol hydrochloride (which contains about 25% dilevalol hydrochloride) was being continually compared with dilevalol hydrochloride, more detailed evaluation and comparison of the hepatic data accumulated on both compounds was undertaken. Interestingly, in the first year of marketing labetalol hydrochloride, 15 hepatic events were recorded/million prescriptions. This rate dropped such that in the 7 years of marketing labetalol hydrochloride to the time of dilevalol hydrochloride withdrawal, only 80 reports of hepatic reactions were recorded for labetalol hydrochloride. In line with this data, it was quickly shown that the patterns of hepatic injury associated with the two medications were not similar. In the case of dilevalol hydrochloride, those patients affected demonstrated a fairly rapid onset of hepatic events, expressed as showing jaundice, dark urine, nausea, vomiting, and fatigue.

The withdrawal of dilevalol hydrochloride represents a unique milestone. As far as the author is aware, this is the first case wherein a deliberately produced chiral API may have demonstrated more toxic liability than the racemic mixture.

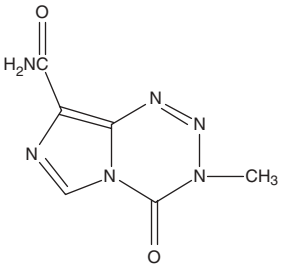
Acknowledgments

I am indebted to the many Chemists, Engineers, Analysts, and Regulatory people whose dedication and hard work led to the technical success of the dilevalol hydrochloride project. In particular, special thanks go to those who worked tirelessly to produce the needed supplies and to engineer the technology to meet the COG target (Messrs. Bruce Shutts, Raymond Werner, and their staffs), to those who "imagined" and carried out the exploratory work on future options [Dr. Richard Draper (chiral epoxides), Dr. Ingrid Mergelsberg (chiral cyanohydrins), the late Dr. William Charney (biological reductions), Dr. Maurice Fitzgerald (*N*-benzyl R-amine approach)], to senior management for their support and encouragement, to those who made suggestions to improve the manuscript, and to Lavonne Wheeler who did all the typing.

CASE 2: EXPLORING IDEAS FOR A BETTER PROCESS FOR THE MANUFACTURE OF TEMOZOLOMIDE

Background

In 1992, Schering–Plough was granted a license by Britain's Cancer Research Campaign Technology Ltd. (CRCT), to develop and market Temozolomide **(XIX)**—a promising anticancer drug, seen as especially useful in treating gliomas (brain tumors).

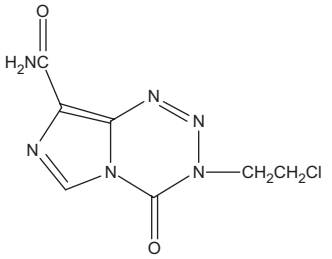


XIX

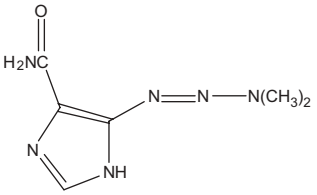
1,2,3,5-Tetrazines were first synthesized in the late 1970s, and bicyclic compounds based on pyrazoles, triazoles, and indazole (analogous to **XIX**) were synthesized shortly thereafter.[18] Later interest in the imidazole series centered on the chloroethyl compound **(XX)** known as Mitozolomide, by structural analogy with the well-known

[18](a) Ege, G., and Gilbert, K. H. *Tetrahedron Lett*., 1979, 4253. (b) Ege, G., and Gilbert, K. H. German Patent 2,932,305,1990 (filed August 9, 1979). Azolo-[5,1-*d*]-[1,2,3,5]-tetrazine-4-ones were shown to possess biological activity of potential value in agriculture and medicine.

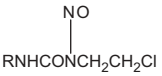
antitumor agents dacarbazine **(XXI)** and the nitrosoureas **(XXII)**.



XX
Mitozolomide



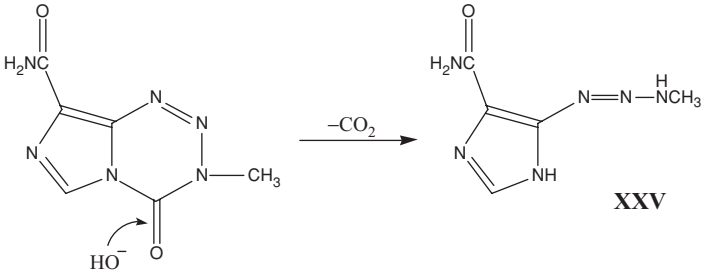
XXI
Dacarbazine
(DTIC)



XXII
R = Cl(CH$_2$)$_2$ (carmustine)
R = Cyclohexyl (lomustine)

All are powerful alkylating agents. The development of Mitozolomide was progressed by May and Baker in Britain. Although it showed clinical activity and a marked advantage over Dacarbazine in crossing the blood–brain barrier, its development was terminated when it was found to cause severe thrombocytopenia (decrease of the blood platelet count).

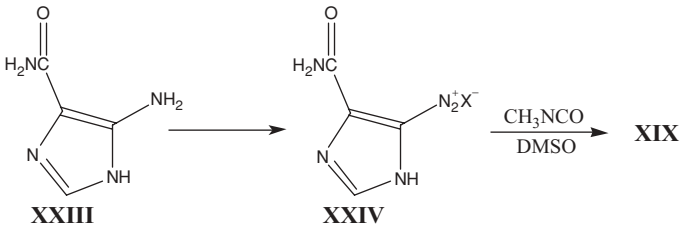
Temozolomide was first synthesized by Professor Malcolm Stevens and coworkers at Aston University, Birmingham, essentially using the same elegant but hazardous chemistry[19] described by Ege and Gilbert[18] (Scheme 14). Temozolomide is a pro-drug. Although stable under physiologically acidic conditions—enabling the molecule to survive oral administration—it opens to the triazene **XXV** prior to alkylating needed sites:



XXV

Several safety issues associated with raw materials, intermediates, and Temozolomide itself needed to be addressed in manufacturing the drug. These were as follows:

[19]Stevens, M. F. G., Hickman, J. A., Stone, R., Gibson, N. W., Baig, G. U., Lunt, E., and Newton, C. G. *J. Med. Chem.*, 1984, **27**, 196. (b) Lunt, E., Stevens, M. F. G., Stone, R., Wooldridge, K. R. H., and Newlands, E. S. U.S. Patent 5,260,291,1993, to Cancer Research Campaign Technology Ltd. (CRCT).



SCHEME 14. Synthesis of Temozolomide.

1. The diazonium intermediate **XXIV** is unstable and is explosive under dry conditions.
2. Methyl isocyanate (b.p. 39°C—often referred to as "Bhopal gas") is flammable and poisonous.
3. Temozolomide itself is regarded as a carcinogen.

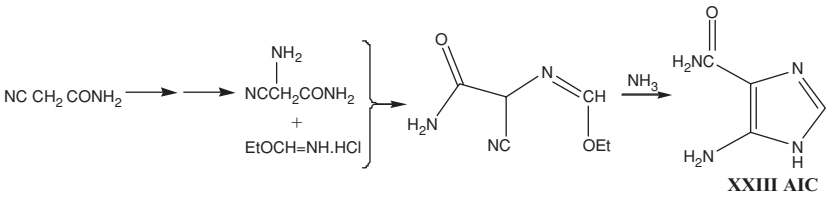
Creating a GMP manufacturing plant in order to protect against all the above hazards, including the in situ manufacture and containment of methyl isocyanate, was clearly an expensive proposition, especially since the scale of operation was projected to eventually reach only a few thousand kilograms a year. An outside partner was found who was both an expert in explosives manufacture and willing to accept all the manufacturing risks in creating a production plant. The small scale and the need to harness specialist technology and explosives experts in a GMP plant led to a cost-of-goods that was far greater than would ordinarily be the case for a drug of such small molecular weight (194).

Introduction

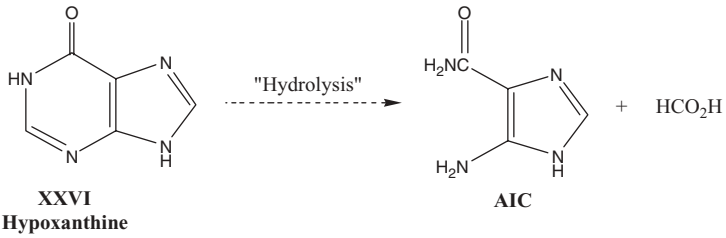
Given the above analysis and also the high cost of purchasing relatively small quantities of 5-aminoimidazole-4-carboxamide **(XXIII, AIC)**, we in Chemical Development were given the backing to explore other possibilities and identify a safer, lower-cost route to Temozolomide that would avoid the hazards and preferably require conventional rather than specialist equipment. Another requirement, made necessary by the heavy workload in our New Jersey Chemical Development operation, was that we find an outside partner to carry out the process exploration work with us.

Exploratory Program to Identify Chemistry for the Preparation of Temozolomide

Several initiatives essentially led us to starting a small exploratory program with Fachhochschule Nordwest Schweiz (FHNS) in Switzerland. In beginning a working relationship with FHNS, we decided to focus initially on finding a better (shorter and less expensive) route for producing AIC.



SCHEME 15. Outline of a commercial route to AIC.[20] .



SCHEME 16. Possible process for producing AIC from hypoxanthine.

Chemistry for Preparing AIC. This seemingly simple molecule is prepared commercially by a multistep synthesis from cyanoacetamide (Scheme 15). The need for several synthesis steps carried out on a small scale inevitably led to a high cost for AIC. Recognizing these weaknesses, our senior chemical engineer, Bruce Shutts, suggested that a shorter, simpler synthesis was needed and proposed that we look at producing AIC by hydrolytically extruding the methine fragment from hypoxanthine **(XXVI)**, a compound that he thought might be low in cost (Scheme 16). Picking up on this suggestion, our Dr. Ernst Vogel, head of our satellite chemical development operation near Lucerne, Switzerland, learned (1997) that low-cost ($28/kg in tonne lots) hypoxanthine, of 99% purity, was indeed available, being offered by Wenzhou No. 3 Pharmaceutical Factory in China. Samples from China validated this information. Dr. Vogel was also instrumental in introducing us to FHNS. Secrecy agreements were signed and we participated with Professors Ernst Hungerbühler and Beat Zehnder, and Dr. Uta Scherer in a fruitful program of work on the AIC project, essentially focusing on Scheme 16.

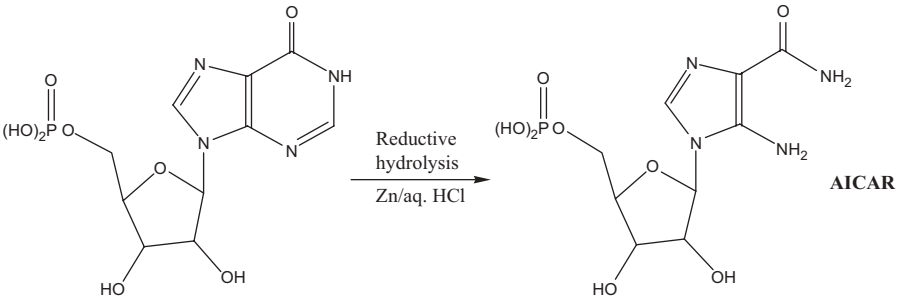
An additional plus was the engagement of our Swiss consultant, Dr. Jacques Gosteli, to aid us in the project. Probably the most indispensable resource, however, was the agreement with Dr. Birendra (Ben) Pramanik, the head of Schering Research's Structural Chemistry group, that he and his team would aid us in analyzing the products of our FHNS experiments. In effect, Dr. Pramanik provided the weight of his considerable experience, especially in mass spectroscopy and nuclear magnetic resonance, to unravel the complexities revealed by FHNS chemists and analysts.

[20]Shaw, G., Warrener, R. N., Butler, D. N., and Ralph, R. K. *J. Chem. Soc*., 1959, 1648.

The following provides an outline of the (unpublished) work undertaken to define a route to AIC from hypoxanthine and also ideas for the conversion of AIC to Temozolomide to avoid most of the hazards associated with the established manufacturing process.

Preparation of AIC from Hypoxanthine. A search of the chemical literature revealed a paper by Friedman and Gots,[21] who found that hypoxanthine was stable to heating in 1 N sulfuric acid. However, the same authors showed that when hypoxanthine was heated in 1.5 N sulfuric acid, with zinc dust added, extensive degradation occurred. The imidazole moiety of hypoxanthine was shown to be stable to the reducing conditions and the product of degradation was found to be a mixture of AIC and a structurally related compound. However, the mixture could not be separated, nor was the unknown compound identified.

Interestingly, the literature also revealed[22] that when inosinic acid was subjected to reductive hydrolysis, the formation of 5-amino-1β-D-ribofuranosylimidazole-4-carboxamide-5'-phosphate (AICAR) was detected. Again, spectroscopic and chromatographic techniques revealed that an approximately equal amount of an unidentified but structurally related compound was also produced. Although the two compounds could be separated using paper chromatography, efforts to separate them using ion exchange chromatography failed.



Inosinic acid

\+

Structurally related compound

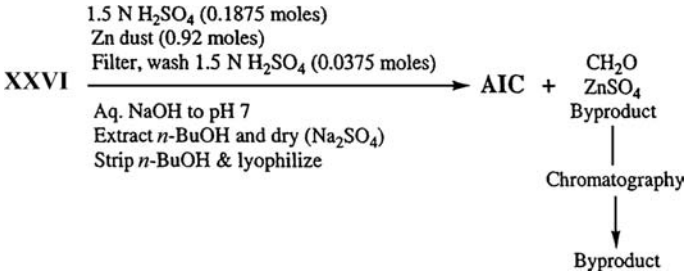
The alkaline hydrolysis of hypoxanthine to AIC has been described in the literature,[23] but seemed unattractive to us. Even under rigorous reaction conditions (150°C in 0.4 N NaOH for 4 hr in a sealed tube!) only approximately 30% of AIC was produced, with most of the hypoxanthine remaining unchanged.

We started our FHNS program by repeating the reductive hydrolysis of hypoxanthine described by Friedman and Gots, confirming their findings. Our interest in the reductive hydrolysis approach was piqued by the thought that if the unwanted reaction

[21] Friedman, S., and Gots, J. S. *Arch. Biochem. Biophys.*, 1952, **39**, 254.

[22] (a) Miller, R. W., and Buchanan, J. M. *J. Biol. Chem.*, 1962, **237**, 485. (b) Wilson, D. W. Bradford University Ph.D. Thesis, 1967, pp. 59 and 60.

[23] Suzuki, Y. *Bull. Chem. Soc. Japan*, 1974, **47**, 898.



SCHEME 17. Reductive hydrolysis of hypoxanthine.

could be avoided, we might improve the yield to AIC. This led us, with the help of Dr. Pramanik et al., to determine the structure of the byproduct in the expectation that, knowing its structure, we would perhaps be enabled to find conditions that would avoid byproduct formation.

The FHNS group prepared a lyophilized sample of the byproduct by chromatographic separation from the crude mixture obtained as outlined in Scheme 17.

The byproduct was analyzed by HPLC (Spherisorb ODS-2 column) using the following processing conditions:

Mobile Phase:	CH_3OH (18)/CH_3CO_2H containing 0.5% H_2O (82) and 5 mM sodium 1-hexanesulfonate
Flow Rate:	1 ml/min
UV Detector:	265 nm

The HPLC chart (Figure 6) revealed the byproduct to be a mixture of a major (90.5%) and minor (approximately 6.9%) product, with similar polarities, along with traces (approximately 2.6%) of other substances.

At this point, Dr. Pramanik and his associates, notably Drs. T. M. Chan (NMR) and P. Shipkova (MS), undertook the task of identifying the structures of the major and minor byproducts.

Proton NMR in CD_3OD as solvent revealed that the byproduct contained two large peaks at 2.83 and 2.92 ppm, consistent with methyl groups, along with two singlets at 7.13 and 7.22, consistent with methine protons (Figure 7). This result suggested that each of the impurities may be carrying a methyl group and an imidazole ring. NMR also revealed the presence of smaller quantities of other impurities, including impurities carrying methyl groups.

The NMR results are in agreement with earlier work[21–23] showing that the pyrimidine ring of hypoxanthine and its glycosides is far more susceptible to cleavage than the imidazole ring.

This information, and recognition that the only source of the methyl groups was through reductive hydrolysis of the methine group in the pyrimidine ring of hypoxanthine, led to the postulation of structures **XXVII** and **XXVIII**, respectively, for the

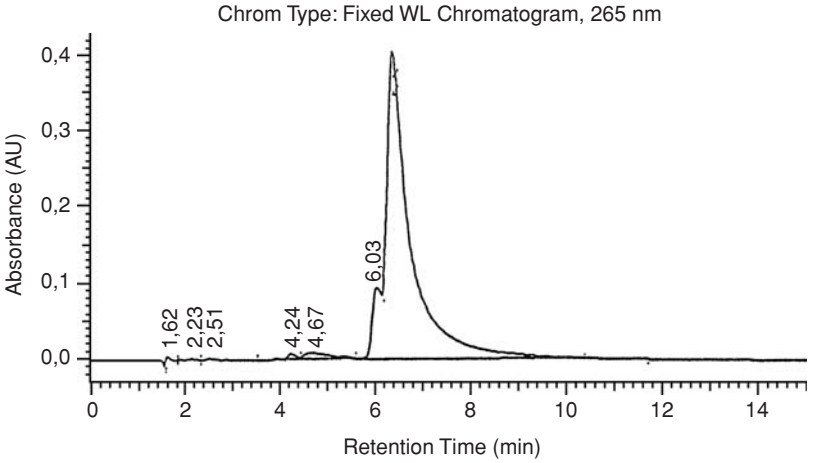


FIGURE 6. HPLC analysis of byproduct from the reductive hydrolysis of hypoxanthine.

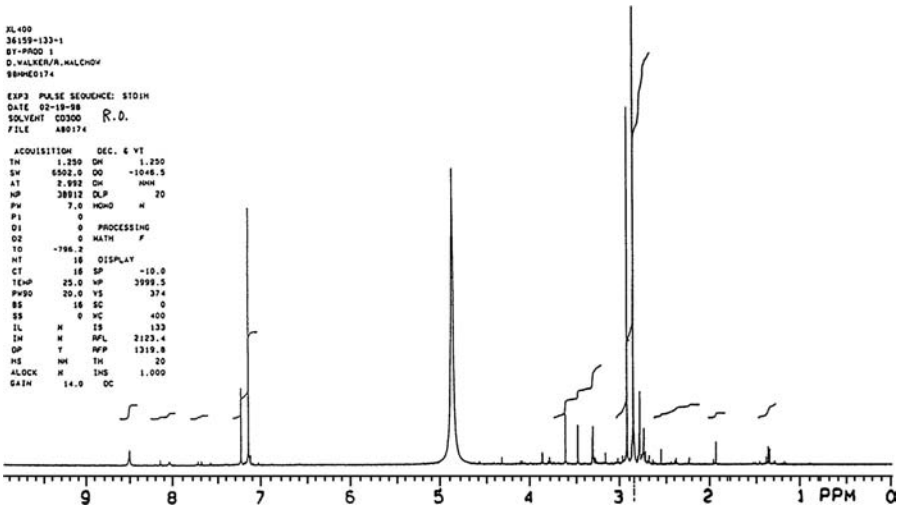
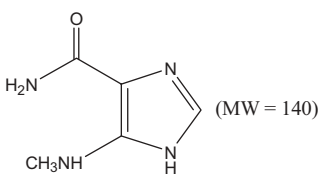


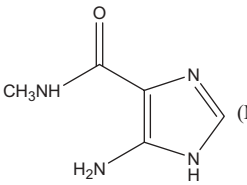
FIGURE 7. Proton NMR of the byproduct (mixture) obtained from the reductive hydrolysis of hypoxanthine.

major and minor products.



(MW = 140)

XXVII



(MW = 140)

XXVIII

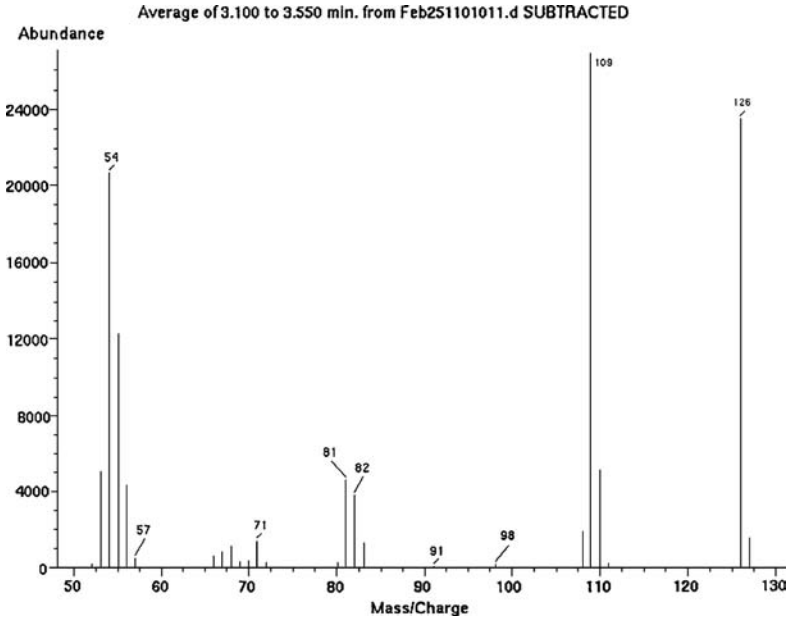


FIGURE 8. EI–MS of AIC itself.

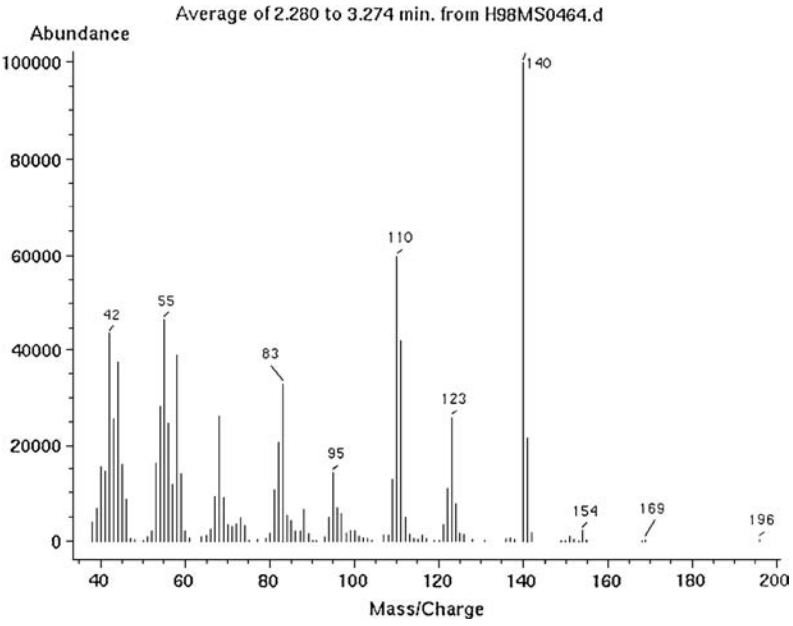


FIGURE 9. EI–MS of byproduct mixture.

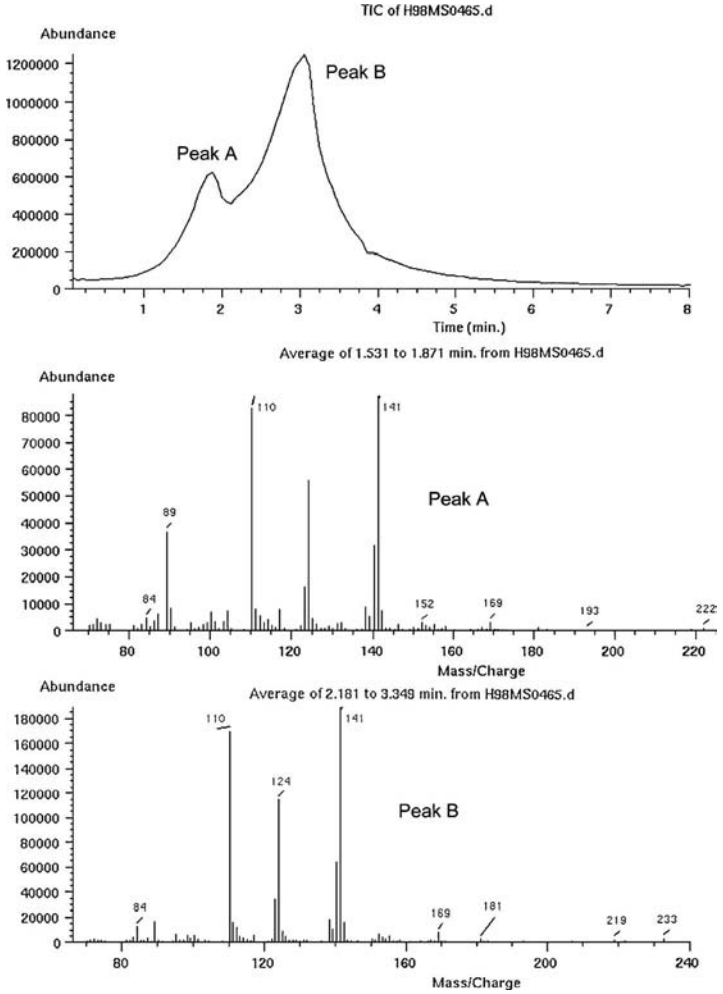


FIGURE 10. APCI–MS of Peaks A and B.

Dr. Petia Shipkova undertook a rigorous mass spectral evaluation of the byproduct mixture and comparison with the MS of AIC **(XXIII)** itself. The EI–MS fragmentation of AIC (Figure 8) and the byproduct mixture (Figure 9) revealed consistent mass ion peaks (126 and 140, respectively) and interesting revelations in the fragmentation patterns.

Dr. Shipkova followed the EI–MS analysis with an APCI–MS evaluation of the mixture showing that the two peaks representing compounds **(XXVII)** and **(XXVIII)** (Peaks B and A, respectively) both gave fragmentation patterns that were very similar to each other (Figure 10).

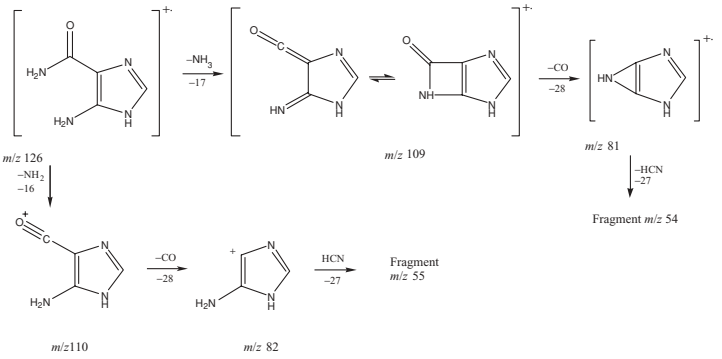
Dr. Pramanik and co-workers, Drs. Shipkova and Guodong Chen,[24] reasoned that the virtually identical fragmentations and peak intensities of Peaks A and B could

[24] We are indebted to Professor Michael Gross, Washington University, St. Louis, for his guidance regarding the structures of the mass spectral fragments.

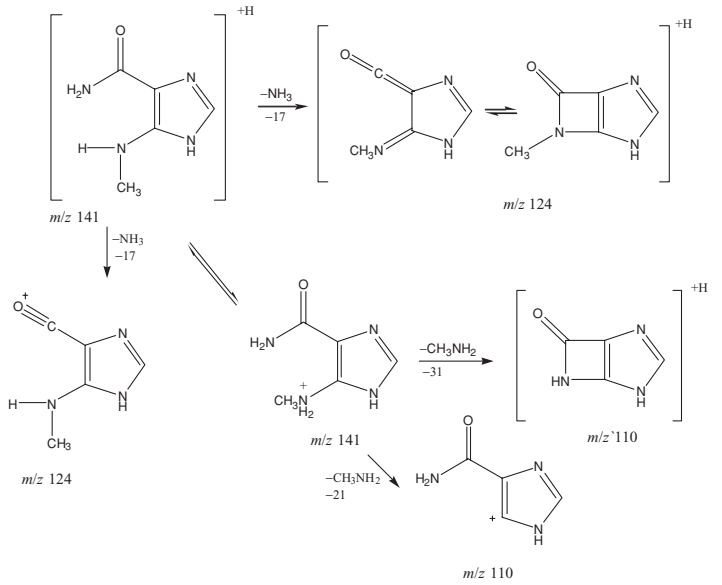
only be accounted for by the two samples being mixtures of **XXVII** and **XXVIII**. Despite this, they proposed that the fragmentation patterns of AIC and byproducts **XXVII** and **XXVIII** could be explained by such breakdown losses as assigned in Table 3.

They went on to suggest that the structural fragmentations needed to account for the major mass peaks could be occurring as follows:

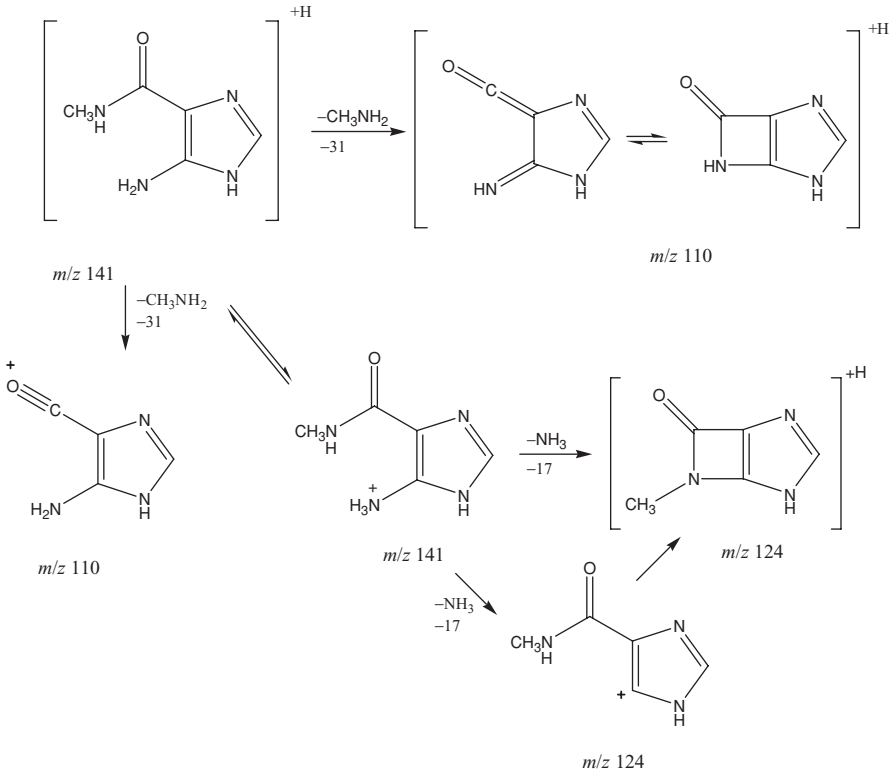
AIC (XXIII) – EI-MS



***N*-Methylamine (XXVII)—APCI-MS**



***N*-Methylamide (XXVIII)—APCI–MS**



The information from mass spectrometry, although incomplete from a mass spectroscopist's viewpoint, was enough to justify the chemical development search for a process that would avoid byproduct formation.

The structural revelations for the major products from the reductive hydrolysis of hypoxanthine, coupled with the earlier observation that hypoxanthine does not degrade when heated with 1 N sulfuric acid alone, suggested that the dissolving zinc caused addition of hydrogen to the methine nitrogen double bond in the pyrimidine ring of hypoxanthine. It then followed that the dihydrohypoxanthine produced underwent hydrolytic cleavage and reduction, perhaps along the lines of Scheme 18.[25]

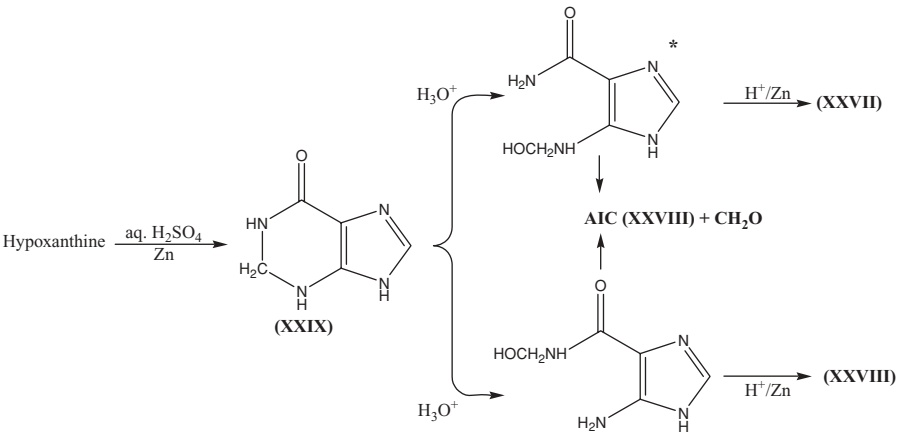
Confirmatory, if incomplete, support for the structures of the *N*-methyl-amine **(XXVII)** and *N*-methyl-amide **(XXVIII)** byproducts was obtained from reactions with AIC as follows[26]:

[25]We have no rigorous proof for the intermediacy of the two *N*-hydroxymethyl compounds versus the alternative of direct addition of hydrogen in two ways.

[26]This work, and especially the MS/MS analyses, revealed that the peak intensities in the fragmentation of **XXVII** and **XXVIII** were different and more consistent with expectation.

TABLE 3. MS Fragmentation Assignments for **XXIII**, **XXVII**, and **XXVIII**

AIC (**XXIII**)			*N*-Methylamine (**XXVII**)			*N*-Methylamide (**XXVIII**)		
Mass	Ions	Losses	Mass	Ions	Losses	Mass	Ions	Losses
126	M^+	—	140	M^+	—	140	M^+	—
			123	$[M-17]^+$	NH_3	123	$[M-17]^+$	NH_3
110	$[M-16]^+$	$\cdot NH_2$	110	$[M-30]^+$	$\cdot NHCH_3$	110	$[M-30]^+$	$\cdot NHCH_3$
109	$[M-17]^+$	NH_3	109	$[M-31]^+$	CH_3NH_2	109	$[M-31]^+$	CH_3NH_2
			95	$[M-45]^+$	$NH_3 + CO$	95	$[M-45]^+$	$NH_3 + CO$
83	$[M-43]^+$	HNCO						
82	$[M-44]^+$	$CONH_2$						
81	$[M-45]^+$	$CO + NH_3$						
			68	$[M-72]^+$	$\left\{\begin{matrix} NH_3 + CO \\ +HCN \end{matrix}\right\}$	68	$[M-72]^+$	$\left\{\begin{matrix} NH_3 + CO \\ +HCN \end{matrix}\right\}$
54	$[M-72]^+$	$\left\{\begin{matrix} NH_3 + CO \\ +HCN \end{matrix}\right\}$						



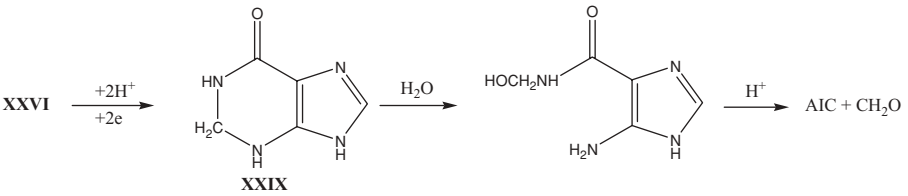
*This structure may dehydrate to the formaldehyde Schiff base prior to the hydrogenation step leading to **(XXVII).**

SCHEME 18. The reductive hydrolysis of hypoxanthine.

- AIC was reacted with formaldehyde under reducing conditions (zinc/sulfuric acid) and the reaction mixture (after "purification" along the lines of Scheme 17) subjected to HPLC/MS and MS/MS analysis. This analysis showed that the main product was the *N*-methylamino compound (**XXVII**). Not surprisingly, the *N*,*N*-dimethylamino compound (Mass 154) was found to be present in significant amount; it is pertinent to also note the presence of traces of *N*,*N*-dimethyl compound in the byproduct mixture from the reductive hydrolysis of hypoxanthine (Figure 9).
- AIC was heated with methylamine under pressure at 70–80°C for several hours, and the reaction mixture was subjected to HPLC/MS and MS/MS analysis. This analysis showed that the expected *N*-methylamide, **(XXVIII)**, had been produced, along with a number of other products (not identified).
- In a related exercise we also reacted formaldehyde with AIC under acidic conditions (no zinc). HPLC/MS and MS/MS analysis of the crude complex product indicated the presence of a small amount of a compound (mass 138) consistent with dihydrohypoxanthine **(XXIX)**, or the formaldehyde Schiff base of AIC.

The identification of the *N*-methylamine **(XXVII)** and the *N*-methylamide **(XXVIII)** during the reductive hydrolysis of AIC raised the prospect that these byproducts might be avoided if the reduction step was separated from the hydrolysis step.

Reduction of Hypoxanthine to Dihydrohypoxanthine. The decision to separate the reduction step from the hydrolysis step led to a further search of the literature



SCHEME 19. Polarographic behavior of hypoxanthine (**XXVI**).[27]

pertaining to the reduction of purine and its derivatives. Bendich et al.[27] reported that neutral or acidic solutions of hypoxanthine did not absorb hydrogen at room temperature, under one atmosphere of hydrogen pressure in the presence of palladium-charcoal. Later, however, Smith and Elving[28] described the electrochemical reduction of purine and a few of its derivatives (adenine, hypoxanthine, and guanine). Prophetically, they interpreted the polarographic behavior of hypoxanthine in terms of a 2-electron reduction leading to dihydrohypoxanthine, which then hydrolyzes (Scheme 19).

None of the compounds in the sequence was isolated or synthesized, but their work validated the idea that the best approach to preparing AIC from hypoxanthine was likely to result from initially reducing hypoxanthine to its dihydro derivative and then hydrolyzing the **XXIX** produced to AIC.

In view of the widespread adoption, by industry, of catalytic hydrogenation, it was deemed most appropriate that, in the first instance, we focus effort on the catalytic hydrogenation of hypoxanthine rather than the electrochemical reduction approach.[29] We also thought it better to avoid the presence of inorganic salts, as used in the buffers employed in the polarographic work, in order to avoid the complication of separating AIC from salts. The main thrust thus became to hydrogenate hypoxanthine in an anhydrous solvent, to give dihydrohypoxanthine **(XXIX)**, and then to separately hydrolyze **XXIX** to AIC. A solvent that could be readily removed by distillation was considered desirable.

Dr. Gosteli pointed out that Schering had earlier patented the hydrogenation of indoles in trifluoroacetic acid (TFA) using platinum oxide as a catalyst.[30] Based on this information, an evaluation of the hydrogenation of hypoxanthine over platinum oxide, in TFA and a few other acid solvents, was undertaken—partly to determine whether the pK_a of the acid was a factor in the hydrogenation. No significant hydrogen uptake was observed when hydrogenations were carried out (1 atmosphere and room temperature) in formic acid (pK_a 3.75), dichloroacetic acid (pK_a 1.48), sulfuric acid

[27] Bendich, A., Russell, P. J., and Fox, J. J. *J. Am. Chem. Soc.*, 1954, **76**, 6073.

[28] Smith, D. L., and Elving, P. J. *J. Am. Chem. Soc.*, 1962, **84**, 1412.

[29] Later, Dr. M. Hürzeler-Müller and Mr. F. Stapf (FHNS) demonstrated that the electrochemical reduction of hypoxanthine could be achieved using a mercury cathode and pH 4.65 acetate buffer. The yield of **XXIX** was 83%.

[30] Neustadt, B. R., Smith, E. M., Magatti, C. V., and Gold, E. H. South African Patent 8600083, 1986 to Schering Corporation.

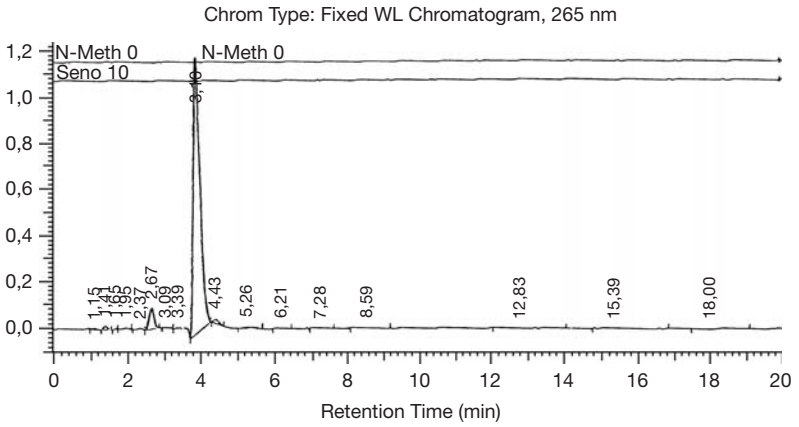


FIGURE 11. HPLC analysis of product of hydrogenation of hypoxanthine.

(pK_a −3 and 1.96), and triflic acid (pK_a −8?). Some hydrogenation was observed in methanesulfonic acid (pK_a −1.2), with the product being primarily AIC (due to small amounts of water?). Trifluoroacetic acid (pK_a 0.5) was the only acid that allowed substantial hydrogen uptake. This "solvent" was considered to be attractive because of its low boiling point (72°C), allowing for easy recycle—a necessary requirement owing to the relatively high cost of TFA ($12–15/kg in tonne quantities in 2004).

Although in the few months before financial support was terminated there was little time to optimize the hydrogenation and hydrolysis steps, the best hydrogenation conditions, giving a yield of dihydrohypoxanthine of >90%, were found to be as follows:

Hypoxanthine (2 g) in trifluoroacetic acid (40 ml) was stirred and hydrogenated (100 bar/35°C/21 hr) over platinum oxide (0.1 g).[31] The catalyst was filtered and the trifluoroacetic acid stripped under vacuum. The product was shown (potentiometric titration) to contain 1.9 moles of TFA.

The product was analyzed by HPLC (Spherisorb ODS-2 column) under the following process conditions (Figure 11).

Mobile Phase:	CH_3OH (9)/Phosphate buffer (pH 3) with 50 mM/liter potassium dihydrogen phosphate and 5 mM/liter sodium heptanesulfonate adjusted to pH 3 with 85% H_3PO_4.
Flow Rate:	1 ml/min.
UV Detector:	265 nm

[31] Later, Dr. Uta Scherer used 0.2 g PtO_2 in this experiment and obtained dihydrohypoxanthine in a yield of 96.8% in 8.5 hr at ambient temperature.

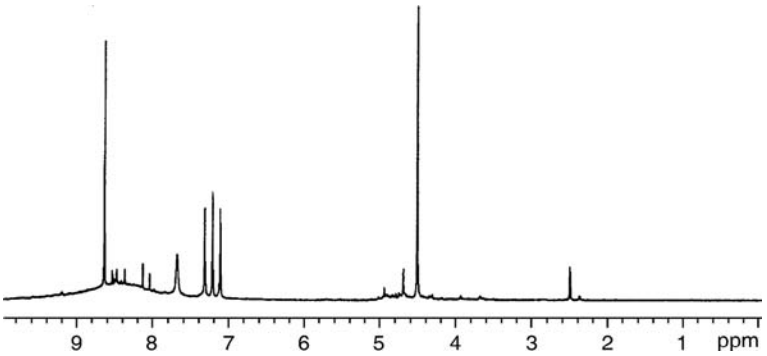


FIGURE 12. Proton NMR spectrum of dihydrohypoxanthine (**XXIX**) trifluoroacetate.

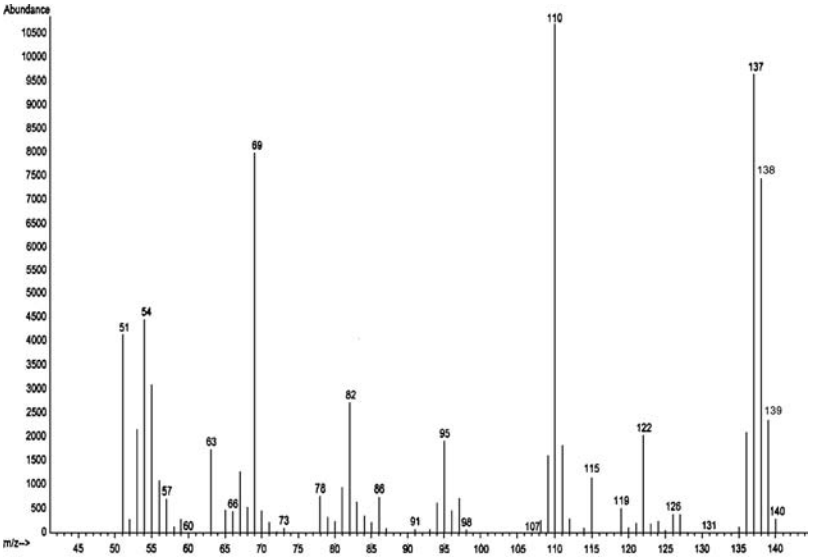


FIGURE 13. EI–MS of dihydrophypoxathine (**XXIX**) trifluoroacetate.

The NMR spectrum (Figure 12) was consistent with the dihydrohypoxanthine structure, though minor unidentified impurities are also present.

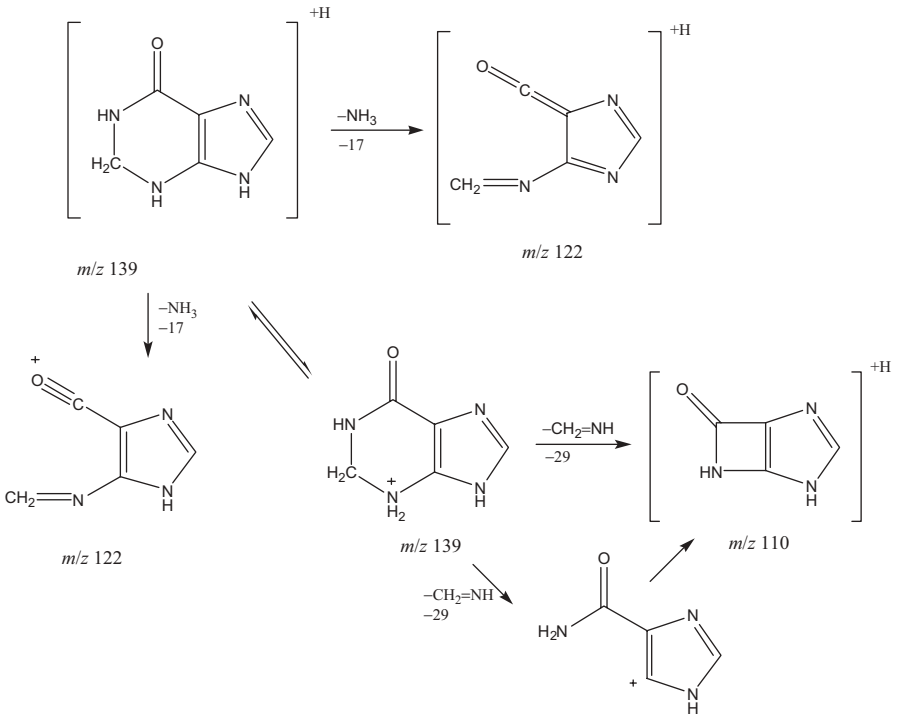
The mass spectrum (Figure 13) corresponds in most ways with those of AIC and its *N*-methyl derivatives, with a closely related pattern of fragmentation (Table 4).

The structural fragmentation corresponding to the major mass peaks may be accounted for as follows for the TFA salt of dihydrohypoxanthine:

TABLE 4. Mass fragmentation assignments for dihydrohypoxanthine (**XXIX**) trifluoroacetate

Mass	Ions	Losses
139 (weak)	$[M+1]^+$	Protonated M
138	M^+	—
137	$[M-1]^+$	·H
122	$[M+1-17]^+$ or $[M-16]^+$	NH_3 from protonated M or NH_2 from M
110	$[M+1-29]^+$ or $[M-28]^+$	CH_2=NH from protonated M

XXIX Trifluoroacetate —EI–MS



The large MS peak at 69 may be the CF_3 radical derived from trifluoroacetic acid. The peak at 126 may represent AIC from partial hydrolysis of the sample.

Hydrolysis of Dihydrohypoxanthine to AIC. There was sufficient time to demonstrate that dihydrohypoxanthine could be hydrolyzed to AIC but not enough time to provide the basis of a workable process to isolate AIC.

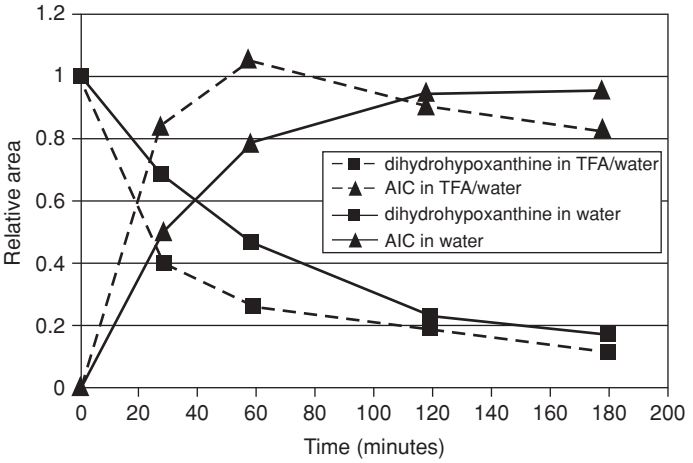


FIGURE 14. Hydrolysis of dihydrohypoxanthine to AIC.

As illustrated in Figure 14, dihydrohypoxanthine (containing ~1.9 moles of trifluoroacetic acid) is hydrolyzed to AIC by refluxing in water or a 1:1 mixture of water and trifluoroacetic acid. Figure 14 (HPLC monitoring) indicates that some loss of the AIC produced is occurring in the trifluoroacetic acid–water case (perhaps by hydrolysis to the aminoimidazole carboxylic acid or through reaction with released formaldehyde, or both?).

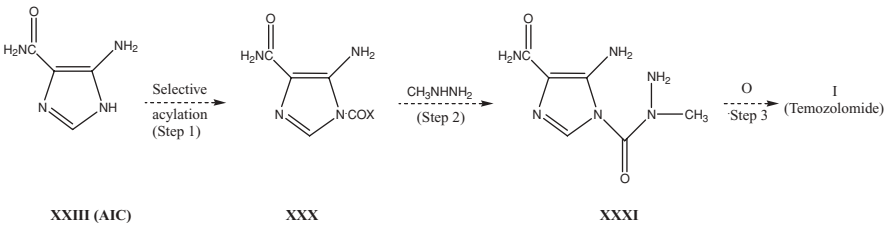
The fate of the released formaldehyde was not determined. For best results it may be necessary to distill the formaldehyde or scavenge it, preferably using such as a phenol immobilized in polymer form to allow ready separation from the aqueous solution of AIC.

This is essentially where the project ended, but it is pertinent to outline some of our work on the preparation of temozolomide itself, especially our efforts to avoid preparation of the potentially explosive diazonium intermediate (**XXIV** in Scheme 14) and the use of methyl isocyanate.

New Chemistry for the Preparation of Temozolomide. The three main disadvantages of the present synthesis (Scheme 14) were outlined earlier. Of these only the first two, the potential explosivity of the diazonium intermediate (**XXIV**) and the toxicity of methyl isocyanate, can be addressed. In the first, the handling of the potentially explosive intermediate is best accommodated by ensuring that this material remains wet at all times. Thus, avoiding the preparation and use of methyl isocyanate became the primary objective.

The use of masked methyl isocyanates has been described,[32] but this seemed to us merely replacing a known hazardous compound with an isocyanate of unknown toxicity which could well be equally hazardous. In this spirit our Dr. Shen-chun Kuo

[32]Shutts, B. P., Stevens, M. F. G., Thomson, W. T., and Wang, Y. *J. Chem. Soc. Perkin I*, 1995, 21.



SCHEME 20. Speculative synthesis of temozolomide.

speculated that it may be possible to avoid isocyanates by using a synthesis sequence such as outlined in Scheme 20.[33]

Although methylhydrazine has a higher boiling point than methyl isocyanate (88°C versus 39°C), and would therefore be expected to be easier to contain, it is a toxic and hazardous compound (rocket fuel). However, methylhydrazine does not have the emotive baggage associated with the Bhopal disaster caused by methyl isocyanate. On these grounds, work to determine the feasibility of Scheme 20 was considered a worthwhile objective.

In the first instance, *p*-nitrophenyl chloroformate was selected for the acylation of AIC (Step 1 in Scheme 20). Reaction of AIC hydrochloride (0.154 mole) in methylene chloride first with an excess of triethylamine (0.323 mole) and then with a solution of *p*-nitrophenylchloroformate (0.169 mole) in methylene chloride at room temperature for 24 hr gave compound **XXX** (X = *p*-nitrophenoxy) in ∼ 93% yield.

Reaction of **XXX** (0.144 mole) in dimethylformamide with methylhydrazine (0.188 mole) at 0°C for 1 hr and the reaction mixture quenched into ethyl acetate gave compound **XXXI** in ∼95% yield.

The cyclization of **XXXI** was studied only briefly but shown to be feasible. Thus, a very dilute solution of **XXXI** (2.5 mmol), along with tetrabutylammonium iodide (0.25 mmol) in 500 ml 1:1 tetrahydrofuran and acetonitrile, was heated at 60°C for 20 min, cooled to room temperature, treated with periodic acid (5 mmol), and stirred vigorously for 1 hr. The excess periodic acid was destroyed by adding saturated aqueous sodium thiosulfate (5 ml) and the solution concentrated to dryness. The residue was treated with acetonitrile (200 ml), filtered, and chromatographed on a silica gel column (1.5–2% CH_3CO_2H/EtOAc) to afford temozolomide in 58% yield.

CONCLUSION

In the decade following the above feasibility studies, much has happened to drive the pharmaceutical industry in new directions and, in particular, to affect the pursuit

[33] Kuo, S. C. U.S. Patent 6,844,434,2005, to Schering Corporation.

of chemical process development in the pharmaceutical industry. Some of the major events are identified below:

1. Because the process of obtaining regulatory (FDA) approval for an API has become more exacting, more paper intensive, and therefore longer, the pharmaceutical industry has tried to find and overcome sources of delay in gaining FDA approval. In chemical process development terms, this has led to efforts to minimize process changes post the IND filing, and particularly in Phase III—significant process changes raise the risk of introducing new impurities and cause delays in the filing of the NDA. As a result, free wheeling (innovation-driven) efforts to identify, develop, and introduce the most cost-effective process for the manufacture of an API are mostly restricted to the pre-IND phase and post-NDA approval. API manufacturing sites thus usually receive only Methods or, at best, partially developed synthesis processes for the production of new API's. By avoiding major process changes between the IND filing and the NDA approval, companies advance their NDAs faster and accept the heavier analytical, regulatory, and manufacturing burdens and the higher cost of goods that go with using partially developed processes.[34] The product of any innovative process work which can be carried out post the IND is generally never qualified for use in any Phase III studies that will appear in the NDA.
2. The majority of pharmaceutical companies have moved away from the manufacture of their own intermediates, and in many cases their own APIs, with the result that outsourcing has become a major program in chemical process development organizations. With more parties involved, and the precise transfer of technology requiring great effort and vigilant follow-up, API costs and the time frame needed to develop the best process have escalated.
3. The trend to outside involvement can compromise a company's control over its own destiny as far as intellectual property and sundry regulatory obligations are concerned. Thus chemical process patents, which often extend a company's exclusivity on an API, may be more in the hands of others, requiring that legal protection of the company's position be given due attention. Outside involvement also brings concerns as to whether or not a partner can meet all the safety, environmental, FDA regulatory affairs, and confidentiality requirements, thereby creating a need for additional legal contracts.

As a result of the above trends, many innovative opportunities for reducing the cost of APIs are put on the back burner awaiting developments which, in those APIs that reach the market place, may bring resurrection. The growth of the market for temozolomide may be just such a case.

[34]There is also a knock-on effect in the pharmaceutical sciences area since they need both to validate that changes in the API synthesis do not affect the dosage form, and also introduce beneficial improvements of their own.

From the foregoing, it appears that relatively little work would be needed to develop a practical process for the manufacture of AIC (**XXIII**) from hypoxanthine (**XXVI**). Much more work would be needed to develop a process based on speculative Scheme 16, but the cost reduction opportunities appear considerable. If successful, significant reduction of the API cost of goods would be achieved by developing a safer process using conventional equipment. Such a process, allowing escape from manufacturing in an explosion-proof and contained environment, would reduce plant depreciation overheads and allow ready development of a second source for insurance of supply. In addition, the patenting of a superior process[33] essentially extends patent protection for the API by restricting eventual generic competitors to the use of the current hazardous and expensive process, a situation that may even deter them from competing at all.

11

THE FUTURE

> The significant problems we face today cannot be solved at the same level of thinking we were at when we created them.
>
> ——Albert Einstein

INTRODUCTION

One cannot think of the global future without it stirring anguished feelings of excitement, tempered by trepidation; optimism, tarnished by cynicism; despair, lifted by hope; and nightmare confusions that cannot be reduced to words. It may seem impossible to imagine the diverse forces now driving the world, coalescing and collaborating for the good of the planet and its occupants, without our first going through some cataclysmic event humbling us into creating a mostly harmonious, constantly evolving steady state. But imagine, and encourage collaboration, we must.

Globally, the inability of some populations to develop,[1] leading to diversity, disagreements and the unhealthy evolution of the "me-phenomenon," set cultures apart. Achieving world intra- and intersocial harmony now only seems possible by generating a global educational curriculum to create understanding and formulae for reform of the world's antagonistic driving forces. Creating new interpretations of such driving forces as democratic capitalism, socialism and religion demands a much

[1]One eloquent explanation is provided by Jared Diamond in *Guns, Germs and Steel*, W. W. Norton and Co., New York, 1999.

The Management of Chemical Process Development in the Pharmaceutical Industry by Derek Walker
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more highly educated population. Melding of these reformed driving forces through a harmonized curriculum seems to offer the most likely path to long-term survival.

This chapter, however, is primarily concerned with creating action strategies for pursuing relatively small specific missions applicable in the chemical process development field. My views merely add to the existing dialogue to create a consensus for moving forward. Since, to paraphrase John Donne, "no single discipline is an island. . .," moving forward requires a multidisciplinary assessment of the potential value of proposed future directions in order to provide an agreed basis for initiating action to create an end product, in our case a holistic commercial chemical process operation. The incorporation of some global issues, such as promoting an interdisciplinary education (chemistry, embracing interacting disciplines), reducing government bureaucracy, recognizing that the world's organic feedstock is finite, and global warming, essentially reflect the need to consider global issues in everyday thinking, even in small endeavors.

The subjects I have addressed in the form of short essays are outlined below, concluding with a fantasy that to many may seem a far-fetched approach to solving one of the world's major "chemistry" problems:

- Education
- Bureaucracy Reduction
- Trends and Technologies:
  - Notes on synthesis
  - Outsourcing
  - Water and enzymes in chemical process development
  - Thoughts on other "solvents"
  - Polymer-supported synthesis and reagents
  - Microwave–assisted chemistry
  - Electrochemistry
  - Sustainable development
- Fantasy

EDUCATION

Introduction

First I would like to express a few "global thoughts" about education. All of us need to regard education as a spirit of pursuit, not only in one specific discipline but as a route to diverse matrix style development—say along the lines that the Therapeutic Teams in the pharmaceutical industry use to promote drug development (see Chapter 3). It seems to me that up until the early decades of the 20th century, education was better regarded than it is today—the teacher, minister, doctor, and lawyer were thought of as largely equal in importance as pillars of the community. In the twentieth century,

industry and business became more dominant and lawyers and doctors managed to leverage their professions into more visible high-standing roles in society. Western capitalism ushered in great material wealth leading to enormous social freedom and liberalism. Education lost ground as decades of industrial growth enticed people into jobs enabling them to gain immediate material gratification in the course of pulling themselves out of the poverty of more socially challenged times. To some extent this 20th-century trend, into feeding the needs of industry and its growth, skewed education toward short-term practical development. Although unprecedented social good was realized, few in power anticipated or dealt with the unhealthy consequences of the subsequent excessive growth of the "me-phenomenon" and the discord and friction generated in both the have-not communities at home as well those in the non-Western world. In different ways, both felt disenfranchised and exploited. In short, education was unwittingly hijacked by industrial, business, and attendant political and social development and accorded a shabbier role than was needed of it.

Fortunately, education is still an evolving and revolutionary force as families often slowly recognize that their children would benefit from getting as much education as they can possibly take. Wider recognition of the vital role of education in shaping the future would allow the education profession to leverage its importance to individuals, families, captains of industry, politicians, and others, thus establishing education as the prime vehicle for improving the social system. In order to contribute more effectively in shaping a better future, the education profession needs massive politically driven funding to reach out, not only to those with a hunger for education, but also to those it loses, often at the grass roots, that is, the downtrodden and forgotten. People need to be lifted to a level where they can more fully express themselves, be appreciated for their contribution, and realize a satisfactory life. In this way they preserve dignity through feelings of being useful and being well regarded, even as they become educated enough to recognize and deal with their own limitations. Supporting education is not something the Western world needs to do merely through money and physical resources. Education needs to be placed on a war footing through a major unrelenting effort to create a permanent self-sustaining hunger for learning. It is just as important (arguably more important) to "educate" the disenfranchised (those unable to get the most out of today's formal education system) as it is to educate tomorrow's "elite." Such a commitment needs to be aimed, inter alia, at overcoming enormous social problems (including compliance, top to bottom, with law and order[2]) and creating dignity in all forms of work. Over time, such a

[2]The political dialogue in Britain in 2004 between Prime Minister Blair and opposition leader, Michael Howard, bears on this point:
Blair (July): "A society of different lifestyles spawned a group of young people brought up without parental discipline, without proper role models and without any sense of responsibility to or for others. All of this was then multiplied in effect by the economic and social changes that altered the established pattern of community life in cities, towns and villages throughout Britain and throughout the developed world. Here, now, today, people have had enough of this part of the 1960's consensus. People do not want a return to old prejudices and ugly discrimination. But they do want rules, order and proper behaviour. They know there is such a thing as society. They want a society of respect. They want a society of responsibility. They want a community where the decent law-abiding majority is in charge; where those that play by the rules do well and those that don't, get punished."

commitment might be expected to create better understanding of the great social needs, to enable adaptation to the changes needed to adjust to emerging economies, and to deal with the challenges that a burgeoning developing population poses to the developed populations, to the environment, and, eventually, to planetary stability.

Present-day educators are either not capable of meeting the challenges or do not have the needed support and encouragement to revolutionise the educational system. Today's forms of education cannot be really fully effective unless they are integrated with the wider social and survival needs. Many young minds are lost by failed anemic institutions ineffectively dealing with dysfunctions in society. A few of those who acquired the least formal education rely on their wits, and often extraordinary "testeronic zeal." Many pursue criminal careers. These are the lost clever minds in the greatest danger of creating something that leaves an atrocity in the wake of their "profit." Education needs to provide for them (and their family "mentors") while at the same time minimizing the crimping effects of formalization on their creativity.

The more educated we are, the easier it is for us to gain a modicum of understanding of the problems we all face; to be accepted as participants in the dialogue with those shaping the future (primarily politicians, captains of industry and social and religious leaders); to be effective in contributing to the solution of problems; and to be successful in overcoming the worldwide frictional forces which create social discord everywhere.

Today the capitalist economies are far too soft and comfortable and are not desperate enough to rebuild decaying social foundations. We have led ourselves deep into our land of plenty by neglecting the consequences of our journey to get there. Dealing with consequences was not considered relevant—they did not seem to matter when we started out. But it has now been evident for some time that, in John Muir's words, "When we try to pick out anything by itself, we find it hitched to everything else in the universe."

Our problems only seem to be exacerbated by today's efforts to maintain and increase our well-being by increasing the speed of our ongoing exploitation of available physical and human resources. We are on a treadmill going faster. The need for changes in behavior becomes both more imperative and equally readily postponed. John Kenneth Galbraith once put it that "Faced with the choice between changing one's mind, and proving there is no need to do so, almost everyone gets busy on the proof."

Dealing with consequences will be enormously difficult and expensive and will require bitter personal, social, industrial, and religious revolution in the way humans coexist with everything on the planet to reach something approaching a "constantly evolving steady state." Since today's industrial, political, social, and religious systems

Howard (August): "Most damaging of all has been the decline in personal responsibility. Many people now believe that they are no longer wholly responsible for their actions. It's someone else's, or something else's fault—the environment, society, the Government. The decline of responsibility and the proliferation of rights have left us in an ethical quagmire, which is undermining our fight against crime. The clear distinction between right and wrong has been lost in sociological mumbo-jumbo and politically correct nonsense. Conservatives will stand up for the silent law-abiding majority who play by the rules and pay their dues. We will put their rights first."

cannot, at present and by themselves, be relied on to work without regulators, getting to the steady-state level becomes an almost incomprehensibly difficult and forbidding task. Transcending the present missions of today's major forces can only be done through a massive program of education for survival. Most present-day educators cannot succeed in this on their own.

It is no easy matter to live up to the political slogan "no child left behind." The fact that many are behind is mostly a consequence of our social systems losing their way. The solution is not simply an education matter. Revolutionary investment is needed to overcome the dysfunctions in families, communities, and countries at their source, to correct the lack of fairness in society, the corruption and crime, and so on. One way may be to deal with one of the greatest challenges, to greatly weaken and restructure the "me-phenomenon" in society (and its attendant malaise, delegating philosophical and social change to the next generation) at the same time as minimizing impairment of the search for new initiatives to enable the Western world to meld with the social and physical challenges posed by the emerging economies. Further education is vital to harmonize the emerged and emerging economies through preparing the rich for the more frugal material but richer cerebral and physical lifestyles needed to adapt to a steady state. The social philosophies emerging under monarchies, dictatorships, communism, and socialism were all corrupted into self-preserving philosophies that intensified their inability to develop the kind of missions needed for permanent survival. Today's democracies seem in danger of following suit. As far as "no child left behind" is concerned, many are trying to move now.[3]

If the developed nations do not deal with their excesses and do not progress education, innovation, and change, they risk foundering, like the old empires, giving way to an even more perilous repetition of the same cycle of rise and fall—and eventually, perhaps, Armageddon. Unfortunately, present-day inertias suggest that it may take a cataclysmic event, perhaps taking the form of a slowly developing "environmental catastrophe," rather than a flash viral pandemic, making it more difficult to deal with, before anything is done. Would it be too late?

From time to time small reassurances appear, often only to evaporate in the heat of short term budget priorities.[4] Politically, leaders with staying power are needed to

[3]They do not want to wait until social programs are integrated into educational ones. William L. Taylor, a retired lawyer, lobbyist, and U.S. Government official, one of the leading spokesmen in urging government progression of the "no child left behind" program, put it: "To say just give more money is not an answer. it is not good enough to say this is a societal problem, though that certainly is the case. If you say everybody is responsible, nobody is responsible."

[4]A recent report, commissioned for the National Academy of Sciences (Rising above the Gathering Storm: Energising and Employing America for a Brighter Future, 2005), and a bipartisan Congressional Bill to "Protect America's Competitive Edge" generated a flurry of initiatives among Senators and Congressmen to deal with the need to invest more in enhancing education and supporting more basic research. One of the major concerns was to find ways of dealing with evidence of decline in the achievement of 12th-grade students in mathematics and science—U.S. mathematics and science 12th-graders rank in the bottom 10% among their international peers (Markoff, J., *New York Times*, February 2, 2006). Congressional legislators, aware of the need to update their science knowledge, also organized a scientific briefing by The Center for Health and the Global Environment at Harvard in January 2006—perhaps a harbinger of further education and action proposals to come? (See Dean, C., *New York Times*, January 31, 2006.)

define and progress solutions and to encourage the population to persevere with their further education.

Progressing Science Education

Science is only one root feeding a complete education. The "magic" of science is appreciated by the general public in those areas that touch their everyday lives, particularly the publicized components that create the "news." These include medicine (e.g., health, diet, disease, surgery, and treatment), chemistry (pharmaceuticals, polymers, chemical safety and toxicity, explosives, analytical chemistry), environmental sciences (pollution, global warming, declining biological diversity), food sciences (agriculture, fishing, brewing), biological sciences (evolution, genetic engineering, virology), material sciences (forestry, glass, ceramics), physics (particle physics, atomic fission and fusion, Einstein's theories, astronomy, computer sciences), geology (earthquakes, volcanoes, mining, oil and gas), engineering (construction, prosthetic devices, flood levels), and so on. Mathematics, on the other hand, is the language of the universe (all other sciences are merely dialects as a Connecticut mathematics professor once put it!). Although mathematics seems remote and austere, simplified connections are made by the general public through computer sciences, economics, and statistics. In reality, we need to appreciate that all of the above disciplines are closely integrated, indeed embedded with "rules" from the others, in creating the "magic" of sciences.

Outside the "magic," people conveniently "opt out" and separate benefits from consequences. This leads to science being widely misunderstood and misinterpreted—its dominant role in daily life seems to become dominating and resented. Most people, it seems, cannot be encouraged to give up a little of the time spent on addictive "diversions" to grasp and deal with all the uncertainties at the interfaces where the "magic" of science, nature, and factual understanding come together. The realization of wider public support and broader understanding can only come if more people can be stimulated into wanting to learn more about science in a way that enables them to gain satisfaction from understanding the problems and goals of science as applied for social good. Not everyone will be willing, nor should they be, to sacrifice the qualitative feeling approach to their lives. No doubt many find mystical comfort, as well as fear, in the unknown and seemingly unknowable. Without detracting from this, there is much to be gained by greater efforts to increase everyone's curiosity in the "magic" of science.

To make science more digestible and to provide a modern foundation, many schools and universities are already working to define and teach a canon of basic knowledge and fundamental principles which integrates the above components, stimulates curiosity, and thereby provides a basis for a rewarding career.

Chemistry is one of the relatively poorly regarded branches of science, despite providing the architectural foundation of our everyday lives. To make the subject more mainstream, a broad universal redefinition of what scientific material should be included in chemistry courses is needed, building on what has been started. The knowledge base today is so vast that selecting the chemistry to be taught, enabling

students to grasp the fundamentals and at the same time to encourage curiosity, is a daunting task. Many inputs are needed to agree on content, at the same time as avoiding rigidity. My thoughts are that a wide range of other disciplines needs to be incorporated from the biological sciences (biochemistry, botany, and microbiology, for example), from physics (e.g., fundamental matter, thermodynamics, kinetics), and from inorganic chemistry (noncarbon elements/compounds in life processes, in catalysis, in energy generation). More specifically, regarding the biological sciences, the relevance of pre-biotic chemistry, evolution, electrochemistry, and photochemistry to life, and the chemistry/biology associated with amino acids, peptides, proteins, enzymes, and DNA seem to offer opportunities to stimulate curiosity. Again, specifically, an introduction to modern analytical instruments and their application to quantitative analysis and an understanding of what is going on in chemical reactions would provide students with a sound basis for quantitative thinking and for experimentation. Analytical chemistry should cover a body of basic knowledge from potentiometric titration all the way to spectroscopy.[5] Perhaps, above all, an education in chemistry needs to emphasize the experimental nature of the subject. Experimentation enables students to intellectually engage and feel the "magic." In short, the classical courses of time past need to continuously evolve and to be continually revitalized in order to raise chemistry to the level of an essential discipline that will enhance the lives of all who participate.

There is, within the broad subject matter of chemistry, the opportunity to be absorbed and stimulated by the esoteric and/or to find equal satisfaction in a devotion to the practical interdisciplinary applications. A chemistry education in either a prestigious university or a school of technology can lead students either way, depending on themselves. In Europe, universities are usually seen as classical while the technology schools lean more to the practice of chemistry. In Europe there is a distinguishing balance between the two kinds of education, with, perhaps, a nod in the technical to the old apprenticeship system of qualification. America, for the most part, hardly distinguishes the classical (Ivy League) schools, as well as the large number of second-tier (definitely not second-class) schools, from the great Institutes of Technology. America embraces more of its graduating high school population in a third-tier community college system than does Europe, and many of the graduates from these schools find their way into jobs all across the business spectrum. However, while there are many good technical and trade schools in America, there is no nationally standardized technical education in chemistry of the sort available in the major science countries of Europe. In particular, few promote a coherent long-term interaction with the industries and businesses in their areas. This is partly because there are fewer places in America where businesses are really concentrated. There are no equivalents to the concentration of the Swiss pharmaceutical industry around Basel (New Jersey is similar but more dispersed), or the huge chemical/pharmaceutical complexes around Ludwigshafen, Leverkusen, and Frankfurt in Germany, or Manchester/Liverpool and the Tees-side in England.

[5] An excellent place for undergraduates to start is *Organic Spectroscopic Analysis*, Anderson, R. J., Bendell, D. J., and Groundwater, P. W. Royal Society of Chemistry, Cambridge, England, 2004.

Ph.D. chemists joining the pharmaceutical industry in America come, literally, from all over the world (one of the great strengths in America). The support and technical personnel usually come from more local universities and technical schools. Most need quite a bit of training in the practical chemistry techniques and most have had no, or little, experience in working, like the old-style apprentice, in industrial laboratories, particularly with the kind of thinking and modern instrumentation needed to address problems in a multidisciplinary and quantitative way.

Building a broader foundation for technical training in the United States, especially in places where there is a fairly heavy concentration of a specific industry (e.g., the pharmaceutical industry in New Jersey), could be achieved through sustained industrial-university collaborations in pertinent scientific disciplines. A few such collaborations go on already, but not with the permanence or depth to be found in European models. One such model I have seen at work in Switzerland might be advantageously adapted to enhance the education of scientifically and technically oriented students to the mutual benefit of both universities and industries in appropriate regions. Switzerland has set up institutes of higher learning, all around the country, which have strong programs of teaching usually greatly relevant to meeting the technical needs of businesses/industries all across the country. In the Basel area the Fachhochschule Nordwest Schweiz (FHNS) provides a technical education in the disciplines of chemistry, mechanical/chemical, and some biological engineering and electronics/computer sciences. FHNS's location draws on the strengths of the region. FHNS is very well equipped with analytical instruments, computers, and a pilot plant for practical chemical and chemical engineering training.

The chemistry department provides a basic education in the conventional disciplines of organic, physical, inorganic, and analytical chemistry and, in keeping with its focus on technical education, provides a great deal of practical training as well as instruction in safety/environment technology, economics, law, organization and management. FHNS draws on the technical expertise of specialists from industry in its teaching activities. FHNS introduces its students to practical chemical work through programs on synthesis and practical topics, where possible of some industrial significance. It also seconds students into industrial laboratories to gain experience in technical problem solving in the industrial world.

The chemistry department emphasizes teaching in the acquisition of practical skills. Students learn how to go about:

- Searching for information in the literature and electronic databases
- Handling chemicals and running chemical reactions safely
- Acquiring analytical instrumentation skills.
- Understanding quality and gaining skills in efficiently producing chemicals of standard quality—they also learn the basics of GLP and GMP
- Learning how to deal with unsuccessful experiments, how to think about their problems, how to improve on their results, and how to guide and motivate others in these areas

- Dealing with "customers," taking responsibility and taking the iniative to repeat experiments when "customers" are not satisfied
- Collaborating with others and working in teams
- Communicating with and presenting work to others, including writing reports
- Becoming especially aware of the importance of safety, environmental, and economic matters in creating and running chemical processes

One way FHNS courses help students to appreciate the importance of the above is through creating teams of four students per team, each team being asked to find a chemical reaction in the literature which should be relatively low in cost to reproduce and also safe to run. The objective in reproducing the reaction is to develop it for scale-up. One student is appointed team leader, responsible for communicating with others and keeping everyone informed on the work program. Each student is allowed to change one parameter in the published reaction (e.g., a solvent to improve regulatory compliance). After the first student has completed the reaction, the results are discussed within the team. Each student justifies to other members of the team the reasons for making a proposed change. The students add "know-how" to each experiment and make a final recommendation, in the form of a short report, on what further work they think should be done on their modified literature procedure to make it suitable for scale-up. Staff members are always available for answering questions and for general guidance.

FHNS's industrial liaisons are of enormous value to the students, enabling them to gain some understanding of the importance of organization, partnerships, innovation, and commercial interests and particularly the place of their technical work in advancing the goals of an increasingly responsible industrial sector. Industrial liaisons promoted by FHNS and local industry sometimes leads to the industrial partner working with FHNS in the FHNS pilot plant.

Summary

In the above, I have tried to illustrate the importance of education in creating the interdisciplinary interactions needed to progress chemistry and increase appreciation of its importance in the modern world. More national publicity of all sciences is essential to increase realization of the vitally important role that science will play in the future. More early exposure to the "magic" of experimentation would help to inspire people to follow a science career. People need to be galvanized to want to learn more. Chemical Process Development is one of the more practical areas of chemistry and, as the thrust of the earlier chapters illustrates, one which particularly requires that practitioners embrace many other disciplines in order to create success in any mission.

The bottom line is that educators everywhere would benefit from an International dialogue with their counterparts to create the chemistry courses needed to equip students for a future career in chemistry.

BUREAUCRACY REDUCTION

Introduction

Many have written, sounding the alarm, on the subject tof overregulation and its impact on the future. First it is important to say that a strong regulatory framework is needed to establish standards, to deal with their maintenance, with unwitting mistakes and particularly with the excesses of the many individuals and businesses around the world who work to create advantage for themselves by bending the rules or criminally exploiting perceived opportunities to profit, and so on. If all people were honest and socially responsible (i.e., by being broadly better educated), we would have no need for the excessive regulations of today. Unfortunately, in developing regulations to build and enforce standards and to counter unwitting mistakes and irresponsible opportunists, the regulatory "industry" has gone too far.

Overregulation is now a fact of life. The legal profession grew dramatically over the last 40 years or so and is now in danger of inhibiting progress, becoming like the Trade Unions! Trade Unions once provided, and particularly in the developing world they still do, the much needed power base to protect industrial working people from raw exploitation by industrial and bureaucratic barons who had little concern for their workers. Despite all the good they did in the past, today's Trade Unions, at least in the developed world, still carry too much adversarial and self-preservation baggage and are more seen as societies for the promulgation of mediocrity—in short they have not fully evolved with the times. To be fair, Unions are still needed in some cases where managements have not done enough to foster better relationships with their workers. In parallel with Trade Union developments, today's regulatory/legal profession has grown to the point of promoting and defending the introduction of new laws, many of which are grossly more costly than the value they provide.[6]

In looking at past major documents ("laws") that established social standards and provided social guidance, one is struck by their brevity and simplicity. The words needed to convey the spirit of social development were relatively few. Granted, dealing with infractions, each on its own merits, in a common law setting undoubtedly introduced more complexity (and words) in particular cases, but the generally law-abiding honest citizen was allowed to run his/her life with relative ease compared with today. To illustrate, consider the number of words in a few of the major guidance documents:

- The Ten Commandments—297 words in the King James version, Exodus 20.[7]
- The Magna Carta (English translation of the Latin original)—4482 words.
- The American Declaration of Independence—1332 words.
- The Bill of Rights (the first ten amendments to the American Constitution)—461 words.
- President Lincoln's Gettysburg Address—269 words.

[6]In addition, in Europe, EU laws are often introduced on top of member country laws without guidance on the melding of the new laws with existing laws or creating "sunset provisions."

[7]The *100-Minute Bible* reduces the Ten Commandments to 59 words.

Compare the simple beauty of these documents with the mountains of paper issueing, for example, from the European Union; for instance, the European Initiative on Caramel Products, issued in the 1980s, uses about 250,000 words (about one-third of the words in the entire Bible)!! Such excesses become the source of ridicule and an embarrassment to the legal profession. Even the legal profession itself recognizes that there are many idiocies in the law. For readers interested in this area, I suggest they read a lawyer's view on the subject.[8]

Bureaucracy in Chemical Process Development

Getting down to the basic issue in the present-day pursuit of chemical process development, most practitioners are appalled by the growth of restrictions on the initiatives of chemists and chemical engineers to change chemical processes for the manufacture of APIs. Granted it is not too difficult to make changes before the IND, or even in the early steps of a process post the IND (i.e., before Phase III—see Chapter 3, Figure 2), provided that one can demonstrate sufficient advantage and no effect, or a beneficial effect, on API quality. However, post the IND, process changes, especially late in the synthesis sequence, are very difficult to introduce and it is virtually impossible to promote a revolutionary new synthesis. This is largely because of regulatory concerns, often most zealously applied by a company's internal regulatory watchdogs (who seek to keep the company "whiter than white"). Restricting change is perfectly understandable to those working to avoid delays since they see restrictions as virtually eliminating the chances that the quality of the API or its biological effect will be adversely affected (e.g., by new impurities); they eliminate the need for the validation of changes (which can be enormously resource- and time-consuming), they eliminate the need to divert often limited regulatory resources into the documentation of changes, and they eliminate the need to go back to the FDA for approval (both also resource-consuming and time-consuming). By avoiding all of these activities, companies feel that they are eliminating the chances of delay in developing, filing, and gaining approval of their NDAs.

The major consequence of virtually eliminating post-IND changes is that API processes essentially become no more than expensive methods, refined into often inadequate processes. Such method processes consume enormous time and present often great difficulty and expense in technology transfer and manufacture since they use sub optimal chemistry (e.g., the employment of chemicals you would rather not use), they require more and sometimes specialized manufacturing equipment, they introduce unwanted waste-disposal and environmental challenges, and they employ far more labor/support resources than a real developed process would use. As a result, the cost of manufacturing APIs is generally far greater than it should be. Pharmaceutical companies are willing to pursue this strategy to get their drugs to the marketplace as quickly as possible, thereby realizing profit as soon as possible. The argument is that this is a reasonable strategy since, generally speaking, the cost of the API is only a relatively minor component of the cost of the marketed drug.

[8]*The Death of Common Sense—How Law Is Suffocating America*, Phillip K. Howard, Random House, New York, 1994.

There are two major downsides to this strategy, in addition to the lost cost-reduction opportunity. First, process development chemists and engineers are greatly diverted from undertaking the sort of intellectual/innovatory work needed to find the best process chemistry and to develop it into a real commercial process. Second, once an NDA process is approved, the time taken to fully resume innovation and prove a new process, as well as to undertake all the testing, validation, and regulatory approval work and to invest in new plant, transfer technology, and so on, adds years more to the time frame. My two Case Studies neatly illustrate the situation (q.v.). In the Dilevalol Hydrochloride case, in the 1980s (see Case Study 1), we were able to demonstrate, late on in the program to file an NDA, that a better manufacturing process had been proven, in scientific terms. We shared the data with the FDA as we were implementing the new process. They agreed with our initiatives. In complete contrast, 10 years later, a seemingly better process for the manufacture of Temozolomide was not pursued despite the promise of dramatically lower costs and replacing the use of specialized equipment with conventional equipment (see Case Study 2). Granted the seemingly better process had not been developed to the point of demonstrating that it was better, largely because the future market projections at the time did not justify the effort. Since that time, market growth has exceeded all expectations, but the seemingly better process system remains in limbo.[9] I should make it clear that I am not suggesting we return fully to the Dilevalol Hydrochloride situation. Nor do I think that we should simply adopt the thinking, which seems current with some companies, namely that they establish, with the regulatory authorities, a chemistry/manufacturing/controls (CMC) section that qualifies a very late intermediate as the starting material for the API synthesis. Qualifying a late intermediate does not free the company from all regulatory control in early intermediate manufacture since the company still needs to build quality into the intermediate by using an approved sequence of reactions and process conditions, all overseen by an exacting analytical control system (see Chapter 6). In addition, qualification of a very late intermediate does not give the synthesis chemist or engineer a carte blanche to change the synthesis sequence, or introduce a revolutionary synthesis. This is because process changes, especially those attendant on a revolutionary synthesis, might reasonably be expected to introduce new impurities. Just the very threat of new impurities would require considerable analysis and lead to process qualification and validation work to prove that the new process intermediate, and the API made from it, gave the same quality drug product as registered in the NDA. From this it can be seen that generating the creative chemistry component of a chemical process takes much less time than the sum of the analytical work (providing assurance that quality has not been compromised), all the pharmaceutical development work (particularly to show that the drug product's physical parameters and stability are unaffected), all the additional validation work, and all the supporting documentation. Add to this any plant modifications, along with

[9]Comparison with the fires that destroyed La Fenice opera house in Venice, 170 years apart, also illustrates the impact of time on getting things done. In 1836 the Austrian government, then in power, took less than a year to rebuild the opera house. After the 1996 fire, started by two misguided electricians, it took the Italian government nine years to rebuild.

the manufacture of three new batches to enable demonstration of API equivalence, and one quickly sees that the time and cost of introducing a new process becomes greatly extended. Clearly an enormous amount of effort, time, and money is needed, under present rules, to introduce new chemistry post the NDA.

Companies engaged in new ventures would gain some relief if suggestions by the late Peter F. Drucker had been adopted. He advocated allowing new venture companies to charge the government for all the efforts taken to meet the regulations. Unfortunately, such an approach does not get to the heart of the problem but it would certainly have encouraged new thinking!

We need to find a way, acceptable to the regulatory authorities, of allowing process innovation to continue, without interruption, not only during the IND to NDA phase of API process development, but continuously throughout the life of a product. Before I retired from the Schering–Plough Research Institute, I proposed a simple direct chromatography-based alternative to the present "no-process-changes-allowed" strategy with the objective of keeping process innovation and change going continually throughout the IND–NDA time frame and beyond. Nothing was done, perhaps because there were downsides I did not think of. Nevertheless, I thought it would be worthwhile summarizing my reasoning and suggestions for greatly reducing regulatory bureaucracy in the hope of stimulating debate enabling process development chemists and engineers to promote innovation overcoming the present discontinuities and costs.

The world of manufacturing APIs is essentially built from two components. One component is the chemical/biological synthesis scheme for producing the intermediates used in the final construction of the API. The other is the API synthesis itself, governed by cGMPs. Today cGMPs greatly affect much of the first component as well as dominating all of the second component. Rather than provide for split activities, companies (trying to be "whiter than white") err on the side of operating virtually everything under cGMP control. In my view they should not. We need a way of operating that restricts the heavy documentation/validation aspects of cGMPs to the last API steps and, in exceptional cases, to the penultimate step. I wish to stress that I am not advocating adoption of a free-for-all in the manufacture of intermediates and APIs and therefore leaving all purification to a final chromatography step. Nor am I advocating making synthesis changes on the basis of good science, adopting them and then gaining FDA approval (as with the Case Study on Dilevalol Hydrochloride).

We have to recognize, as scientists and engineers, that the FDA changed the landscape for producing APIs. Today responsible chemists and engineers have refined and formalized their approach to chemical process development to firmly and irrevocably build it on sound science. They have also adopted a collegiate, collaborative approach to process development, working closely with all those who have a voice in creating a commercial process—principally personnel in analytical departments, pharmaceutical development, safety, environmental, manufacturing, and regulatory affairs disciplines. Companies, especially the major pharmaceutical companies (and most of the fine chemical companies which serve them), have built solid reputations with the FDA for creating sound processes. There is no doubt in my mind that the FDA should take a great deal of the credit for raising and maintaining professional

standards; they also need to be continually involved in auditing to ensure that high standards continue to be maintained in qualifying newcomers who seek to be suppliers of intermediates and APIs.

Given that high professional standards in the field of chemical process development have been secured in responsible companies and given that FDA audits of pharmaceutical companies continue to ensure the maintenance of high standards, the quality of APIs only very rarely becomes an issue today. Such high standing established with the FDA could, I believe, be taken to the point where the responsible companies are given the freedom[10] to continue innovatory process development work and implementation of new processes on a continuous basis, including through the IND to NDA phase, given that the responsible companies add one safeguard—namely a validatable chromatographic purification step at the API formation step or the previous step. I would not make this chromatography step a clean-up step for any kind of chemistry done in preceding steps. Chemists and engineers in designing innovatory new processes must keep a record, as now, showing that they really understand the chemistry being introduced, including establishing a mass balance accounting for byproducts and impurities and showing that they can be eliminated or reduced to very low levels before the validatable chromatography step. The chromatography step thus serves as a bulwark process step to provide a guarantee of quality. I see the chromatography step as an aid to "building in quality" and not a means to remove rubbish from sloppy chemistry at earlier steps. In this risk-based approach I would ask that the FDA allows pharmaceutical company chemists and engineers the freedom to undertake any chemistry they think can improve intermediate quality or process economics without affecting API quality, at all steps up to the final or penultimate step, without needing more than their professional notebooks and SOPs to prove they are meeting the needed quality criteria in the final API. I would still insist on subjecting the early step activities to independent (QA) audit but not subjecting process changes to the bureaucratic approval requirements seen today.[11] In reality, as in the Dilevalol Hydrochloride case, responsible chemists and engineers do not need the draconian, professional-morale-busting attention (however well-meaning) of bureaucrats trained to drive compliance activities by a book of regulations. Nevertheless, for everyone's peace of mind, auditing of the early steps must be continued.

I recognize that the cost of introducing a chromatographic process step will, correctly, be regarded as expensive,[12] but I hypothesize (I have only a feeling based on experience rather than a proven example) that the cost of creating and validating a chromatographic step or steps (including capital costs, operating costs, solvent costs, cGMP, and validation costs) will be far, far less than the costs, outlined earlier, associated with developing and implementing a method-process and delaying innovation to a later date. As seen in the case of Temozolomide, it takes a Herculean

[10]Perhaps such freedom could be accommodated under the refined FDA guidance role outlined in its publication *Pharmaceutical cGMPs for the 21st Century—A Risk-based Approach*.

[11]In some respects, qualifying the process steps up to the chromatography step is similar to qualifying plants that produce chemical products under the European ISO 9000 system (see Chapter 6).

[12]Except when chromatographic purification is successfully applied to aqueous solutions (see footnote 7 in Chapter 9).

effort (and cost) to replace even a poor and very expensive manufacturing process post NDA approval—in my view the potential lost opportunity cost (i.e., savings in manufacturing cost) that might have been realized has probably been enormous.

To fit with the philosophy expressed in the chapter on regulatory affairs, I would argue that the proposed chromatographic purification step be built into the program for working out the last step first (see Chapter 6). In short, the bulwark quality-assuring chromatography step should be built in from the very beginning of the API supply program.

The introduction of a chromatographic purification step, while at the same time allowing well-worked-out process changes, or new chemistry, to be introduced cautiously but continuously, places added requirements on validating the final step(s) [from the chromatographic step to the final API]. There will need to be assurance that the chromatography step itself is not introducing new factors (e.g., traces of resins[13]) to the API. Work may also have to be done up front if new impurities (which must never exceed the 0.1% level) are introduced into the API, despite chromatographic purification. It is essential to ensure that no unwanted toxicity has been introduced (as was the case when process changes were made in the L-tryptophan process (see Chapter 6). Isolation/preparation of introduced new impurities and their toxicological evaluation should, generally, be undertaken to provide assurance on this point.[14]

The chromatographic separation and purification of organic compounds has been widely practiced, particularly in the anti-infectives field, for several decades. Examples include elution from resin-extracted fermentation broths (e.g., aminoglycosides), absorption and selective elution from filtered broths (cephalosporin C and derivatives), and the purification of proteins (interferons), inter alia. The merits of chromatography as an industrial scale purification technology have been greatly extended in the last few decades to other fields and APIs—for example, the cyclic heptapeptide, Integrilin, an antithrombotic, and the synthetic substituted phthalan, Citalopram, an antidepressant. In short, despite the perceived costs associated with chromatography as a process step, I suggest that when considered in the same context as the consequences of inhibiting process innovation post the IND phase of chemical process development, as outlined above, the routine introduction of a chromatographic process step in every API synthesis should be considered as a bargain.

Chromatographic purification might not be applicable to every API synthesis—for example, when the API itself is very insoluble. However, in these circumstances, ways might be found of introducing the technology, say at the penultimate step, in the bulwark purification of more soluble fragments.

The range of chromatographic purification technologies is very broad, ranging from the relatively low-cost water-based classical resin systems (see footnote 12) on

[13]Such might be removed by an additional step (e.g., ultrafiltration, removing particles in the 4- to 25-Å range or reverse osmosis, removing particles in the 1- to 5-Å range) which will introduce its own validation requirements.

[14]Where the difference in the structure of the new impurity versus the original one is relatively small (as in structures **XIIIa** and **XIIIb** in Chapter 9), an expert judgment may eliminate the need for additional toxicology work.

to related solvent-based systems and on to high-performance liquid chromatography (used in the production of tonnes of Integrilin) and simulated moving bed chromatography (used in the production of tens of tonnes of citalopram). The separation of optical enantiomers on a large scale represents one of the more valuable contributions made by chromatography specialists to the pharmaceutical industry; this is surely a growing field as single-enantiomer APIs are increasingly being recommended for development.

It behooves anyone interested in testing the above concept to take a proven system to the FDA to gain their feedback, to examine their suggestions for fine-tuning the specific case, and, ultimately, to gain FDA approval. It follows that ongoing process changes, in terms of outlining new chemistry and providing the data showing that API quality is unaffected, will need to be lodged with the FDA. These steps, without the current regulatory bureaucracy governing early steps, not only have the potential to greatly reduce API costs but also spur thinking chemists and engineers to express themselves freely, to the benefit of companies and chemists/engineers alike.

Summary

In the pharmaceutical industry, regulations are essential for the protection of the public against egregious events (however innocent) that adversely affect API quality and place the public at risk. During the last 30 years the FDA has been the major force in causing the pharmaceutical industry to quantify its science and to create systems guaranteeing they produce quality APIs. In the slow progress toward "perfection," rules and guidelines, abetted by company failures and aided by the growth of often draconian internal Quality Assurance and Audit groups, have generated a bureaucracy that has greatly suffocated the innovatory spirit in chemical process development as well as in other departments responsible for API production, at least beyond phase III. In this 30-year time period, quantitative science has come to the fore, and process understanding has enabled scientists to create processes that control quality to exacting FDA standards, even though the process chemistry has often been suboptimal in terms of molecular elegance, plant and labor requirements, environmental, and ultimately cost considerations.

Stifling innovation has had a significant adverse impact on the cost of drugs and particularly on the creative scientists and engineers frustrated in their efforts to express their creative talents. Recognition of the adverse effects of bureaucracy on the rate of progress toward lower cost drugs and on company competitiveness has led to the present proposal to try to keep innovation going through the simple device of introducing a validatable chromatographic purification step at the final stage(s) of API manufacture. By introducing such a step, without sacrificing scientific understanding and control in the earlier process steps, the innovation process could continue and be implemented on a continuous basis.

Readers may have other and better ideas and should be encouraged to express and evaluate them.

TRENDS AND TECHNOLOGIES

Notes on Synthesis

Organic chemistry, on its own, is no longer the frontier discipline it was. Its enormous contribution to the identification of the chemical structures of diverse natural products, along with the enhancement of the properties of these products by structural manipulation, led to the applications that created major new industries and social prosperity. In those days, roughly the first half of the 20th century, organic chemistry became the cornerstone of such industries as the dyestuff industry, the pharmaceutical industry, the agricultural chemical (including insect control) industry, and the fiber industry. These industries, and the explosives and polymers industries, were greatly enhanced by experimental research, often simply empirical synthesis endeavors. The rapid expansion and diversification of all these industries, which occurred in the second half of the 20th century, led to greater appreciation of both the good and the adverse effects of the organic chemicals being synthesized, which stimulated the search for better molecules and ways of dealing with adversity. Hybrid disciplines (e.g., chemical engineering, biotechnology, the ecological sciences) were developed and industry, often prompted by social activists, began the process of integrating practical organic chemistry with many other disciplines (see Figure 3 in Chapter 3).

Schools and universities teaching chemistry never really accommodated the needs of industry to integrate chemistry with other disciplines and lost ground as some of the newer integrated disciplines, particularly environmental sciences, marine biology, forensic sciences, and political sciences, emerged in the education curriculum and the so-called pure sciences—chemistry, physics, and mathematics—attracted fewer students. Chemistry departments in institutes of higher education need to integrate the new disciplines into their fundamental chemistry courses and also recognize that many of their students will want to branch out into the newer disciplines. By not embracing the practical new areas, chemistry has limited itself. This trend has undoubtedly been a factor in the closing of a few university chemistry and mathematics departments, or their merger into a general sciences curriculum. Understandably, left to their own devices, the newer hybrid courses "cherry pick" by only incorporating those parts of a pure chemistry course which they see as relevant to their own course. This leads not only to loss of much of the fundamental rigor of the pure sciences but also to a tragic loss of historical perspective and that indefinable "magic of science" which are so important to future creativity. In synthesis terms, if the foundation for building imaginative ideas is not there, we will not be able to reach the intellectual heights needed to progress.

Organic synthesis is evolving rapidly and I am not close enough to current research to identify those ideas that will create the best chemical process development prospects; the ideas needed will also be dependent on the structure of the molecular targets. I can only take shelter behind parts of an inspirational statement[15] on the

[15] Danishefsky, S. J. *Tetrahedron*, 1997, **53**, 8689–8714.

challenges facing synthesis chemistry made several years ago by one of America's great organic synthesis chemists, Professor Samuel J. Danishefsky, in paying tribute to Dr. Sarah Jane Etheredge:

> The opportunities for discovery are greater than ever for those who are willing to study and practice synthesis with scholarly dedication and experimental exactitude.
>
> The playing field of synthesis today encompasses all but the rarest elements of the periodic table. The debt of total synthesis to methodology development goes well beyond the convenient availability of many new methods, important as they are. The new technologies liberate and, indeed, beckon the architects of synthesis to think in much broader and sweeping terms about tomorrow's problems. Clearly, the most dramatic advances have been registered from the mobilization of transition metals and other organometallic reagents to achieve specific transformations even in multifaceted contexts. It is well to recognize that these breakthroughs were, on the whole, achieved by scholars of chemistry and even curiosity seekers—unconcerned with any apparent application to total synthesis. The synergism of methodology, mechanism, and strategy constitutes the core of synthesis.
>
> There is a diminishing need for the logistically intensive multistep assaults simply because the mountains are "there." The syntheses that will warrant the greatest interest are those that convey new ideas and new chemistry arising from a willingness to explore ambitious and risky propositions. It is in the context of dreaming such dreams—and, above all, in the struggle to reduce them to a "do-able" state—that the power of our science, as well as its beauty, flourishes.
>
> The devotees of synthesis have good reason to be particularly optimistic about their field. The opportunities in the design of high "value added" structures of either theoretical, material science, or biological impact fire the imagination. Moreover, as bioassay systems become more and more sophisticated, and as more lead compound types, including structurally fascinating natural products, become increasingly amenable to deduction at the level of mode of action, the number of potential projects of high promise will continue to increase.
>
> Quite properly, organic synthesis will be drawn to multidisciplinary undertakings. I would urge that, in these ventures, the synthetic organic chemist assume a significant leadership position. Those who accomplish the synthesis of a target are apt to have gained a privileged vantage point as to its true molecular nature. *However, it is in a class by itself in terms of its capacity for creation.* To fully exploit this power, chemists must be particularly well informed and venturesome in the broader contexts and applications of their accomplishments. Only through such activism can the formidable heuristics inherent in organic chemistry find full expression in multifield coalitions.
>
> The future will be particularly bright for those who sort carefully and select wisely from an ever expanding menu. Again, I urge the emerging leaders of tomorrow to conduct their synthesis more with daring and imagination and less with reflexive recourse to well-trodden paths. In such settings, synthesis will surely provide more magic moments, first to its creative enthusiasts and then to the larger scientific enterprise and, hopefully, to the public we all seek to serve.

Outsourcing

The outsourcing of many functions in the process of developing a drug to the marketplace is a long-standing but still growing practice in the pharmaceutical industry. Outsourcing enables companies to leverage their physical and intellectual assets, enabling them to do more with their core resources and, at least partially, to transform themselves into more of a guiding service organization. In the heavily regulated pharmaceutical industry, outsourcing requires a major dedication of pharmaceutical company resources to ensure the receiving company (RC) has the physical and intellectual capabilities needed to take on the work to be outsourced. Once the credibility of the RC has been established, legal agreements are usually reached, including on recompense for and ownership of any RC discovery of advantageous (e.g., cost-reducing) intellectual property, and the supervision of technology transfer begins. Following the transfer of technology and associated regulatory responsibilities, the pharmaceutical company becomes involved in monitoring and periodically auditing the RC to ensure regulatory compliance and the achievement of yield/quality expectations.

By adopting outsourcing as a legitimate practice, pharmaceutical companies usually gain significantly, especially from overseas transfer, where, for the moment, much lower operating costs often prevail. They may also gain from reducing the internal regulatory burden—most API manufacturers have more regulatory oversight, to ensure they are "whiter-than-white," than is generally required. Another major gain can be in capital expenditure avoidance for the physical facilities needed to produce the transferred intermediate or API. Even if the pharmaceutical company has the facilities, it may prefer to deploy the scientists and engineers not involved in technology transfer in the development of other experimental API candidates. Some tax advantage may also accrue from transfer to another country.

There are of course many risks associated with outsourcing. The technical capabilities of the RC may not be sustainable if key scientists/engineers leave them. In these circumstances, API quality, and even intellectual property, may be compromised. Safety and environmental commitments may also be endangered. The reliability of supply (mostly quality, delivery times, and costs, in that order) from the RC will depend on many parameters, including the personnel they assign to the work, the RCs investment in needed capital equipment and analytical instrumentation, their raw material sources and quality, their support resources and commitment, and their professional training to undertake needed tasks. Outsourcing companies also need to guard against changes in the RC's status. For instance, takeover of the RC could change legal agreements. For these reasons, pharmaceutical companies need to have contingency plans to deal with cataclysmic events, such as the possibility of an Asian disease pandemic. Cultivating a second source elsewhere is an essential component of every technology transfer scenario that has developed, or appears to be developing, to a production scale.

Outsourcing to reliable RCs in underdeveloped nations (e.g., India and China) provides enormous benefits to these nations, greatly enhancing their economies and stimulating the educational process needed to develop national culture—not only to

deal with introduced environmental and safety issues but, not incidentally, to fund efforts to deal with their own "socio-politico-religious" imbalances. The outsourcing nation faces different consequences, especially where people in the developed world are laid off when their work moves overseas. Increasingly, all the developed world's populations need to be prepared for this. If education can be transformed into a lifelong spirit of pursuit, those put out of one kind of work may be in a better position to re-engineer themselves to do another. To support re-engineering, the governments of outsourcer nations could impose a kind of tax on the outsourcer, say in the form of obliging the outsourcer to spend part of the "outsourcing profit" on funding the research needed to create "new industries" and/or improve existing ones (e.g., by tackling environmental issues) and to help re-educate those thrown out of work. Experience suggests that the outsourcer tax would best be spent in the private sector rather than by big government. As an aside, few of the millions who are or will be put out of work will benefit from such a task in the short term. They will need support and training supplied by programs such as the U.S. government's Trade Adjustment and Assistance programs, originally developed in the 1960s to aid those affected by tariff cuts. It will be a harrowing process for the displaced, but taxing to support education and R&D will eventually lead to new industries and improvement in core competencies in both industry and the workforce.

Returning to the main theme, the company personnel responsible for and undertaking technology transfer need to be well-versed and trained in all the disciplines required to ensure that a chemical process conducted elsewhere is carried out to meet both the NDA requirements and local situations.[16] In transfer overseas, personnel also need to be educated in the customs and culture of the receiving country to ensure that the technology transfer is not compromised by misunderstandings.

The above indicates that outsourcing, rather than being merely an instrument to reduce short-term costs, should also be a spur for longer-term innovation to ensure competitiveness. Since the companies overseas who do the work also see a new opportunity for innovation, the onus on the outsourcer is to ratchet up the discovery effort to a bigger picture, higher level—embracing, for example, more innovative programs to identify "new businesses" and new patent protections. Another example would be to adopt a spaceship earth mentality by supporting innovation to deal with the future impact of more rigorous environmental and safety laws.

It is clear that outsourcing, and dealing with the risks associated with outsourcing—ensuring quality, suffering time delays, losing intellectual property, addressing the downside of domestic layoffs—will be in vogue for as long as cost advantages, in terms of cheap labor and low-cost capital equipment (and, unfortunately, relaxed environmental and safety laws), continue to hold in developing countries. It

[16]When Schering–Plough transferred a corrosive reaction to China, the Chinese RC said they would prefer to work in a low-cost regular steel reactor available in China rather than go to the expense of purchasing a Hastelloy reactor. This could only be agreed to by repeatedly running the reaction in the presence of the Chinese regular steel and establishing that leached metals did not compromise process yield or product quality. This proved to be the case, leading the Chinese to invest in a system whereby a second back-up reactor was available on site to replace the corroded reactor when it failed. The turn-around time in removing the corroded reactor and installing and testing the new one proved to be remarkably fast.

will probably take decades for outsourcing harmonization to be achieved—that is, to the point that carbon dioxide emissions and "chemical miles" (the distance molecules have to travel from source to final API) and the application of worldwide standard safety/environmental laws will enter into the cost equation. Until that time, outsourcing nations need to spend that outsourcing "tax" on innovation (and patents) and education to maintain competitiveness, and the receiving countries need to pass and enforce safety and environmental laws and promote (also through education) those facets of their social, cultural, and economic life needed to transform themselves into responsible, developed nations. In conclusion, it seems to be particularly necessary for both outsourcer and "outsourcee" to aggressively address the many opportunities and consequences associated with outsourcing in order to reach a constantly evolving steady state where invention benefits all and where waste and antisocial, self-serving activities are addressed to the satisfaction of all parties involved.

Water and Enzymes in Chemical Process Development

Water is the "solvent" for most of the organic chemical processes of life itself. In contrast, in the last 150 years the birth and growth of the organic chemicals processing industry has been largely dependent on the use of organic solvents as vehicles for carrying out chemical transformations. These solvents became available as a result of the growth of the coal-fired energy industry in the 19th century. The organic chemicals industry continued its inextricable link with the energy industry as coal gave way to oil and gas in the 20th century. Although the organic chemicals industry is only a minor offshoot of the energy industry, in terms of its production volume, it is nevertheless linked with it as the world begins to deal with the substantial environmental, economic, and social consequences associated with the use and disposal of the world's organic feedstock. The energy industry's caused-emission of greenhouse gases (particularly carbon dioxide) and particulates, as well as the not infrequent coal mine or oil tanker disasters, have had substantial impact on public health, wildlife, and the climate. The public recognizes that the energy industry is promoting work to harness alternative sources of energy to the existing finite organic feedstock. Yet, despite this, all recently promoted "clean" forms of energy (harnessed from hydroelectric, solar, wind, waves and tides, geothermal, and nuclear sources) provide only a small proportion of the world's energy needs; and all of them, especially nuclear sources, have their detractors. Paradoxically, the public themselves, as consumers, are only now reluctantly recognizing that their "addiction" to energy is driving the slow-moving energy industry to a socio-political tsunami, with, likely, immense adverse consequences for the planet. Although no one can predict the enormity of the consequences, few in power appear willing to take a proactive stance to deal with trends. In short, no leaders have yet emerged to marshal the social and political will needed to promote energy conservation and to "treat" energy addiction.

The organic chemicals industry, although operating at a small fraction of the scale of the energy industry, nevertheless makes a substantial contribution to planetary problems, seen in the creation of polar "ozone holes" and in the damage inflicted,

from time to time, by chemical spills and accidents involving noxious, flammable, and explosive chemicals.

As for using water-based systems for the manufacture of organic chemicals, it is useful to recall that the fermentation industry once provided part of the base of the organic chemicals industry, with the fermentation of *n*-butanol, acetone, acetic acid, lactic acid, and monosodium glutamate, inter alia. Chemical methods have superseded fermentation for the first three of these compounds through interest in fermenting *n*-butanol for fuel purposes has been rekindled. The recent growth of fermentation for the production of ethanol from corn, to provide a replacement for *t*-butyl methyl ether as a gasoline additive, has highlighted the merits of the water-based production of organic chemicals. Although the production of ethanol by the fermentation of corn has serious downsides,[17] its development has helped to raise interest in the use of enzymes for the manufacture of some organic chemicals. In addition, plain interest in the safety, low cost, and non-flammability of water has spurred many to build on revelations on the use of water, some published decades ago.[18]

Today, the drive to consider water as a solvent has been greatly stimulated by growth of interest in so-called "green chemistry," representing a desire to employ sustainable renewable resources for the safe and environmentally advantageous production of organic chemicals. Chemists doing so also realize that there is still a need to deal with aqueous process wastes and to think in terms of conservation and recycling. Water will not, of course, be universally applicable, and a substantial shift to its optimal use will take time to achieve.

Dealing with water as a solvent for conventional organic chemical transformations first, many have picked up on the earliest observations[18] to create a solid and growing body of literature validating the movement to water as a solvent for conventional organic chemistry.[19] The Kobayashi reviews[19(d)] describe many remarkable achievements in the area of developing catalysts for use in aqueous systems (particularly for enantioselective hydrogenation, carbon–carbon bond formation, hydroformylation,

[17]The use of ethanol as a fuel additive has several worrisome features. First, it is based on government subsidies. Second, making a gallon of ethanol from corn in the United States is said to require 29% more energy from fossil fuels than a gallon of ethanol can provide (see Patzek, T. W., and Pimentel D. *Natural Resources Res*., 2005, **14**, 65); biological production from cellulose would change this. Third, crop diversity is being destroyed in the state of Iowa, which is now almost exclusively a corn-growing State.

[18](a) Joó, F., and Beck, M. T. (*Magyar Kémiai Folyóirat*, 1973, **79**, 189) the first to sulfonate phosphine hydrogenation catalysts for aqueous hydrogenation reactions. (b) Breslow, R., and Rideout, C. J. (*Am. Chem. Soc*., 1980, **102**, 7816) showed that cyclopentadiene and methyl vinyl ketone underwent Diels–Alder cycloaddition 700 times faster in water than in isooctane, even though, on its own, cyclopentadiene has no solubility in water. Chemists are now more aware that sparing solubility is often all that is needed for reactions to occur. Indeed it is recognized that water can have a profound effect in biphasic systems by promoting hydrophobic interactions.

[19](a) Lubineau, A. *Chem. Ind*., 1996, 123. (b) Li, C. J., and Chan, T. H. *Organic Reactions in Aqueous Media*, John Wiley & Sons, New York, 1997. (c) *Organic Synthesis in Water*, Grieco, P. A., Ed., Blackie Academic and Professionals, London, 1998. (d) Kobayashi, S., Ed. *Advanced Synthesis and Catalysis*, 2002, **344**, 219–451.

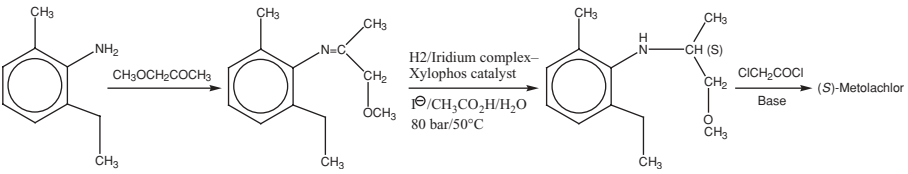
alcohol oxidation, inter alia). Reviews by Sinou[20] and by Dwars and Oehme[21] are of particular interest to the pharmaceutical industry in their description of catalysts for inducing the enantioselective hydrogenation of C=C, C=O, and C=N bonds. The Kobayashi process for preparing certain esters from carboxylic acids and alcohols, using tailor-made polymer-supported sulfonic acids as catalysts, in water, is conceptually intrigueing.[22] Interest has been extended by chemical engineers, exploring organic reactions in supercritical water[23] and in a creative combination of microwave activation, of mostly intramolecular reactions, in supercritical water.[24]

The research chemist's successful demonstration of a synthesis based on water as the solvent does not necessarily mean that the reaction can be shaped into a superior, safer process. For example, probably most homogenous enantioselective reduction processes are actually carried out in water/organic solvent systems. The process development chemist, in considering whether the water-based process should be developed to a commercial scale, in a pharmaceutical industry setting, needs to ask many questions (see Chapter 6). If the process is different from that previously used for preparing the API batches used in the toxicology studies, have new or greater levels of impurities been introduced? Is the physical form and stability of the API (or even the intermediate) acceptable? What is needed to deal with solvent handling if the enantioselective reduction uses a solvent, often, say, to make catalyst recycling easier? (Catalyst turnover—the number of times the catalyst can be usefully recycled—becomes a critical factor when both the water-soluble ligand and the rare metal forming the catalyst are very expensive.) What process is needed to eventually recover and purify spent catalyst components for recycle? What equipment does the manufacturer need to carry out the process, recycle catalyst and solvents, dispose of wastes, and so on? How does the cost of manufacture by the homogeneous enantioselective reduction process compare with, say, an existing process or other, more conventional ones?

It is obvious that considerable effort is needed to make a good enough case to justify investment, even when, on the surface, the merits of a water-based process appear so appealing.

As an aside, decades of work have gone into the study of enantioselective homogeneous hydrogenation processes in both organic and aqueous systems. There is increasing commercial interest in this field spurred by the spectacular, time-encrusted development of a complex catalyst for the enantioselective hydrogenation of an imine to a chiral amine needed for manufacture of the important herbicide, (*S*)-Metolaclor. The technical success of this program (Scheme 1)[25] owed much to the perserverance

[20]Sinou, D. *Adv. Synth. Catal*., 2002, **344**, 221–237.
[21]Dwars, T., and Oehme, G. *Adv. Synth. Catal*., 2002, **344**, 239–260.
[22]Kobayashi, S., and Manabe, K. *Adv. Synth. Catal*., 2002, **344**, 270–273.
[23]Savage, P. E. *Chem. Rev.*, 1999, **99**, 601.
[24]Strauss, C. A. *Australian J. Chem*., 1999, **52**, 83.
[25](a) Bader, R., Flatt, P., and Radimerski, P. X. Y. U.S. Patent, 5430188, 1995 (to Ciba-Geigy). (b) Blaser, H. U., Buser, H.-P., Coers, K., Hanreich, R., Jalett, H.-P., Jelsch, E., Pugin, B., Schneider, H. D., Spindler, F., and Wegman, A. *Chimia*, 1999, **53**, 275. (c) Blaser, H.-U., Adv. *Synth. Catal*., 2002, **344**, 17. (d) Blaser,



Xylophos = 1-[1-(di-3,5-dimethylphenylphosphino)ethyl]-2-(diphenylphosphino) ferrocene.

SCHEME 1. Enantioselective homogeneous hydrogenation in the manufacture of (*S*)-metolaclor.[25]

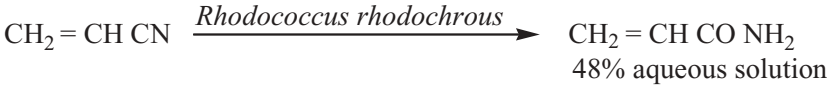
and courage of adventurous people in different chemistry cultures who designed the catalyst.

Efforts to use water as a solvent in conventional organic chemical transformations will continue to grow with the increasing interest of chemists and engineers in cleaner, more efficient, lower-cost and "greener" chemistry. However, the well-established, very large parallel field of endeavor, utilizing enzymes in various forms to produce needed chemicals in the bulk chemical, commodity chemical, and fine chemicals fields, is also growing very rapidly—this includes the production of both achiral and chiral molecules, the latter being of prime interest to the fine chemicals, and particularly the pharmaceutical and agricultural chemicals, industries.

Man has long been harnessing enzymes in "processing" organic chemicals, notably in sewage treatment, garden composting, the brewing industry, starch hydrolysis and isomerization, cheese manufacture, the baking industry, and even the manufacture of detergents. Most of these are of ancient origin, long preceding the fermentation of butanol, acetone, and so on, mentioned earlier. For instance, the Japanese have been exploiting fermentation, quite apart from the fermentation of rice for sake, for hundreds of years with soybean fermentation for soy sauce, having led them to create enormous fermentation businesses, to produce amino acids and proteins, most of them with a link to the food industry. Building on their ancient fermentation industry, over the last few decades the Japanese have achieved considerable success in producing bulk chemicals as well as fine chemicals. One recent notable achievement in the bulk chemical field is Mitsubishi Rayon's elegant process[26] for producing concentrated acrylamide solutions by the selective enzyme-mediated partial hydrolysis of acrylonitrile (Scheme 2). This process promises to completely replace the mineral-acid-based partial hydrolysis of acrylonitrile which suffers the disadvantage of requiring separation of the mineral acid from the water-soluble acrylamide product. It is worth pointing out, at this point, that enzyme-based processes often require a longer time to

H.-U., Pugin, B., Spindler, F., and Togni, A. *Comptes Rendu Chim*., 2002, Vol.5, 379. (e) Blaser, H.-U., and Schmidt, E. *Asymmetric Catalysis on Industrial Scale: Challenges, Approaches and Solutions*, John Wiley & Sons, New York, 2004.

[26]Ishi, K., and Murao, K. U.S. Patent 6,043,061, March 28, 2000, and references cited therein.



SCHEME 2. Enzyme-mediated partial hydrolysis of acrylonitrile to acrylamide.

develop to their maximum potential compared with chemical processes, and for this reason it has usually taken many years for enzyme-mediated processes to supersede chemical ones.[27] This may well change, especially in the pharmaceutical industry, as more chiral APIs are identified.

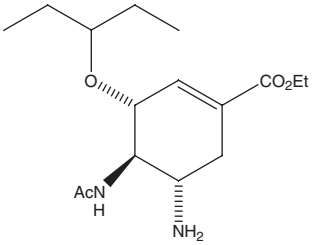
Growth of the chiral chemical industry will require greater emphasis on the education of chemists, chemical engineers, and others in the fundamentals and applications of biotransformation. Such an education, involving a sort of hybridization with microbiologists, geneticists, biochemists, and biochemical engineers, will need, also, to accommodate new manufacturing requirements, including new regulatory and environmental considerations.

In the last two to three decades the growth in applications of enzymes in the pharmaceutical industry (both in isolated form and in whole cell fermentations) has been little short of phenomenal. This short essay can do no more than stimulate classically trained chemists and chemical engineers to gain further education by referring them to a few of the many books and reviews that have been published in the biotransformation field.[28] These publications provide, respectively, comprehensive overviews on hydrolases and accounts of what has worked previously to provide a guide for (a) applying enzymes to other synthesis problems, (b) mechanisms used by enzymes to catalyze particular organic transformations, (c) source information for successfully using enzymes, (d) enzyme mimics, and (e) combining catalytic process steps without intermedicate recovery.

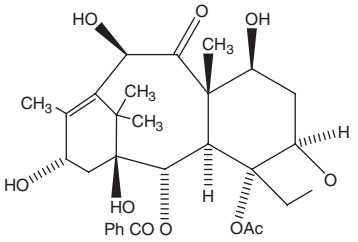
The search for new sources of drugs via both greater biochemical understanding of disease and continued screening of nature's encyclopedia of natural products will create new APIs and new challenges for chemical process development practitioners. The main challenges lie in finding practical ways to simulate nature's "enzymic sleights of hand" in manufacturing complex molecules. Consider, for example, four of the most successful APIs of the last 20 years, namely,

[27]Examples of this, in addition to the above acrylamide example and the related enzymatic conversion of 3-cyanopyridine to nicotinamide, are the amidase cleavage of penicillins to produce 6-aminopenicillanic acid (6-APA) and the corresponding (more complex) process for converting cephalosporin C to 7-aminocephalosporanic acid (7-ACA) (see Chapter 9, footnote 8.)

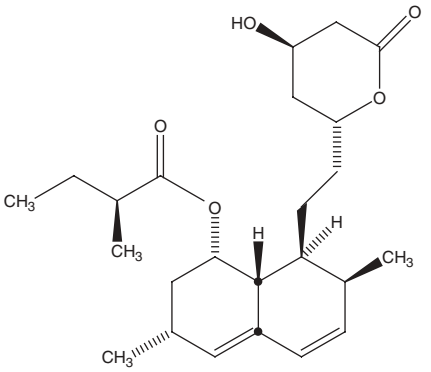
[28](a) Bornscheuer, U. T., and Kazlauskas, R. J. *Hydrolases in Organic Synthesis*, John Wiley & Sons, New York, 2006. (b) Silverman, R. B. *The Organic Chemistry of Enzyme-Catalysed Reactions*, Academic Press, New York, 2002. (c) Drauz, K., and Waldman, H., Ed. *Enzyme Catalysis in Organic Synthesis* (3 Volumes), John Wiley & Sons, New York, 2002. (d) Breslow, R. *Artificial Enzymes*, John Wiley & Sons, New York, 2005. (e) Bruggink, A., Schoevart, R., and Kieboom, T. Concepts of nature in organic synthesis (Review). *J. Org. Proc. Res. Dev.*, 2003, **7**, 622.



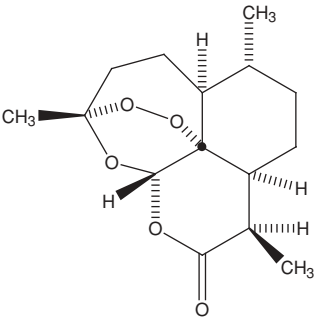
Oseltamivir (Tamiflu) is derived from shikimic acid, itself extracted from various plant sources (e.g., Quinic acid ex the bark of various Cinchona trees and Shikimic acid ex the Star Anise plant).



10-Deacetylbaccatin III (isolated from leaves of *Taxus baccata* L.)
Intermediate for the synthesis of Paclitaxel (marketed as the antineoplastic drug, Taxol).



Lovastatin (fungal metabolite from *Aspergillus terreus*)
Marketed as the antihypercholesterolemic drug, Mevacor. (The closely related statin, Zocor, is produced from lovastatin by replacing the 2-methylbutanoic acid side chain with the 2, 2-dimethylbutanoic acid side chain).



Artemesinin (Isolated from *Artemesia annua* L. - Wormwood bush found in China)
Now marketed, pure, as Artemesinin, but known for almost 2000 years in China as a component of the Chinese antimalarial, Qinghao.

In developing practical processes for producing structures of the above complexity, process development chemists and engineers need to increasingly collaborate with biotechnology partners, indeed often to play an important supporting role to the biotechnologist. Support is essential in the form of analysis, establishing stable process conditions, aiding in isolation and purification efforts, and so on. Manufacturing complex natural products, such as the above, eventually requires that "intermediates" are sourced which protect the wild source.[29] In this spirit, biotechnology strategies are emerging for the manufacture of intermediates for Tamiflu,[30] Artemisinin,[31] and Vinblastine analogues.[32] Discovering and understanding the processes that Nature uses to create the unique chemical structures in complex molecules such as the above is an ongoing endeavor that will undoubtedly enable access to completely novel structures some of which will provide drugs of the future.

The once-obscure field of exploring potential uses of bacteria and their enzyme systems that thrive in hot or boiling water (extremophiles)—from geysers and sea bed vents in tectonically active areas—is another instance of nature generating practically valuable resources. The use of hyperthermophilic enzymes to speed the fermentation of ethanol from starch is a case in point.[33]

Adapting existing natural systems to undertake chemical transformation is now well established, although this appears to be only the beginning. The field is going beyond evolution, which cannot do more than work with what nature provides. Thus, on the periphery of biological development, two avant-garde engineering professors at the Massachussetts Institute of Technology, Drs. Drew Endy and Tom Knight, are working on "Bio-bricks" to link strands of DNA with one set of desired functions in one "brick" to another strand with other functions in another "brick." These may be linked to the DNA of a cell to control its activity in the production of new things. At least that is the idea, but, in this arena, the propensity of living organisms to evolve may mete against survival—tinkering with the unknowns in modifying genetic material needs to be handled with great care.

Although substrate insolubility in water need not always be a deterrent to the use of water as a solvent in organic reactions [see footnote 18(b)], viscerally, the probabilities would seem to preclude the wide use of water for carrying out reactions with insoluble substrates. However, in the spirit of Professor Breslow's initiative [see footnote 18(b)], water must be tried. Furthermore, the reality is that water is such an attractive solvent from a commercial point of view that, under some circumstances, it would be worth undertaking "artificial" steps to bend the required sequence of reactions to enable

[29]Thus, in the case of Taxol, it was eventually found that the destruction of yew trees themselves could be avoided by harvesting yew tree needles as a source of intermediates.

[30]Shikimic acid (for Tamiflu) can be produced from genetically engineered bacteria as a less threatening alternative to harvesting from Star Anise (work of Professor John W. Frost and co-workers, Michigan State University, *New York Times*, Business Section, November 5, 2005.)

[31]The limited supply of wormwood is encouraging efforts to engineer genes, from the wormwood bush and yeast, into *E. coli* with the objective of getting their genes to work together to produce precursors to Artemisinin which can be readily converted, chemically, to Artemesinin itself. Jay Keasling, University of California, Berkeley.

[32]McCoy, E., and O'Connor, S. E. *J. Am. Chem. Soc.*, 2006, **128**, 14276.

[33]Corfield, R. *Chemistry World*, September 2005, p. 51.

them to be carried out in water ("process hydration"). The concept is no more than an extension of the already well-established field of protecting functional groups during transformations that would otherwise change that functional group. Thus in order to solubilize a given substrate in water, the insoluble substrate would have to be readily substituted at a reactive site by a water-solubilizing group capable of being readily removed later in the reaction sequence, without introducing undesirable impurities to the final API. Water-solubilizing protecting groups can be imagined wherein the water-solubilizing moiety carries, for example, a carboxylic, sulfonic, or phosphoric group to introduce water solubility.

The circumstances wherein process hydration would be justified will depend on both the ease of introduction and removal of the water-solubilizing group and the cost of both manipulations. Process hydration would seem likely to be more readily justified in a situation where a sequence of high-yielding process steps could be arranged; the longer the sequence, the less the impact of the cost of process hydration. Process hydration may be of particular value in enabling a great variety of chemical transformation technologies to be considered, including those mediated by enzymes, homogeneous catalysis, electricity, microwaves, and photochemical technologies.

As in all other endeavors, a movement toward using water as a solvent may be promoted by an individual chemist or chemical engineer, but its success will depend on harnessing all the other disciplines needed to create a practical process. In the particular case of enzyme-mediated transformation, many chemists and engineers have been stimulated by the results of biological science work to team up with biochemists, microbiologists, geneticists, biochemical engineers, inter alia, to drive chemical process development in new directions. In ending on a speculative note, it seems more than likely that enzyme-mediated transformation will be shown to do more than is generally thought and that the interdisciplinary dialogue will increasingly show that needed chemical transformations will find a biological system that can meet the need. It behooves all chemists and chemical engineers, and especially those in the pharmaceutical and agricultural industries, to educate themselves in the life science disciplines, at least to the level of understanding needed to appreciate how they may need to work with the microbiological disciplines, among others, to get things done.

Clearly, there is a healthy drive, already going on, to promote the wider use of water as a solvent for organic chemical reactions. This might even extend to looking at reactions in sea water for coastal manufacturing plants! The literature also suggests [see footnote 28(d)] that the use of enzymes could well grow outside the box of conventional biological systems.

For those of us at the end of our careers, it seems a pity to have to leave such an exciting future.

Thoughts on Other Solvents

In keeping with the experimental nature of chemistry, many individuals have championed the use of alternative solvents to the ubiquitous organic solvent option. As indicated in "Water and Enzymes in Chemical Process Development," water has its limitations as a solvent for insoluble substrates, though, as stated, water always

needs to be tried. Even sea water may have a place in situations where sea salts are tolerable—for example, in utilizing extremophile microorganisms or enzymes from deep-sea tectonic plate vents.

From a practical chemical process development point of view, other solvents, or, indeed, no solvent at all, are considered, because their use may be advantageous over all other options.

Supercritical Fluids. These solvents, particularly supercritical carbon dioxide, have been used for the safe extraction of food components (e.g., hop extracts for beer production), in arranging selective extraction (selectivity can be manipulated by controlling pressure and temperature), and in ensuring that extracts are essentially free of solvent residues. They have also found use in supercritical chromatography and associated analytical applications. Supercritical fluids, again particularly carbon dioxide, are, presently, mostly used as extraction solvents rather than reaction solvents. The largest use is in the extraction of caffeine from coffee beans, but the technique is also used in the extraction of oils from soybeans, inter alia, and in the production of small quantities of perfumes and flavors. These uses all depend on another advantageous property of supercritical fluids, namely that they are generally superior to conventional liquids in being able to penetrate the micropores of a solid structure; this phenomenon has even been applied in coal extraction. Other formidable advantages associated with using carbon dioxide are its low toxicity, nonflammability, ready availability, relatively simple removal and recycle, the ease of isolating extracted products, and its low cost. One surmountable disadvantage is the capital expenditure requirement for pressure equipment and overcoming the usual reservations concerning new technology.[34] Wider adoption needs the ingenuity and leadership of chemical engineers, with data from successful pilot plant work, to make the economic case for the needed investment. Acceptance will also be enhanced by the "greening" of those involved in decision making, especially if there are credible projections that other applications of the technology may be achievable.

In the last 20 years, meaningful successes in projects outside classical extraction applications, especially in using supercritical carbon dioxide as a reaction solvent for hydrogenation, are increasing industrial interest in the technology. If there is one intrinsic property of supercritical fluids which has changed the landscape of hydrogenation technology, it is their ability to dissolve hydrogen, and most organic substrates, in high concentration. This property, coupled with the use of noble metal catalysts in many varieties, has enabled the creation of efficient high mass transfer hydrogenation systems with significant advantages over the classical heterogeneous organic solvent/noble metal catalyst systems. Thus hydrogen and the substrate move directly to the catalyst surface and reduced products move off easily, avoiding the hydrogen transport rate issues associated with classical hydrogenations. Tailoring

[34]Supercritical carbon dioxide was considered by Schering–Plough for the extraction of diosgenin from Barbasco roots in Mexico, but, despite being an efficient extractor and less energy intensive versus continuing to use solvent extraction, the capital cost of the high-pressure equipment and operating considerations meted against its adoption.

reaction parameters such as hydrogen concentration, pressure, temperature, and flow rates (in a continuous system) is more facile than in classical hydrogenation systems, enabling mild or extreme hydrogenation conditions to be engineered.[35] Enormous increases in reaction throughput have been engineered by developing continuous-flow reaction equipment. The recovery of product is also simplified. Hydrogenations in supercritical carbon dioxide are inherently somewhat safer as well as being more environmentally friendly.

Although supercritical carbon dioxide is a poor solvent for many highly polar substances, and the reactivity of carbon dioxide will always limit its use as a reaction solvent, university-based champions of the use of supercritical carbon dioxide, working with adventurous industrialists, initially in the area of a range of hydrogenation reactions, will help to pave the way for other applications.

Poliakoff et al., University of Nottingham, England, have built on their early work[36] demonstrating the hydrogenation of aromatic rings, olefins, aldehydes, and ketones in supercritical carbon dioxide, and of nitro and imino compounds in supercritical propane, using a laboratory scale stainless steel continuous reactor, to create a working relationship with Thomas Swan and Co. Ltd., Consett, Co. Durham, England.[37] Hydrogenations in supercritical carbon dioxide, have, inevitably, been explored as routes into chiral molecules. For example, given identification of an effective chiral catalyst that can be easily recycled, the use of supercritical carbon dioxide as a solvent in the enantioselective reduction of the prochiral imine leading to the intermediate for the commercially useful herbicide, Metolachlor (see Scheme 1), would seem to be an attractive target.[38]

In the United States, several academic groups are collaborating with industry, especially in the area of hydrogenations (both hydrogenolysis and hydrogen addition to double bonds) in supercritical carbon dioxide. DuPont is perhaps the leading company in the drive to adopt "green chemistry" in its manufacturing base, with particular interest in working with several universities in the fields of hydrogenation[39] and polymerization.[40] In the latter case, DuPont has already built a supercritical carbon dioxide pilot plant unit capable of manufacturing over two million pounds/year

[35]Mild conditions will reduce only the double bond and not the keto group of isophorone. Extreme conditions will reduce nitrobenzene to cyclohexane and ammonia. However, it should be noted that carbon dioxide itself can be reduced to carbon monoxide and water under extreme conditions; see footnote 36 and *Chem. Eng. News*, 2001, May 28, 32.

[36]Hitzler, M. G., Smail, F. R., Ross, S. K., and Poliakoff, M. *J. Org. Process Res. Dev.*, 1998, **2**, 137.

[37]Thomas Swan and Co. Ltd. built a 1000-tonne/annum multipurpose supercritical carbon dioxide demonstration plant at its Consett site to explore hydrogenation and Friedel–Crafts type acylations and alkylations, inter alia.

[38]The enantioselective hydrogenation of imines, such as the Metolachlor intermediate, in supercritical carbon dioxide has been investigated by Walter Leitner et al., Max Planck Institute for Coal Research, Mülheim, Germany; but as always, replacing an established technology is a difficult task.

[39]Chemical engineering professors B. Subramaniam, University of Kansas, and J. Brennecke, University of Notre Dame, along with their groups, are two collaborators.

[40]Chemistry/chemical engineering professor, J. DeSimone, University of North Carolina, has long been a protagonist of "green" polymerizations in supercritical carbon dioxide. A major achievement has been his patented findings on the use of alkylsilyl and perfluoroalkyl polymer fragments as "surfactants" in creating high-molecular-weight polymers previously unachievable in this solvent.

of Teflon co-polymers using carbon dioxide as the solvent. Other areas of interest include oxidations,[41] hydroformylations, and Friedel–Crafts reactions—that is, reactions that utilize process conditions on the acid side.

As with all new technological applications, much pioneering experimental work needs to be done. A start could be made if chemical process development groups would all acquire a piece of equipment, such as that described by Poliakoff (see footnote 36) to undertake the evaluation of the use of supercritical carbon dioxide as an integral component of chemical process development programmes. Alternatively, and probably advantageously, liaisons with university groups already working in the area would be beneficial.

Liquid Sulfur Dioxide. Although sulfur dioxide has a pungent choking odor, it has been of interest as a solvent, especially in academia, for over 100 years. Its boiling point (-10°C) allows that it can be handled safely under its own vapor in a sealed glass vessel without special precautions.[42] Its reactivity with water requires that liquid sulfur dioxide be generally used as a solvent under anhydrous conditions. Sulfur dioxide also forms solvates, charge transfer complexes, or adducts with many compounds—for example, tertiary amines, ethers, alcohols, and primary amines. In part, this behavior undoubtedly contributes to some of the unique character of liquid sulfur dioxide as a solvent. Liquid sulfur dioxide has also proved to be a useful medium for carrying out electrochemical reactions.

Despite its reactivity toward nucleophilic substances, liquid sulfur dioxide has found minor use as a solvent in many reactions. This is largely because it has strong ionizing powers and is a very good solvent for most organic compounds, including amines, acids, alcohols, esters, and aromatic hydrocarbons. The ease of stripping and recycling sulfur dioxide at the end of a reaction is also an ecologically positive attribute. Indeed, another major attribute is the availability of liquid sulfur dioxide in tank car quantities for, very approximately, 35 cents/liter (2007). In this regard, it seems rather odd that organic chemists, inured as they are to the use of organic solvents for organic chemical reactions, have essentially ignored sulfur dioxide as a potential solvent. In today's world, with process emissions a serious process chemistry concern, it is surprising that more chemists and engineers have not picked up on the notion that to properly use sulfur dioxide, it is essential to contain it safely. Building a relatively simple, safe, general-purpose laboratory containment unit, suitable for handling those kinds of reaction where sulfur dioxide might be used, would bring sulfur dioxide into the main stream as a solvent for organic chemical reactions. A unit with the capability of handling reactions up to, say, one to five atmospheres would increase the evaluable range of temperature/pressure conditions. Extending process conditions in this way may reveal other process benefits worthy of further exploration and optimization. The general-purpose containment unit referred to above

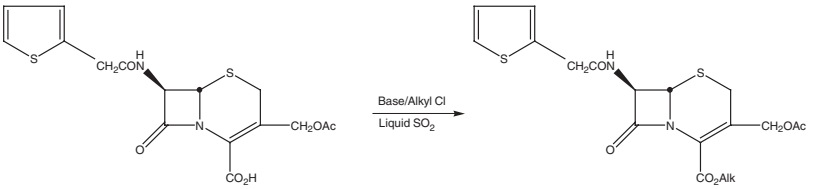
[41] The oxidation of hydrogen to hydrogen peroxide in supercritical carbon dioxide is a case in point Hancu, D., and Beckman, E. J. *Green Chemistry*, 2001, **3**, 80.

[42] Waddington, T. C., in *Non-aqueous Solvent Systems*, Waddington, T.C., Ed., Academic Press, New York, 1965, p. 253.

would also be valuable in enabling the evaluation of other noxious reactions and more "adventurous" process conditions.[43]

A couple of published reaction types serve to illustrate uses and some benefits in employing sulfur dioxide as the solvent.

(a) Esterification of cephalosporins under conditions[44] that avoid Δ^3-bond rearrangement.



Alkyl can be benzhydryl (89% yield), methoxymethyl (98% yield), inter alia.

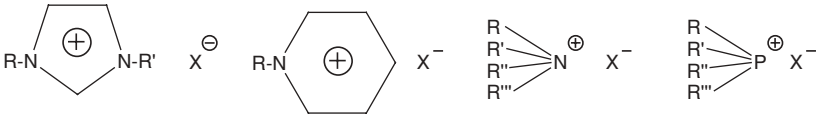
(b) Solvent effects in the bromination of alkylbenzenes.[45]

Alkylbenzene	SO_2 $T = -9°C$ (Reflux)			CF_3CO_2H $T = 25°C$			1,2-$C_6H_4Cl_2$		
	Ortho	Meta	Para	Ortho	Meta	Para	Ortho	Meta	Para
Toluene	11.4	0	88.6	17.6	0	82.4	22.8	0	77.2
Ethylbenzene	8.9	0	91.1	13.0	0	87.0	15.3	0	84.7
i-Propylbenzene	2.6	0	97.4	8.1	0	91.9	10.3	0	89.7
t-Butylbenzene	0	0	100	0	0	100	1.6	0	98.4

It seems that the noxious properties of sulfur dioxide and its limitations as a general-purpose solvent have been largely responsible for the continued lack of interest in its use in the organic chemical manufacturing industry. To change the perception requires that entrepreneurial people put together the laboratory and pilot plant equipment, undertake experiments, and publish their results.

Ionic Liquids. In the last 20 years, much attention has been given to the use of certain ionic liquid salts, compounds comprising an organic cation, and usually, an inorganic anion as "solvents."[46] The most common classes of ionic liquids have the following general structures:

[43]The unit might also incorporate the capability to accommodate reactions in supercritical carbon dioxide.
[44]Seki, S., Nakabayashi, S., Nishata, K., Ito, N., and Fukatsu, S. *Tetrahedron Lett*., 1977, 2915.
[45]Canselier, J.-P. *Bull. Soc. Chim. France*, 1972, Number 2, 762. See also Canselier, J.-P. *Bull. Soc. Chim. France*, 1971, Number 5, 1785.
[46]Wasserschied, P., and Welton, T., Eds. *Ionic Liquids in Synthesis*, Wiley-VCH, Weiheim, 2002.



R, R′, R″, and R‴ are usually lower alkyl

X is a variety of cations, including $AlCl_4^{\ominus}$, $BF_4^{\ominus}$, $PF_6^{\ominus}$, $R_3PF_3^{\ominus}$, etc.

Structures can be tailored to provide a range of liquidity from -100°C to $+200^{\circ}$C.

Interest in ionic liquids, early on mostly in academia, centered around their remarkable properties as solvents and catalysts for supporting and enhancing reactions, many of which are often difficult to carry out using conventional process conditions. The perceived advantages of ionic liquids have been widely publicized, and enthusiasm has encouraged scientists to look upon these advantages sometimes with disproportionate favor. The main advantages that attract attention are as follows:

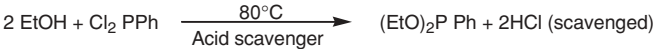
- They are nonvolatile (no air pollution issues).
- They are nonflammable (many have high thermal stability).
- They provide a highly ionizing medium, which has enabled scientists to enhance reaction rates and increase reaction selectivity. The ionizing properties of ionic liquids have also proved to be valuable in electrochemical transformations and in battery uses.
- They often offer processing advantages, in terms of easier separation of products or catalysts, greatly facilitating recycle and reuse. However, as often happens in separation operations, any solubility of the ionic liquid in another phase can compromise the efficiency of recycling these expensive liquids.

A few examples of the broad applicability of ionic liquids are as follows:

- As vehicles for the electropolymerization of benzene to form the conducting polymer poly (*p*-phenylene).[47] Ionic liquids are said to be good alternatives to liquid sulfur dioxide.
- As a medium to facilitate the acid-catalyzed transfer of the acetyl group from acetylmesitylene to anisole.[48]
- As a solvent for the asymmetric epoxidation of 2,2-dimethylchromene mediated by Jacobsen's chiral (salen)-manganese catalyst.[49]
- In tandem with the use of supercritical carbon dioxide, in ester synthesis employing Candida Antarctica lipase B, adsorbed on silica gel, as the esterification catalyst under minimum water conditions.[50]

[47]Endres, F., Zein El Abadin, S., and Borissenko, N., Electrochemistry Commun., 2004, **6**, 422.
[48]Laali, K. K., and Sarca, V. D. *Green Chem*., 2004, **6**, 245.
[49]Song, C. E., and Roh, E. J. *Chem. Commun*., 2000, 837.
[50]Lozano, P., de Diego, T., Gmouh, S., Vaultier, M., and Iborra, J. L. *Biotechnol. Prog*., 2004, **20**, 669.

Commercially, the most elegant use of ionic liquids, perhaps discovered serendipitously,[51] is the BASF application for acid scavenging in their manufacture of the photoinitiator intermediate diethoxyphenylphosphine.[52]



BASF's original acid scavenger, triethylamine, created viscosity and work-up problems because of the need to maintain anhydrous conditions. BASF's use of 1-methylimidazole instead of triethylamine, at their reaction temperature of 80°C, led to the formation of two liquid phases, an upper diethoxyphenylphosphine phase, and a lower methylimidazolium chloride phase (fortuitously, this ionic liquid melts at 75°C!). Moreover, methylimidazolium chloride proved to be a nucleophilic catalyst. The processing revolution generated by these discoveries enabled creation of a high-productivity continuous process for diethoxyphenylphosphine manufacture and created a whole new business in acid scavenging technology.

An analogous technology commercialized by IFP, Paris, is their continuous, chloroaluminate ionic liquid dimerization of *n*-butene to isooctane, promoted by a Ziegler–Natta-type homogeneous catalyst. The poorly miscible isooctane product is readily separated.

Ionic liquids are also being evaluated as alternatives to the use of hydrofluoric acid and sulfuric acid—for example, in simplifying aromatic alkylations by directly using olefins instead of alkyl halides to carry out the alkylation.

Despite the impressive achievements of those working in the ionic liquids field, chemical process development scientists and engineers, being aware of their disadvantages, generally take a more cautious view of their potential value. The main disadvantages are as follows:

- Their high cost, which both limits their appeal as solvents and highlights the need for safe, efficient recycle.
- The instability of some anionic components of ionic liquids (e.g., $AlCl_4^{\theta}$, PF_6^{θ} types) to water limits the applicability of these types in processes involving water.
- Concerns re biotoxicity and biodegradability.

Many quaternary ammonium compounds are known to possess bactericidal properties, a factor taken into account in the marketing of quaternary ammonium fabric softeners. However, in the spirit of the European REACH initiative (See Chapter 5), many of the ionic liquids in common use are being scrutinized for toxicity potential. For instance, in the aquatic world there are indications that exposure to as little as 10 mg/liter causes skin and gill hyperplasia in zebrafish, leading to respiratory

[51] But, to repeat Pasteur, "Chance only visits the prepared mind."
[52] Vagt, U., and Emanuel, C., *Chem. Processing*, June 2006, 45.

problems, behavioral effects, and some deaths.[53] Long-chain alkylammonium salts appear to be the most toxic. Despite these concerns, BASF continues to progress its ionic liquid businesses with the understanding that toxicity issues need to be addressed and accommodated. To this end, BASF, in collaboration with Degussa, has published toxicology data on three of the ionic liquids marketed by them (see footnote 52).

There is little doubt that intrepid entrepreneurs will continue to champion ideas for the application of ionic liquids. Without a doubt, further uses of these materials will be found and justified for commercial use. However, the perceived disadvantages, and particularly the toxicity issues, will temper enthusiasm until the data obtained provide reassurances that an ionic-liquid-based process satisfies all the economic, toxicological, safety, and (in the pharmaceutical industry) FDA regulatory criteria to justify implementation.

When process development chemists consider supercritical fluids and nontraditional solvents in their process research, the unconventional aspects enhance the importance of integrating the chemical engineering discipline and all the regulatory disciplines into their evaluation. In the case of supercritical fluids, chemical engineering becomes a core discipline with respect to creating the physical equipment and guiding the work program of unit operations in systems that are outside the chemist's normal glassware world, including evaluating prospects for a continuous process.

In evaluating ionic liquids for practical operations, the chemical engineering discipline is not only a necessary partner in the more conventional aspects of equipment utilization, process engineering, and so on. In new fields the engineering purview may encourage consideration of unconventional technologies in ways that make the difference between success and failure. For instance, since the field of using ionic liquids in the pharmaceutical industry is relatively new, the chemist may be stymied if toxicity concerns create potential FDA issues (e.g., trace contamination) or environmental issues (e.g., eliminating toxic materials from process wastes). Such issues could derail a potentially promising technology. The chemical engineer, open to the use of solventless manufacture, might offer the possibility of using analogous alternatives, including, say, the reevaluation of even older technologies such as the use of urea/choline chloride melts, or even the use of liquid sulfur dioxide.

Polymer-Supported Synthesis and Reagents

Process development chemists, seeking simplicity in creating manufacturing processes, have long been intrigued by the seeming elegance of polymer-supported synthesis, and also the benefits to be gained by harnessing polymer-supported reagents. On paper, undertaking the multistep synthesis of a molecule on a polymer support, despite its lack of synthesis convergence, looks as though it could revolutionize chemical manufacturing. Thus, combining a sequence of reactions on a single polymer, using only one reaction vessel—or, better, one reaction column—would

[53] Chiappe, C. et al., News@Nature.com (doi: 10.1038/news 051031-8) and *Chemistry World*, 2005, December, p. 19.

contain and massively reduce the unit operations associated with using conventional multiple batch reactors and associated work-up equipment.

Such a concept offers practical advantages over and above the ready separation of reactants from the substrate being manipulated. First, process containment embodies intrinsically safer operation, decreasing the exposure of workers to chemicals and minimizing the leakage of volatile chemicals into the atmosphere. Second, the need for investment in conventional capital equipment (reactors, filters, driers, etc.) would be substantially reduced, leading to fewer building requirements, including warehouses for equipment and chemicals. This, in turn, leads to lower requirements for plant services, including maintenance, chemicals handling, and energy, as well as providing opportunities to simplify process automation. The astute reader will of course appreciate that many of these advantages can be, and frequently are, realized by working to combine very efficient reaction sequences in one conventional reactor—it is the work-up between reaction steps which still represents the major equipment burden associated with the use of conventional batch processes. Thus the key factor, for best realizing the benefits of polymer-supported synthesis, is to achieve high efficiency in each step of the series of reactions on the polymer in order to avoid perhaps insurmountable purification problems at the end of the synthesis.

The related polymer-supported reagents field affords useful if lesser advantages than polymer-supported synthesis in that the polymer support allows the ready removal of a reagent promoting only a single reaction step. Polymer-supported reagents, and especially catalysts, have nevertheless become very important in numerous chemical manufacturing situations.

Without a doubt, many of the above advantages were recognized in awarding the Nobel prize to Rockefeller University's Professor R. Bruce Merrifield for his seminal work on polymer-supported peptide synthesis.[54]

Polymer-Supported Synthesis. The passage of time, the publication of thousands of papers, several books,[55] and many commercial successes, especially in small-scale applications of Merrifield-type polymers in the peptide field, have led to the realization that harnessing polymer supports for large-scale synthesis work has many hurdles to overcome to become more widely accepted for use in practical large-scale synthesis.

From a chemical process development point of view the main issues/limitation are as follows:

- Determining the best resin to use to maximize the loading of reactive groups, to allow efficient complete reactions and to permit some recycle of the spent polymer.

[54](a) Merrifield, R. B. *J. Am. Chem. Soc*., 1963, **85**, 2149. (b) Merrifield, R. B. *J. Am. Chem. Soc*., 1964, **86**, 304.

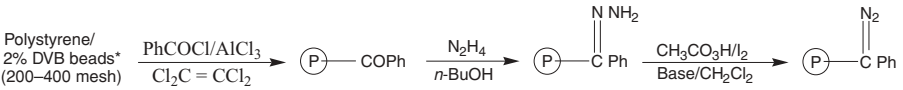
[55]For example, Dorwald, F. Z. *Organic Synthesis on Solid Phase: Supports, Linkers, Reactions*, John Wiley & Sons, New York, 2000, and publications cited therein.

- Accommodating the likelihood of lower productivity when concentrations of the substrate on the polymer are low.
- Ensuring that the slow diffusion of reactants to reactive sites in the polymer matrix reaches as many buried sites as possible.
- Overcoming the problems generated by incomplete reactions, especially the impurity burden created when both the desired product and byproducts are unhitched from the polymer.
- Working out and optimizing the synthesis sequence to accommodate the known vagaries of working on a polymer, especially minimizing the need to change solvents (this can be a time-consuming process needing large volumes of solvent).
- Finding ways of reducing solvent usage if reaction solvents have to be changed.
- Creating analytical monitoring methodologies to follow reactions on the polymer.
- Persuading management, in a commercial, project-oriented, time-managed setting, to allow the thinking and R&D time needed for evaluation and development.
- Judging the probabilities of commercial success.

Advancing a field with such formidable hurdles (and yet such practical promise) requires people of vision, enthusiasm, and experience to champion the technology. Peptide manufacturers have shown that polymer-supported synthesis can be made practical, albeit at a price necessitated by the small scale of operation. High costs and the limitations outlined above have no doubt inhibited the field but in my view, the development of polymer-supported synthesis has been more inhibited by the absence of inputs from chemical engineers. Practical people recognize that the chemistry and engineering disciplines need to work together in order to comprehensively evaluate the perceived potential of technologies such as this. I can illustrate the point through my own all-too-brief flirtation with polymer-supported synthesis when working in Glaxo 40 years ago!

My colleagues and I backed into the field as a result of our commercially successful development of the use of the diphenylmethyl (DPM) group as a temporary protecting group in the synthesis of cephalexin (see Chapter 9). Initially, we employed a separately prepared solution of diphenyldiazomethane (DDM) to prepare diphenylmethyl esters until we demonstrated an esterification process using DDM prepared in situ. Polymer-supported DDM seemed to us to offer a much safer prospect, especially since we reasoned that the benzene rings of the polystyrene backbone could become the benzophenone starting material. We quickly demonstrated the following high-yielding reaction sequence:[56]

[56](a) Chapman, P. H., and Walker, D. *J. Chem. Soc., Chem. Commun*., 1975, 690. (b) Walker, D., and Chapman, P. H. U.S. Patent 4,038, 469, 1977.



The polymer-DDM was used by us as it was prepared, but it appeared reasonably stable.[57] Polymer-DDM reacted rapidly with penicillin G sulfoxide acid, with the nitrogen evolution perhaps helping to "stir" the reaction mixture(?).[58] The subsequent ring expansion of the penicillin sulfoxide moiety to a 3-methylcephalosporin and the cleavage of the phenylacetyl side chain to give polymer-supported 7-ADCA (Scheme 1) gave surprisingly good yields[59] (Scheme 3).

The ring expansion and cleavage reactions revealed two of the major hurdles that face scientists trying to use polymer supports. First, in adapting the solution chemistry used for ring expansion of the monomer to the polymer-supported penicillin G sulfoxide, we found out that the switch from methylene chloride, used for the immobilization of the penicillin, to dioxane, needed for the ring expansion, exposed some of the limitations of working on the polymer. Thus, when the cephalosporin resulting from the ring expansion was removed from the polymer, the yield was somewhat lower and the product was of poorer quality than the corresponding product obtained using conventional solution chemistry. Second, the PCl_5-mediated amide cleavage reaction, in this case between two insoluble compounds, would not, a priori, be expected to occur. However, the partial solubilization of PCl_5, by the pyridine used as the base, was sufficient for conversion of the side-chain amide in the polymer-supported cephalosporin to an iminochloride. The iminochloride side chain was then easily converted, via the iminoether, to the desired polymer-supported aminocephalosporin. Third, the need to thoroughly remove all the debris from each reaction necessitated extensive washing before the next reaction could be undertaken. Large volumes of solvent were required to do this effectively.

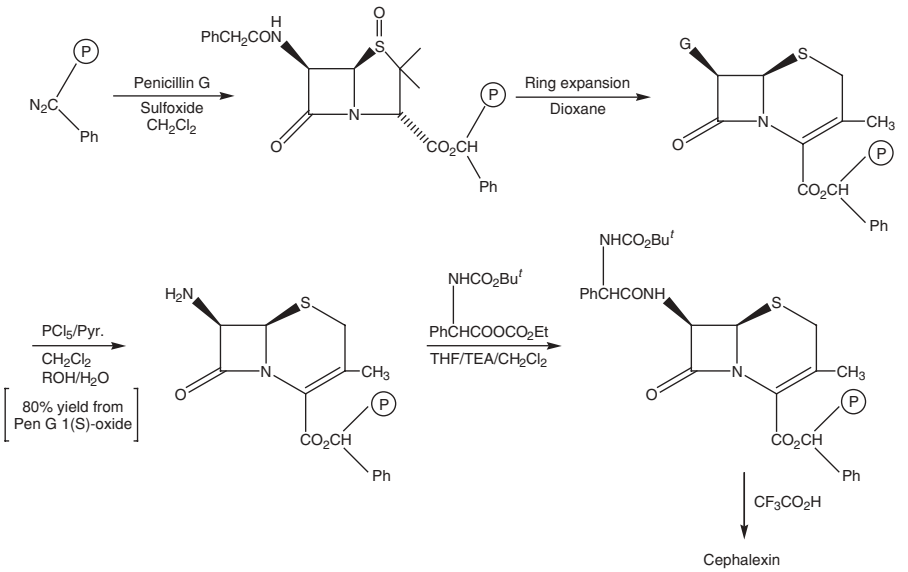
There was not enough time during my career with Glaxo (1966–1975) to address the above hurdles. We had plenty of ideas but little time to explore them. Reasoning, as protagonists of working on glass bead surfaces had done, that diffusion problems

*It should be noted that the evaluation of beads from different sources showed those from Dow Chemicals to be the best.

[57]Our expectation was that polymer-DDM would have the same stability as the monomer (see Chapter 9, footnote 20). Polymer-DDM is now available commercially in small quantities from Bachem, CH-4416 Bubendorf, Switzerland. In addition, Bachem scientists have published data on the stability and uses of their polymer: (a) Mergler, M., and Nyfeler, R. In *Innovation and Perspectives in Solid Phase Synthesis and Combinatorial Libraries*, 1998. Collected Papers, 5th International Symposium, London, England, Epton, R., Ed., Mayflower Scientific Ltd., Birmingham, 1999, pp. 351–354. (b) Mergler, M., Dick, F., Gosteli, J., and Nyfeler, R. *Tetrahedron Lett*., 1999, **40** 4863–4864. (c) Gramberg, C. W., Dick, F., and Vorherr, T. In *Peptides 2000*, *Proceedings of the Twenty-sixth European Peptide Symposium*, September 2000, Martinez, J., and Fehrentz, J.-A., Eds., EDK Publishers, (Probably Santarcangelo di Romagna, Italy, according to the Internet! EDK is a partner of the Karnak group and linked with Pragma 2000 an Automated Publishing Solutions service), 2001, pp. 289–290. Publications (b) and (c) cover reactions with Fmoc-aminoalcohols.

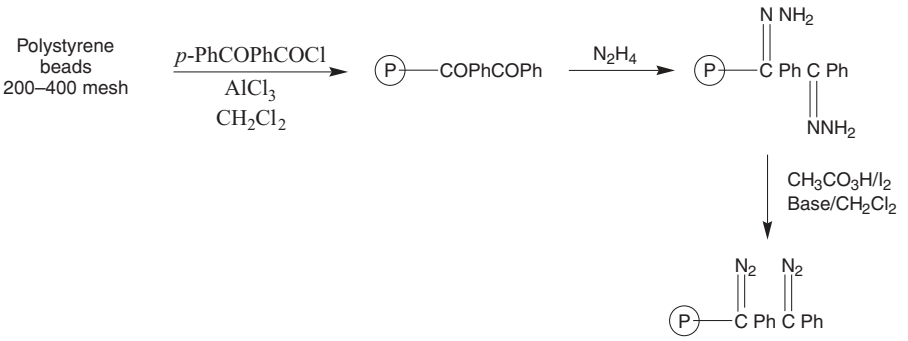
[58]Walker, D., and Chapman, P. H. U.S. Patent 4,067,858, 1978 (to Glaxo).

[59]However, the yield across these two steps was somewhat lower than that obtained using solution chemistry. It takes time and patience to adopt and reoptimize efficient solution reactions for use in polymer systems.



SCHEME 3. Polymer-supported synthesis of Cephalexin[59]

would be minimized by working as much as possible on the surface of such as a 200–400 mesh bead, I proposed that it may be possible to double the loading of the diazomethylene groups on the surface of the bead. Thus, it should be possible to undertake a mild Friedel–Crafts acylation, to minimize deep penetration of the beads, by acylating with a bulky reagent such as *p*-benzoylbenzoyl chloride. Such an approach may also allow increased loading of a desired substrate on the polymer:



Despite the prospect of some productivity gains, the idea was never tried. We also never had a chance to determine whether a single phenylene ring separating immobilized substrate molecules would have other consequences in terms of neighboring molecule interactions, especially if applied to peptide synthesis where tangling of elongated chains may be problematic.

The problem of switching solvents and minimizing solvent usage between reaction steps, especially if almost complete removal of the original reaction solvent is necessary, poses one of the biggest challenges impeding the adoption of polymer-supported synthesis in commercial synthesis operations on a larger scale than polypeptide manufacture. From my vantage point the problem needed more involvement of chemical engineers. One seemingly promising avenue of exploration was demonstrated in a chromatography column by my colleague, Dr. Eric Martlew. Dr. Martlew fitted the column with a vertical plunger and showed that the solvent swelling the resin beads could be squeezed out to a large extent by lowering the plunger under increasing pressure. Dr. Martlew demonstrated that reduced solvent useage was achievable. In the hands of chemical engineers, working at higher pressures, perhaps with a pulsating plunger carrying perforations with one way valves, could provide a dynamic flushing effect in the beads. There was no time to determine whether repeated mechanical compression and relaxation of solvent swollen beads would have any adverse effect on the physical stability of the beads.

We made another unpublished (unfinished) modification of our polymer diphenyldiazomethane to try to expand the scope of reaction possibilities to include aqueous systems. We could greatly improve the hydrophilicity of our beads by sulfonating the benzoylated polystyrene before carrying out hydrazone formation and subsequent oxidation of the hydrazone groups to diazo groups. The resulting polymer, as a sodium salt, did exhibit hydrophilic behavior, but there was insufficient time to investigate any of the uses we envisaged for it (see later).

It appears that the field of polymer-supported synthesis would be worth further exploration with a view to exploiting possibilities for applications beyond the peptide synthesis field. Its amalgamation with chemical engineering to evaluate combinations of other technologies, such as using microwave energy to promote more complete reactions,[60] say in concert with the use of pulsating pressure plungers, would seem to be well worthy of further exploration.

One of the greatest advances that could be made to promote the use of compounds such as polymer DDM would be to find ways of reducing its cost and also to recycle the spent beads by oxidation of the polymer benzhydrol waste back to the polymer benzophenone and repeating the reaction sequence needed to produce polymer DDM. Regarding manufacture, the development and scale-up of existing processes to an industrial scale would obviously reduce polymer-DDM costs. The opportunity for recycle has also been demonstrated (see Example 24 in footnote 58) using 30% aqueous nitric acid as the oxidant. However, the polymer DDM produced possessed only ~78% of the original activity. Other cost reduction opportunities may be feasible. Thus for those reactions not needing the very reactive diazomethylene group (e.g., in the preparation of polymer benzhydryl esters), it may be possible to use the polymer benzhydrol resin to directly produce the corresponding ester using chemistry already established for producing benzhydryl esters from benzhydrol.[61]

[60] Yu, H.-M., Chen, S.-T., and Wang, K.-T. *J. Org. Chem.*, 1992, **57**, 4781 (see Section 4.6).
[61] Yoshioka, M. *Pure Appl. Chem.* 1987, **59**, 1041.

The application of polymer-supported synthesis methodology in the peptide field continues to grow. Refinements in the area of reducing the impurity burden in both peptide synthesis[62] and in applying polymer-supported synthesis techniques in the field of combinatorial chemistry[63] will undoubtedly be useful in influencing the further exploration of the use of polymer supports in the broader field of chemical synthesis.

Polymer-Supported Reagents. This field has grown enormously in the last few decades as chemists and engineers have harnessed the obvious merits associated with carrying out a reaction using a readily removable reagent. The concept is essentially an elaboration of the immobilized catalyst field that has been widely applied in industry, especially the petrochemicals industry, for over 50 years.

In recent times the polymer-supported reagents field has grown enormously, reflecting its application to the generation of novel "chemical libraries" for the pharmaceutical and agrochemical industries. An excellent review of this field by Ley et al.[64] provides a comprehensive overview and also "an extensive listing of known supported reagents, catalysts and scavenging agents . . . as an aid in the future design of synthesis programmes."

In regard to chemical process development, the polymer supported reagents field offers legion opportunities for the use of almost any reagent imaginable, limited only by what can be immobilized and still be effective. This definition allows that even hazardous and noxious reagents, made safer by being immobilized on a polymer, can be considered. The scope may, again, be limited by cost, difficulties in the immobilization process, or the need to recycle the polymer-supported reagent or its residue.

Use of a readily separable, polymer-supported reagent to facilitate a chemical transformation is not always a panacea. Yields should preferably be high, and the recovery and purification of the desired product from the reaction mixture should be practical. Polymer-supported scavenging agents to scavenge byproducts have been employed, as also have polymer-supported reagents that capture the desired product from a reaction mixture.[64]

Capturing desired products from aqueous reaction mixtures (in a form useful for further synthesis steps) using monomeric agents is well known. We successfully applied such a technology to the extractive esterification of cephalosporin derivatives from a filtered cephalosporin fermentation broth[65] and a solution of a 3-

[62]For instance, it has long been known that missed sequences can be avoided by acetylating amino terminals of incompletely reacted sites of a growing polymer peptide – (see Bayer, E., Eckstein, H., Hagele, K., Konig, W. A., Bruning, W., Hagenmaier, H., and Parr, W. *J. Am. Chem. Soc*., 1970, **92**, 1735) and using fragment synthesis methods for large peptides.

[63]Dolle, R. E., Le Bourdonnec, B., Morales, G. A., Moriarty, K. J., and Salvino, J. M. *J. Comb. Chem*., 2006, **8**, 597. (b) Parlow, J. J., Devraj, R. M., and South, M. S. *Curr. Opin. Chem. Biol.* 1999, **3**, 320.

[64]Ley, S. V., Baxendale, I. R., Bream, R. N., Jackson, P. S., Leach, A. G., Longbottom, D. A., Desi, M., Scott, J. S., Storer, R. I., and Taylor, S. J. *J. Chem. Soc., Perkin Trans. 1*, 2000, 3815–4195.

[65](a) Bywood, R., Robinson, C., Stables, H. C., Walker, D., and Wilson, E. M. In *Recent Advances in the Chemistry of* β*-Lactam Antibiotics*, Elks, J., Ed., Special Publication No. 28, The Royal Society of Chemistry, London, 1977, p. 139. (b) Robinson, C., and Walker, D. U.S. Patent 4,059,573, 1977 (to Glaxo).

exomethylene-7*R*-glutaroylaminocepham-4-carboxylic acid 1(*S*)-oxide obtained by the electrochemical reduction of the corresponding 3-acetoxymethylcephalosporin.[66] Although it was never tried, it seems likely that polymer-DDM beads, swollen in methylene chloride, would undertake the same extraction reactions.

We envisaged that the aforementioned sulfonated polymer-DDM may prove useful for the extractive esterification of those water-soluble acidic materials from aqueous solution that would not dissolve in methylene chloride for reaction with swollen polymer-DDM beads. Such compounds could include enzymes with some acidic character, but the risk is that desired enzyme activity may be lost by reaction with the DDM group.

From a chemical process development point of view, there seems little doubt that pursuit of the fields of polymer-supported synthesis and reagents, especially with chemical engineers, will result in new applications of these fields in the future.

Microwave-Assisted Chemistry

The use of microwave ovens for cooking and for the rapid heating of foods and beverages has been one of the most important domestic success stories of the last 30 years. The successful application of microwave energy to promote organic synthesis was described by Gedye[67] and Giguere[68] and their co-workers in 1986, using closed Teflon vessels to contain the reactants. The safety issues raised by the use of solvents, along with the occasional reports of explosions in early laboratory work carried out in domestic microwave ovens, provided cautionary restraint but did not dampen the enthusiasm raised by findings that extraordinary reductions in reaction times, often with cleaner reactions, could be achieved using microwave irradiation to promote desired chemical transformations.[69]

Several small firms market more sophisticated equipment than the domestic microwave oven, and research departments in a number of pharmaceutical companies continue to work with the technology to aid their synthesis of APIs and their intermediates. Several microwave equipment companies[70] are developing larger-scale equipment to produce kilogram quantities. Their systems are evolving to meet some of the needs identified by the earlier practioners such as:

[66]Bernasconi, E., Lee, J., Sogli, L., and Walker, D. *J. Org. Process Res. Dev.*, 2002, **6**, 169.

[67](a) Gedye, R. N., Smith, F. E., Westaway, K. G., Ali, H., Balderisa, L., Laberge, L., and Roussell, J. *Tetrahedron Lett.*, 1986, **27**, 279. (b) Gedye, R. N., Smith, F. E., and Westaway, K. G. *Can. J. Chem.*, 1988, **66**, 17.

[68]Giguere, R. J., Bray, T. L., Duncan, S. N., and Majetich, G. *Tetrahedron Lett.*, 1986, **27**, 4945.

[69]For reviews see (a) Mingos, D. M. P., and Baghurst, D. R. *Chem. Soc. Rev.*, 1991, **20**, 1. (b) Caddick, S. *Tetrahedron*, 1995, **51**, 10403. (c) Deshayes, S., Liagre, M., Loupy, A., Luche, J.-L., and Petit, A. *Tetrahedron*, 1999, **55**, 10851.

[70]Equipment vendors include Prolabo Co., France; Personal Chemistry Ltd., Cambridge, England; Milestone Inc., Monroe, Connecticut, USA and CEM Microwave Technology, Matthews, North Carolina, USA.

TABLE 1. Solvents that Are Transparent or Absorb Microwave Energy and their Dielectric Constants

Transparent		Absorb			
Solvent	ϵ	Solvent	ϵ	Solvent	ϵ
n-Hexane	1.9	Water	80.1	Acetone	21.0
Cyclohexane	2.0	Methanol	33	Ethyl acetate	6.1
Benzene	2.3	Ethanol	25.3	Methylene chloride	8.9
Toluene	2.4	Glycol	41.4	Chloroform	4.8
p-Xylene	2.3	Formic acid	51.1	Dimethyl formamide	38.3
Carbon tetrachloride	2.2	Acetic acid	6.2	Methyl formamide	189.0
PTFE (Teflon®)[a]	2.0	Chlorobenzene	5.7	*N*-Methylpyrrolidone	32.6
		1, 2-Dichloroethane	10.4	Dimethyl sulfoxide	47.2
				Trifluoroacetic acid	8.4

[a]Often used for the construction of pressure vessels for small-scale microwave reactors. Gedye (see footnote 67) has noted that, owing to microwave power requirements, scale-up is not feasible using large Teflon vessels.

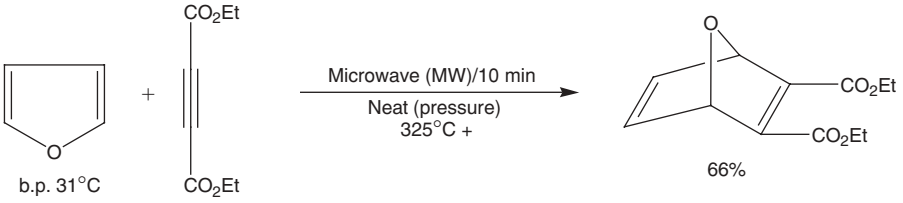
1. Homogeneous energy supply.
2. Reaction temperature determination and feedback control.
3. Provision for open vessel systems as well as pressure systems.
4. Pressure determination and feedback mechanisms.
5. Continuous-flow reactors with residence time control for larger-scale preparation.

As in domestic applications, the microwave heating of chemical reactions provides a way of rapidly obtaining high temperatures. It is this rapid attainment of high temperatures, rather than some special microwave effect, which is believed to be responsible for most observed results.

The literature indicates that a significant proportion of microwave reactions have been carried out in an organic solvent. The solvent choice is dependent on the dipole properties of the reactants. If none of the reactants couples with microwaves, a solvent which does is needed. Some of the most used solvents that can be categorized as those essentially transparent to microwaves and those which absorb, and thus heat rapidly, are identified in Table 1.

Many microwave-assisted reactions have been described using neat conditions; such conditions can be attractive from an environmental and process productivity point of view. Neat reactions may be assisted by the presence of, or by support on, a microwave active solid, such as a zeolite (e.g., a molecular sieve) or Montmorollinite clay. A great deal of processing flexibility is possible using combinations of the above with microwave irradiation inputs of varying intensity.

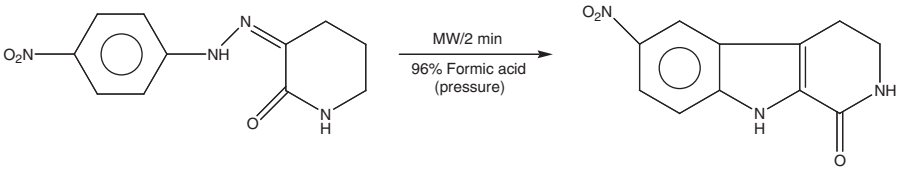
The use of microwave energy to speed analytical sample dissolution and chemical reactions can be of great value in analytical departments, in laboratory synthesis work in research departments, and in chemical process development, but is not necessarily worthwhile in chemical production operations for various reasons. Each case has to be considered on its own merits. As in all scale-up situations to an eventual industrial scale, the volume requirement of the product is one of the more important factors, along with safety, environmental considerations, and the prospects for outsourcing, inter alia. Product volume, multiplied by the potential savings/kilogram obtainable using microwave chemistry versus conventional chemistry, provides the dollar amount that is used in cost calculations needed to justify investment in new equipment. If a conventional plant suitable for running the conventional thermal alternative is already in place, or a third party can take on the process, the economics may not favor in-house investment in equipment for large-scale operation (particularly for manufacturing) unless other important supporting circumstances apply—for example, a patentable surprise in the microwave chemistry result which encourages confidentiality, a vision of future applications, a safety or environmental advantage, inter alia. Comment on a few published reactions illustrates the above:



EXAMPLE 1. Diels–Alder reaction.[68]

The same reaction carried out (neat) at 100°C (pressure) for 4 hr gave a yield of 95%.

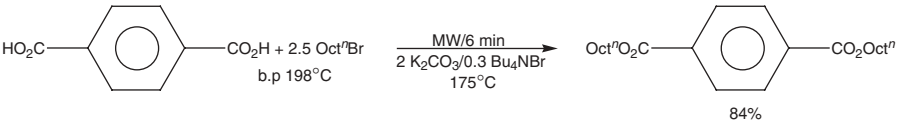
Comment. Even if development work improved the microwave reaction to 95+%, the volume requirement of the product would have to be quite large to justify the cost of developing the microwave reaction and investing in a high-pressure plant to capture the potential plant productivity gains achievable with microwave chemistry. In short, time is not the only important factor in adopting a particular technology.



EXAMPLE 2. Fischer indole synthesis.[71]

The cyclization did not occur in boiling formic acid alone.

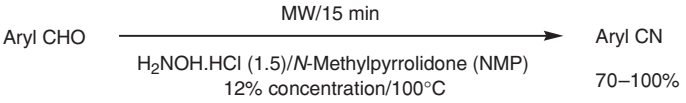
Comment. Although a 20% solution of the nitrohydrazone in polyphosphoric acid could be cyclized by heating,[71(c)] the use of polyphosphoric acid is not particularly desirable. The microwave-assisted process could be worthy of development if there was no other, more economical, way of accessing this specific indole derivative—for example, by nitration of the more readily prepared 1,2,3,4-tetrahydro-1-oxo-β-carboline.[71(a)]



EXAMPLE 3. Esterification/alkylation.[72]

The identical reaction without microwave-assistance, again carried out without solvent and heating for 6 min at 175°C, gave a yield of only 20%.

Comment. This bisesterification (bisalkylation) reaction demonstrates a principle. It would not be industrially feasible for dioctylterephthalate production since the cost of the octyl fragment in the *n*-octyl bromide is at least three times the cost of the same fragment in 1-octanol, the classical esterifying agent. The large-scale use of quaternary ammonium compounds, such as tetrabutylammonium bromide, also raises concerns because their biocidal, algicidal, and fungicidal properties make them toxic to some sewage systems; however, despite these reservations, quaternary ammonium compounds are produced on a large scale for use as fabric softeners, bactericides, and phase transfer catalysts.



EXAMPLE 4. Aldehydes to nitriles.[73]

Comment. Superficially, this one-pot microwave-assisted process looks very attractive. However, in this case, development of a microwave-assisted process will depend on comparison with classical procedures.[74] For instance, Ganboa and

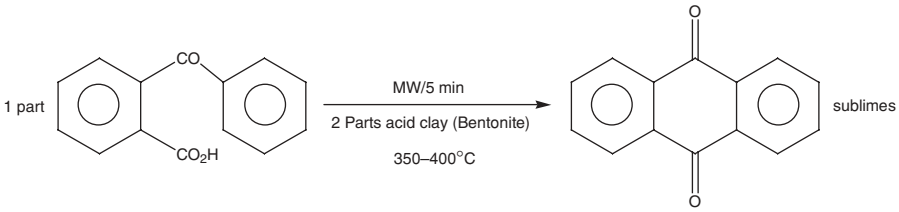
[71](a) Abramovitch, R. A., and Bulman, A. *Synlett*, 1992, 795. (b) Abramovitch, R. A., and Shapiro, D. *J. Chem. Soc*., 1956, 4589. (c) Abramovitch, R. A. *J. Chem. Soc*., 1956, 4593.

[72](a) Loupy, A., Pigeon, P., and Ramdani, M. *Tetrahedron*, 1996, **52**, 6705. (b) A much more promising approach has been described by Shieh and co-workers (*Tetrahedron Lett*., 2002, **43**, 5607), who advantageously produced methyl esters in high yield by the microwave irradiation of carboxylic acids using dimethyl carbonate.

[73]Chakraborti, A. K., and Kaur, G. *Tetrahedron*, 1999, **55**, 13265. See also Villemin, D., Lalaoui, M., and Ben Alloum, A. *Chem. Ind*., 1991, 76.

[74]March, J. *Advanced Organic Chemistry*, 4th edition, Wiley-Interscience, New York, 1992, p. 907.

Palomo[75] report that various aromatic aldehydes can be converted to nitriles in 94–97% yield by refluxing the aromatic aldehyde, hydroxylamine hydrochloride, and magnesium sulfate in toluene or xylene, with *p*-toluenesulfonic acid as catalyst for 1.5 to 3 hr. The microwave-assisted process may prove better for aliphatic aldehydes and may be made even more attractive if the above process conditions could be refined to reduce or eliminate NMP—for instance, if both aldehyde and nitrile form a homogeneous liquid at the reaction temperature.



EXAMPLE 5. Lewis acid-type cyclization.[76]

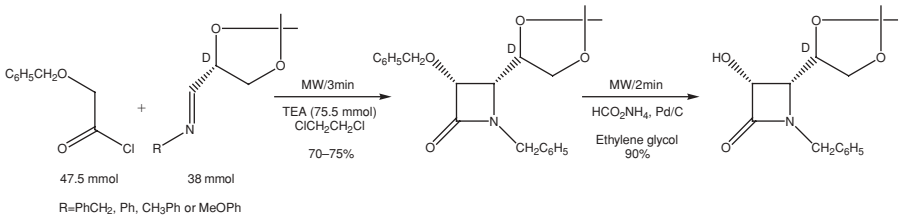
This microwave-assisted reaction was carried out on a 3-g scale in a glass vessel placed in a "bath" of alumina/magnetite. The anthraquinone (m.p. 284°C) produced was collected as it sublimed from the reactor. Further, *o*-benzoylbenzoic acid was added and the reaction repeated. The main advantage of the microwave-assisted reaction lies in the recycling of the catalyst. The yield in the conventional heating process falls to 50% after four uses of catalyst, whereas in the microwave-assisted process the yield is still 84% after fifteen uses.

Comment. The classical industrial process comprises cyclizing *o*-benzoylbenzoic acid (from reaction of phthalic anhydride with benzene) with acid using a solvent or a ball mill process. It is difficult to see how the Bram process could be made competitive. All solid support processes would seem to require pumping a solid slurry through a tubular microwave reactor.

EXAMPLE 6. Polymer-supported peptide synthesis.[60]

Comment. There may be considerable advantage in commercial polymer-supported synthesis by employing microwave heating techniques; see earlier section entitled "Polymer-Supported Synthesis and Reagents."

[75]Ganboa, I. and Palomo, C. *Synth. Commun*., 1983, **13**, 219.
[76]Bram, G., Loupy, A., Majdoub, M., and Petit, A. *Chem. Ind*., 1991, 396.

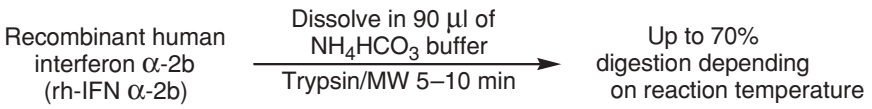


EXAMPLE 7. β-Lactam synthesis and transformation.[77]

The authors described the preparation of 25 g of the chiral *cis*-hydroxylactam using these two microwave-assisted reactions in one day. Purification of the product was achieved using chromatography on silica gel.

Comment. The Bose group at Stevens Institute of Technology, New Jersey, has been especially active in applying microwave-assisted chemistry to the preparation and further transformation of β-lactam synthons into other lactams, Taxol® precursors, amino sugars, and hydroxyamino acids.[78] Some steric control has been observed.[78(c)]

The Bose group's prolific applications of the microwave-assisted ketene–imine annelation process suggest that research laboratories everywhere should be able to justify acquisition of microwave equipment to accelerate research programs via the rapid preparation of a variety of new structures. In a process development setting, the microwave technique should find application in the rapid evaluation and optimization of process parameters, such as solvent, reaction concentration (and neat reactions), temperature, time, pressure, the structure of catalyzing bases/acids, rates of addition, and so on.



[10 µl of a 3µg/µl solution]

EXAMPLE 8. Accelerating enzyme reactions.[79]

Comment. This remarkable study[79] of an enzymic cleavage enabled the authors to establish that considerable enhancement of the reaction rate could be achieved at temperatures (>60°C) above those normally used (~37°C) in conventional enzyme cleavage reactions. Simulating the rapid temperature elevation in the same trypsin

[77]Banik, B. K., Manhas, M. S., Kaluza, Z., Barakat, K. J., and Bose, A. K. *Tetrahedron Lett*., 1992, **33**, 3603.

[78](a) Bose, A. K., Banik, B. K., Mathur, C., Wagle, D. R., and Manhas, M. S. *Tetraheddron*, 2000, **56**, 5603. b) Manhas, M. S., Banik, B. K., Mathur, A., Vincent, J. E., and Bose, A. K. *Tetrahedron*, 2000, **56**, 5587. (c) Reference (a), p. 5611.

[79]Pramanik, B. N., Mirza, U. A., Ing, Y. H., Liu, Y-H., Bartner, P. L., Weber, P. C., and Bose, A. K. *Protein Sci*., 2002, **11**, 2676.

digestion using a preheated block at 60°C gave the same result as obtained under microwave conditions. This novel observation suggests that microwave enhancement (superheating) of enzyme reactions deserves exploration in all enzyme-mediated cleavages, at least of proteins. The authors postulate that protein unfolding at the higher temperatures may be enabling enzyme access to the sites of cleavage. In the above case, relatively large quantities of enzyme are needed, indicating that the enzyme is also being deactivated—addition of fresh enzyme after 10 min of microwaving enhances the enzyme reaction.

Despite more than 20 years of study, the application of microwave irradiation to chemical process development is still in relative infancy. Microwave equipment companies continue to address the requirements for large-scale continuous flow and other reactors.[80] The availability of versatile equipment, and preferably a "champion" in a chemical process development department, would encourage evaluation of the technology to identify those reactions where the main advantage, enormous reduction in reaction times (often with cleaner reactions and yield increases beyond those achievable using conventional conditions), can be harnessed in practical terms.

Evaluation of microwave technology has added merits. Organic synthesis chemists working in the chemical process development field generally limit themselves to (a) working at atmospheric pressure in conventional laboratory glassware and (b) carrying out their reactions using conventional heating techniques. By screening reactions under microwave activation conditions, chemists expand the range of process parameters they normally consider. In essence, they move toward the world of the chemical engineer whose training familiarizes him/her with chemical operations at higher pressures and temperatures. Bringing chemistry and engineering disciplines together generally creates invaluable synergy in the chemical process development field. In this case the chemical engineer may encourage the process development chemist to collaborate in the design and evaluation of a continuous flow microwave heated pressure tube reactor to study the effects of "instant" superheating on chemical reactions.

If increased reaction yields and/or cleaner reactions are demonstrable, to add to large reductions in reaction time, one has the best of all possible opportunities to profitably partner the process development chemist and chemical engineer in the development of a pilot plant scale microwave reactor as an alternative to conventionally heated plant equipment. As with any relatively new technology, sober-minded and realistic evaluation is needed in order to gain credibility with one's supporters and to overcome the inertia, often born of skepticism, which is frequently associated with excursions into the unknown.

The future of microwave technology thus lies with the identification of reactions with a potential for advantageous results vs. other means. An industrial success would undoubtedly bring microwave technology into mainstream thinking as a chemical process development tool.

Our own appreciation of the possibilities of applying microwave technology arose from a single experiment carried out by Dr. Y.-H. Ing, working in Dr. Birendra

[80]Following the lead of Peterson, C. *New Scientist*, 1989, **123**, 44, working at CSIRO, Australia.

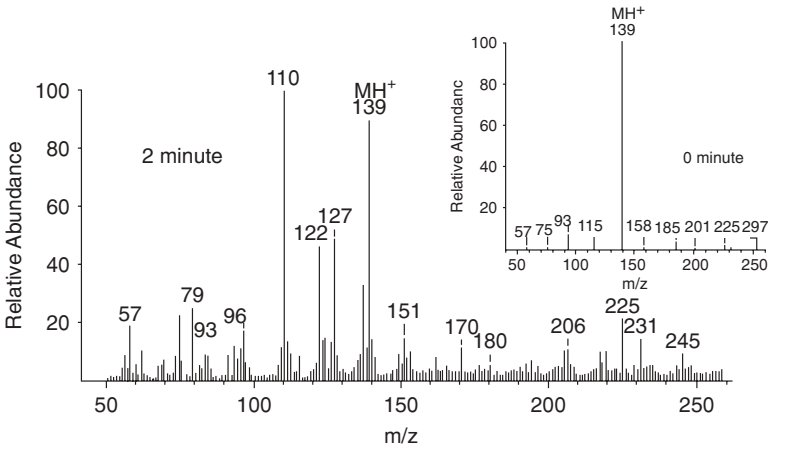


FIGURE 1. Electrospray–MS of microwave-assisted hydrolysis of dihydrohypoxanthine trifluoroacetate.

Pramanik's group. He reasoned that the hydrolysis of dihydrohypoxanthine to 5-aminoimidazole-4-carboxamide (AIC) (see Scheme 19 and Figure 14 in Case Study 2) might be conveniently carried out using microwave irradiation. He dissolved dihydrohypoxanthine trifluoroacetate salt (81.1 mg) in 1:1 trifluoroacetic acid:water (2 ml) and micronized the solution for 2 min at ambient pressure. After this time the electrospray–MS spectrum of the solution indicated that substantial AIC formation had occurred (Figure 1).

Should the economics of the above-described new process favor a switch from the present AIC process (see Case Study 2) to one based on dihydrohypoxanthine new investment might be justified in new production equipment.[81] A switch to the microwave option versus the conventional heating option would depend on the outcome of process optimization work on both. If a rapid clean reaction in near-quantitative yield were realized by optimizing the microwave conditions, then it would prove worthwhile to engineer a simple continuous flow reactor for further development work. The case in favor of adopting the microwave-assisted process would be further enhanced if the solution from the microwave reactor could be used directly in the next process step (thus eliminating the need for isolation equipment).

Conclusion. From a chemical process development perspective, the principal advantage favoring the use of microwave irradiation in promoting chemical reactions lies in achieving shorter reaction times. If cleaner reactions giving higher yields are also demonstrated, they add greatly to the attractiveness.

As indicated by comments on a few published microwave-assisted reactions, microwave technology is no panacea and appears likely to be applicable only to selected

[81] New situations generally provide the best opportunity for the evaluation and introduction of new technology.

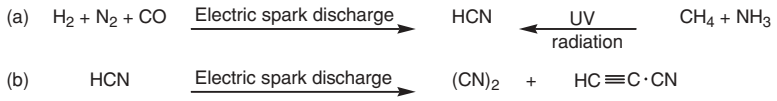
cases. Much work will also be needed to validate the technology for commercial use.

Nevertheless, the availability of a microwave oven, and a champion of the technology in the laboratory, would allow chemical process development scientists and engineers to satisfy themselves on questions concerning the limitations of conventional heating. The rapid evaluation of superheating effects may well reveal opportunities missed by restriction to conventional heating, including demonstrating transformations that cannot be achieved under conventional conditions. Also, in process development terms, a given microwave-induced reaction might be developed more efficiently by the rapid screening and evaluation of process parameters.

The bottom line is that the broader application of microwave technology is worth pursuing. Any eventual commercial adoption of technology such as a microwave-irradiated continuous reactor system generating attractive economics, both in capital and operating terms, would stimulate broader interest in evaluating the technology.

Electrochemistry

Electricity has generally been recognized as a probable promoter of organic synthesis going back billions of years. A report by Sutherland and Whitfield summarizes some of the evidence for this.[82] Thus, electrical spark discharges in the presence of simple molecules believed to be present in the planet's prebiotic atmosphere have been shown to produce a few of the building blocks needed for the creation of life. The sun also provided other forms of energy (e.g., infrared and ultraviolet radiation, inter alia). Some of the processes proved by laboratory experiments are:



The melting of ice around 4 billion years ago introduced the water needed for the beginnings of the organic chemical processes essential for the production of the amino acids, purines, and pyrimidines required for the evolution of early life forms. Thus

Interestingly, the proportions of the mostly racemic amino acids produced in this mixture are approximately the same as those found in fragments of the Murchison meteorite, which fell near the village of Murchison, Victoria, Australia in 1969.[82,83]

The self-condensation of hydrogen cyanide has been shown to lead to the formation of the purines adenine and guanine, two of the bases needed for the formation of DNA.

[82]Sutherland, J. D., and Whitfield, J. N. *Tetrahedron*, Report Number 425, 1997, **53**, 11493–11527, Prebiotic Chemistry: A Bioorganic Perspective.

[83]Some N^{15} enrichment in individual Murchison amino acids (versus terrestrial counterparts) suggests an extraterrestrial origin for an L-enantiomer excess-Engel, M. H., and Macko S. A. *Nature*, 1997, **389**, 265.

TABLE 2. Comparison of the Cost of Electricity and the Costs of Chemicals Commonly Used in Oxidation and Reduction

Reagent	Cost/kg[b] ($)	Moles/kg	Cents/Mole	Cents/Equivalent
Electrons at 6c/kWh, 3.5 v[a]				0.6
Sulfur dioxide	0.54	15.63	3.5	1.75
Chlorine	0.65	14.08	4.6	2.3
Hydrogen peroxide	2.27	29.4	7.8	3.9
Zinc (metal)	1.80	15.2	11.9	5.95
Chromic acid (CrO_3)	4.10	10.0	41.0	6.8
Sodium (metal)	3.10	43.4	7.2	7.2
Hydrazine	5.85	31.2	19.17	9.58 (4.79)[c]
Sodium hydrosulfite	1.85	5.74	32.1	16.05
Potassium permanganate	3.45	6.33	54.47	18.1
Magnesium (metal)	19.84	41.6	47.9	23.95
Sodium borohydride	74.00	26.3	299.5	159.75

[a]Information kindly provided by the Electrosynthesis Company, Lancaster, New York.
[b]Figures from *Chemical Marketing Reporter*, April 2007, and Dr. Prashant Savle, Schering–Plough.
[c]Bracketed figure assumes that four hydrogens are available.

It has also been found that, of the two pyrimidines needed for the preparation of DNA, cytosine can be produced from cyanoacetylene.[82]

However, despite its apparently fundamental role in creating the building blocks of life, electricity has not become one of the foremost means of manipulating organic molecules to useful end.[84] Nevertheless, where it can be applied to remove or add electrons in specific ways, electricity offers unique and often advantageous approaches to carrying out oxidation and reduction reactions. The interested reader is referred to several of the books published on the subject for further education.[85]

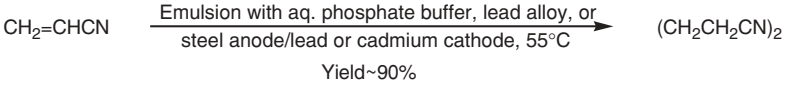
Obviously, air (oxygen) is the lowest-cost reagent for carrying out certain oxidation reactions. Added to this the electrolysis of water affords a convenient, low-cost means of producing oxygen, and hydrogen, in concentrated form, for a large range of oxidation and reduction reactions practiced commercially today. It follows, in going back to fundamentals, that the removal or addition of electrons could provide the lowest cost route for carrying out oxidation or reduction reactions. This can be illustrated by comparing the cost of electricity with the cost of some of the common chemicals used in oxidation and reduction in the organic chemistry field (Table 2).

[84]Electrochemistry is, of course, commercially very well established in the inorganic chemicals industry—for example, for the manufacture of chlorine, aluminum, sodium, and sodium hydroxide, inter alia.

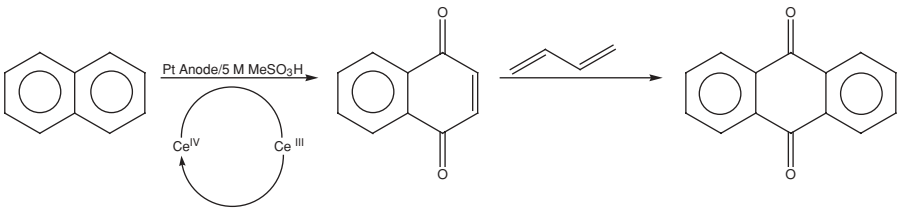
[85](a) Torii, S. *Electroorganic Synthesis, Methods and Applications*, Kodansha Ltd., Tokyo; VCH, Weinheim, Germany; VCH Publishers, Deerfield Beach, Florida, 1985. (b) Pletcher, D., and Walsh, F. C. *Industrial Electrochemistry*, 2nd edition, Chapman and Hall, London, 1990. (c) Lund, H., and Baizer, M. M. *Organic Electrochemistry, An Introduction and Guide*, 3rd edition, Marcel Dekker, New York, 1991.

Although relatively few organic chemicals are produced on a commercial scale using electrochemical means, those that are produced owe their existence to the commitment and perseverance of individual scientists, and no doubt to the wisdom of the visionary leaders who supported these scientists' inspiration and provided the funding.

There are always setbacks which damage the credibility of a technology.[86] Again, Nalco's elegant electrochemical process for the manufacture of tetraalkyl lead, installed in the mid-1960s, was highly successful until lead was phased out of gasoline in the 1980s. Probably the most successful electroorganic process, which has been running commercially for more than 40 years, is the Monsanto process for the hydrodimerization of acrylonitrile to adiponitrile (reference 85(c), p. 1317).



This reaction is conducted on a scale of >200,000 tonnes/annum. More recently, another elegant application of electrochemistry on a multi-thousand-tonne scale has been HydroQuebec's investment in a cerium (IV)-mediated oxidation of naphthalene to naphthaquinone, a process licensed from W.R. Grace.[87] HydroQuebec then uses the naphthaquinone in a Diels–Alder reaction with butadiene to produce anthraquinone:



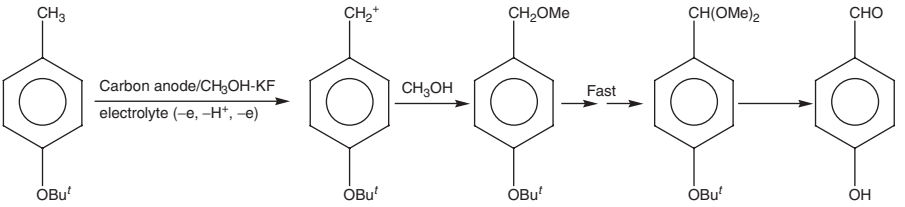
This reaction is noteworthy in its use of the expensive cerium IV salt, which is recycled very efficiently in the anodic oxidation process thus reducing its contribution to the cost of the anthraquinone product.

A further illustration of the variety of reactions that can be carried out by electrochemical processes is BASF's production, on a small scale, of *p*-hydroxybenzaldehyde.[88]

[86]The Atlas Powder Company's large plant for the manufacture of mannitol and sorbitol by the cathodic reduction of glucose was rendered obsolete within a few years by a high-pressure catalytic hydrogenation process.

[87]Kreh, R. P., Spotnitz, R. M., and Lundquist, J. T. *J. Org Chem*., 1989, **54**, 1526.

[88]Barl, M., Degner, D., Siegel, H., and Hoffmann, W. European Patent, 0025883, 1983 (to BASF).



ex *p*-cresol

The above are but a few of the many reactions that have been carried out by electrochemical means. Reference 85(c) describes these and several other processes that have been conducted on a semicommercial or pilot plant scale, in greater depth.[89] A complementary review of organic electrosyntheses in industry, by Degner (BASF),[90] provides an extensive review, with 633 references, of the patent literature into 1987. Degner expresses the opinion that the most likely successes with electroorganic chemistry in the future will come from continuing work in the areas outlined above—that is, from cathodic hydrodimerization (e.g., the C–C couplings such as the above-described approach to adiponitrile manufacture), the electrochemical regeneration of expensive reagents (see the above naphthaquinone example), and the functionalization of alkenes and aromatic compounds, as in the BASF *p*-hydroxybenzaldehyde process. Other reviews[91] provide further examples of such reactions and suggest that electrochemistry has a larger role to play in the pharmaceutical industry. Indeed all three reviews provide examples of the use of electrochemical methods especially in the deprotection of a variety of amino protecting groups and in the transformation and functionalisation opportunities afforded by electrochemistry. It also appears that electrochemistry has a valuable part to play in chiral synthesis—for example, through the use of electrochemical systems to control the oxidation state of enzymes. A review by Steckhan[92] describes many opportunities for the application of electroenzymic oxidations and reductions, opening up a new field in bioelectrosynthesis.

Our own interest in applying electrochemistry grew from the highly successful process developed for the manufacture of the third-generation cephalosporin antibiotic, Ceftibuten.[93] The electrochemical reduction component of the process and the product extraction step are, in outline, as follows:

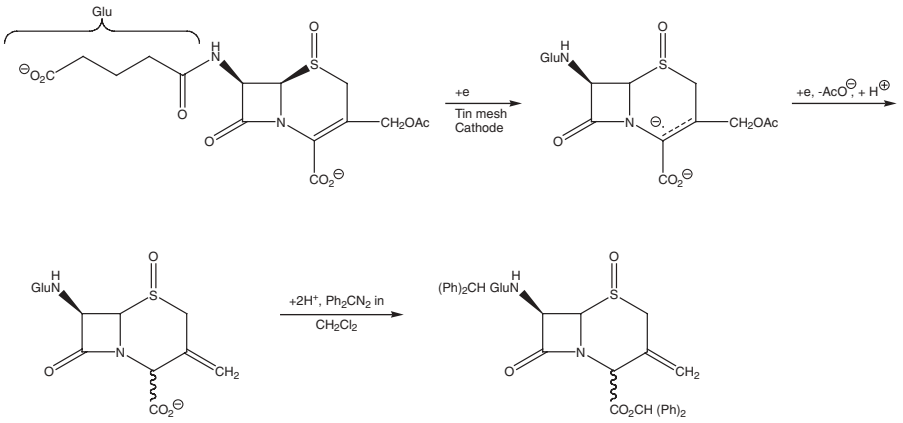
[89] See Danly, D. E., and King, C. J. H. Chapter 31 in reference 85(c), p. 1285.

[90] Degner, D. *Topics Curr. Chem.*, 1988, **148**, 1–95.

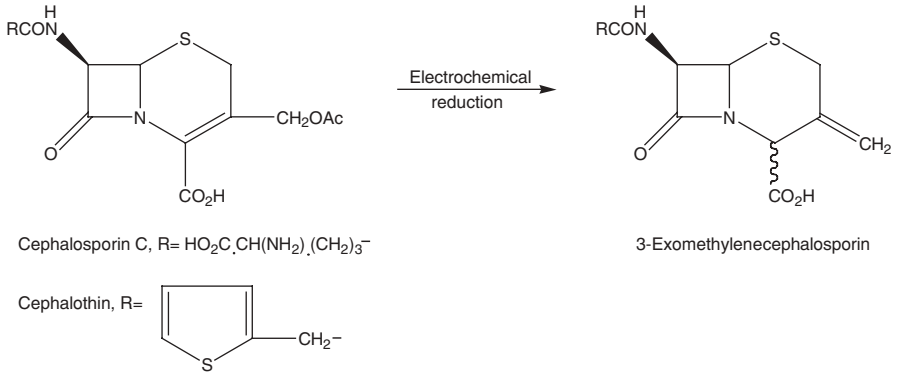
[91] (a) Utley, J. *Chem. Ind.*, 1994, 215. (b) Genders, J. D., and Pletcher, D. *Chem. Ind.*, 1996, 682. (c) Ban, Y. Chapter 19, Natural Products and Pharmaceuticals, in reference 85(c), p. 765.

[92] Steckhan, E. *Topics Curr. Chem.*, 1994, **170**, 83.

[93] Detail of the entire process is provided in Chapter 9 (q.v.) and in the papers by (a) Bernasconi, E., Lee, J., Roletto, J., Sogli, L., and Walker, D. *J. Org. Proc. Dev.*, 2002, **6**, 152. (b) Bernasconi, E., Genders, D., Lee, J., Longoni, D., Martin, C. R., Menon, V., Roletto, J., Sogli, L., Walker, D., Zappi, G., Zelenay, P., and Zhang, H. *J. Org. Proc. Res. Dev.*, 2002, **6**, 158. (c) Bernasconi, E., Lee, J., Sogli, L., and Walker, D. *J. Org. Proc. Res. Dev.*, 2002, **6**, 169. (d) Chai, D., Genders, D., Weinberg, N., Zappi, G., Bernasconi, E., Lee, J., Roletto, J., Sogli, L., Walker, D., Martin, C. R., Menon, V., Zelenay, P., and Zhang, H. *J. Org. Proc. Res. Dev.*, 2002, **6**, 178.



This process grew out of earlier efforts by several pharmaceutical companies, Eli Lilly, Takeda and Shionogi, to electrochemically reduce 3-acetoxycephalosporins, such as cephalosporin C and its derivatives to 3-exomethylenecephalosporins.[94]



Cephalosporin C, R= $HO_2C.CH(NH_2).(CH_2)_3^-$

3-Exomethylenecephalosporin

Cephalothin, R=

Evaluation of the process as a candidate for scale-up and further development evidently did not meet the Lilly or Takeda requirements. It could be that a champion of the new technology never emerged. Indeed, when Schering–Plough took up the idea for the manufacture of Ceftibuten intermediates, our partner, Shionogi, based on their earlier knowledge of Eli Lilly and Takeda work, were only lukewarm supporters. The main objections were as follows:

[94]As happens from time to time, the beginnings of this electrochemical process emerged from work undertaken by another pharmaceutical company, Glaxo Laboratories for quite different reasons. Thus, Glaxo analytical chemists, investigating the use of polarographic methods for the quantitative analysis of cephalosporins, especially cephaloridine, were the first to observe that these compounds underwent electrochemical reduction (Jones, I. F., Page, J. E., and Rhodes, C. T. *J. Pharm. Pharmacol*., 1968, **20**, 455). Fundamental investigations by Lilly and Takeda workers led to further exploration of the above electrochemical process (Hall, D. A. *J. Pharm. Sci*., 1973, **62**, 980; Hall, D. A., Berry, D. M., and Schneider, C. J. *J. Electroanal.Chem*., 1977, **80**, 155; and Ochiai, M., Aki, O., Morimoto, A., Okada, T., Shinozaki, K., and Asahi, Y. *J. Chem. Soc., Perkin 1*, 1974, 258).

1. The use of a mercury cathode is environmentally unacceptable. (Our early work was done using a conventional electrochemical cell using a mercury pool cathode—see later).
2. The electrochemical reduction process applied to cephalosporins gave $<70\%$ yield of desired exomethylene product, thereby introducing substantial purification problems to add to the yield losses.
3. The productivity of the process (reaction concentration) was low (concentration $\sim$5 g/liter).
4. The current density, again impacting productivity, was low.
5. No practical means of extracting the product was known.
6. In the early 1970s, electrochemical technology for processing organic compounds was in its infancy and pharmaceutical manufacturers were inexperienced in it and wary of it.
7. Concern was expressed regarding the possible impact of new technology on product quality.
8. Why change? The production process operated by Shionogi was working well, if not as cheaply as the projected costs (we were reminded that our projections were unproven!) of the electrochemical route. However, limitations on Shionogi plant capacity for larger Ceftibuten production volumes, originally anticipated, were such that Shionogi supported evaluation of the electrochemical option through the pilot plant phase of process development.

The events that followed resulted from confluence of several critical factors:

1. The vision, leadership, and support of senior Schering–Plough executives, particularly Dr. Hal Wolkoff, Senior V.P. of all Development, and Mr. John Nine, Senior V.P. of all Manufacturing operations, encouraged further exploration of the electrochemical process.
2. Continued and expanded funding of the Colorado State University program under the enthusiastic direction of Professor Charles R. Martin was agreed to be an essential component of the research effort.
3. Enlargement of the evaluation and development of the electrochemical component of the project, by engaging the Electrosynthesis Company, Lancaster, New York, and particularly harnessing the experience of their industrial electrochemistry experts, Drs. Norman Weinberg and David Genders, was agreed to offer the best means of gaining industrial perspective.
4. Commitments to purchase pilot plant quantities of key intermediates from Antibioticos, our cephalosporin-producing partner in the development of the electrochemical reduction process, was also considered essential in the securement of a cost-effective supplier of raw materials.
5. Legal agreements covering objectives and intellectual property ownership approved by all parties involved, were drawn up to ensure that all parties knew where they stood.

6. Agreements on regular minuted meetings with all parties, including Shionogi, to report progress and share information were considered the best vehicle to ensure that progress was based on everyone's understanding of the issues.
7. Day-to-day coordination of activities was agreed as best run by Schering–Plough to ensure all the players in all the organisations involved were working together as effectively as possible. Most of the Schering–Plough component of this was very ably handled by Dr. Junning Lee.

As a result of this organization, rapid progress was made in overcoming the list of objections (outlined earlier) which had not been overcome by Eli Lilly and Takeda and which were, initially, legitimate concerns to Shionogi. In brief, the milestone events were as follows.

Alternative Substrates. Although we in Schering–Plough did not find advantage in replacing the acetoxy leaving group in the cephalosporin with better leaving groups (e.g., pyridinium, chloro, chloroacetoxy), we quickly discovered that oxidation of the cephalosporin sulfide atom to its sulfoxide produced a superior substrate for the electrochemical reduction; yields to the desired exomethylene sulfoxide intermediate exceeded 90%, and none of the thiazole-type impurities generated in the reduction of the earlier cephalosporin sulfide were produced. Preparation of the sulfoxide was easily carried out in situ by Antibioticos such that their preparation of glutaroyl-cephalosporanic acid sulfoxide became the favored route to provide the substrate of choice. We expected, and later proved, that the sulfoxide group could be readily reduced to the sulfide later in the process (see Chapter 9 and previously cited references[93]).

Replacing the Mercury Cathode. Professor Martin and his colleagues undertook an entrepreneurial evaluation of alternative cathode materials and process conditions using the new sulfoxide substrate. They identified tin as the closest to mercury. Dr. David Genders proposed that a greatly increased surface area of the cathode would help to increase the yield of the desired exomethylene sulfoxide and speed the reaction. This indeed proved to be the case.

The work in both Colorado State University and the Electrosynthesis Company, drawing on the free expression of university colleagues and the practical know-how and experience of industrial Electrosynthesis experts, enhanced the rate of progress leading to the technical success of the project.

Process Productivity. We quickly showed that, starting with the more stable sulfoxide, the reaction concentration could be advantageously increased to 50g/liter, and the current density to 100–200 mA cm^{-2}.

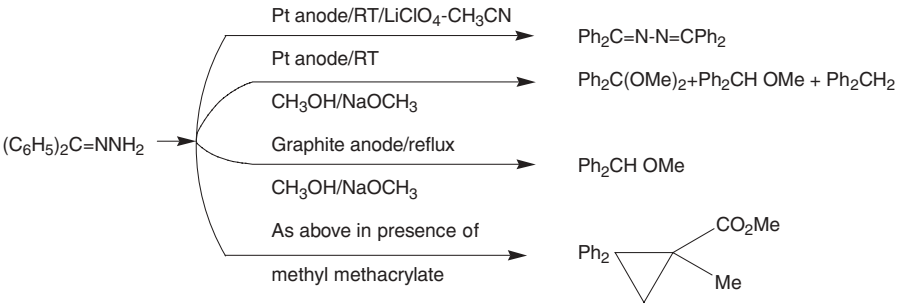
Product Extraction. The little used but very efficient method of using diphenyldiazomethane for the extractive esterification of acidic materials from aqueous solution proved to be very effective [see footnote 93(c)].

Product Quality. Work was undertaken to show that the Ceftibuten product produced via the electrochemical route was analytically acceptable (indeed at least as pure) as that produced by the Shionogi process.

Why Change? The pilot plant work carried out by the Electrosynthesis company[93(d)] enabled us to validate our earlier cost calculations. However, by this time the market for Ceftibuten was declining and the justification for investment in new plant disappeared. Thus although the process proved to be an enormous technical success, it was a commercial failure.

In completing our R&D contract with Professor Martin, we tested two other potential uses of electrochemistry in fields of interest. The first was to improve the well-established Marker chromic acid (chromium VI) oxidation process for converting diosgenin acetate to the 20-keto intermediate needed for the manufacture of Schering–Plough's line of betamethasone products (see Scheme 3 in Chapter 9). The improvement sought was to use anodic oxidation to recycle the chromium III waste back to chromium VI, for reuse on-site, thus avoiding or greatly reducing the need to precipitate chromium hydroxide from the waste and pay to have it sent to chromium waste disposers for recycle. Unfortunately, despite our demonstrating the feasibility of the process, the return on investment (ROI) did not justify expenditure in anodic oxidation equipment for the relatively small quantity of chromium III waste generated in our Mexican plant.

The second project was to determine whether the anodic oxidation of benzophenone hydrazone could be manipulated to produce diphenyldiazomethane (DDM) as the end product in high yield. Literature evidence[95] indicated that the anodic oxidation of benzophenone hydrazone using either a platinum or graphite anode under various conditions with a variety of electrolytes gave a number of products that were shown to derive from the intermediacy of DDM:



Chiba and co-workers gave no indication that the anodic oxidation of benzophenone hydrazone could be stopped at the DDM stage. Professor Martin and Dr. John Hulteen, Colorado State University, were, however, able to devise conditions, based

[95]Chiba, T., Okimoto, M., Nagai, H., and Takata, Y. *J. Org. Chem.*, 1983, **48**, 2968.

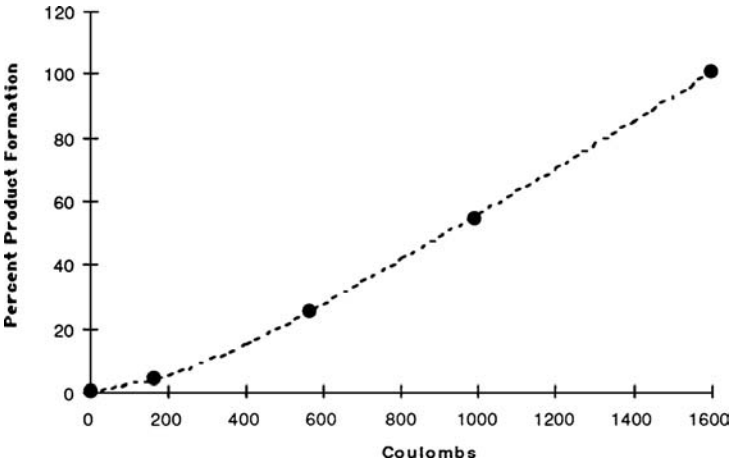


FIGURE 2. Electrochemical oxidation of Benzophenone Hydrazone to Diphenyldiazomethane.

on those described by Glaxo workers,[96] which produced DDM, using a platinum anode in the divided cell described in an earlier publication [see footnote 93(b)]. The process conditions were as follows:

Benzophenone hydrazone (5.88 g, 20 mM) was dissolved in methylene chloride (20 ml) and over-layered with 1 M sodium hydroxide (40 ml) containing, as phase transfer catalyst, tetrabutylammonium sulfate (0.68 g) and sodium iodide (300 mg). The cathode half cell contained 1 M sodium hydroxide (60ml). The whole cell was cooled to 0°C, the anode compartment stirred and electrolysed at a current of 50 mA. Formation of DDM was followed using the DDM absorption peak at 525 nm. The chart obtained was as shown in Figure 2.

Conclusion. The above outline of successes achieved in using electrochemical methods to carry out oxidation and reduction reactions in the field of organic chemical transformations underlines the merits of electrochemistry.

These successes, the relatively low cost of electricity and especially the environmental advantages that electrochemical methods afford, justify the wider evaluation of electrochemistry as a first-line technology for oxidations and reductions in chemical process development work. Today, the only factors standing in the way of this are the lack of some education in the practical applications of electrochemistry, management encouragement to reach out to university chemistry departments, as well as to specialist industrial companies, working in the field, and the availability of an electrochemical cell in chemical process development laboratories everywhere. Regarding electrochemical cells, the reader is referred to the Lund and Baizer book

[96](a) Adamson, J. R., Bywood, R., Eastlick, D. T., Gallagher, G., Walker, D., and Wilson, E. M. *J. Chem. Soc., Perkin Trans. I*, 1975, 2030. (b) Bywood, R., Gallagher, G., Sharma, G. K., and Walker, D. *J. Chem. Soc., Perkin Trans. I*, 1975, 2019.

[see footnote 85(c)] and specifically the chapter by Professor Lund, which describes laboratory cell construction, electrode materials, operating parameters, solvents for electrolysis, and electrolytes.[97] A sketch of the cell used in our work in Colorado State University is provided in reference 93(b).

Going back to the beginning, I hope that this somewhat superficial outline of electrochemical process successes will be enough to stimulate the imaginations of chemical process development scientists and engineers everywhere to explore the universe of electron transfers which is out there and to adopt electrochemical technology as a first-line endeavor.

Sustainable Development

Introduction. Since present human development is not sustainable the concept of sustainable development requires that human expression has, in this century, to be harmonized to control all the world's runaway dangers, not only the profligate use of the finite resources of the natural world, in order to create and maintain a stable slowly evolving steady state designed to ensure long-term survival. A vast re-education of all the world's diverse cultures and social systems is becoming increasingly necessary to create forms of human living that lead to harmonious development and "growth" of a sugstainable kind.

Science, which has been the badly exploited core of development to this point, will inevitably continue to be one of the main engines of the re-education process. The power of current driving forces has to be urgently revolutionized, and more sustainable forms of living have to rapidly emerge in order to secure greater world harmony and stability. A re-education plan needs to be formulated and aggressively funded, worldwide. In short, re-education for the near future, evolving into a long-term program of education for long-term survival has to be placed on a war footing.

Self-preservation has always been the supreme motivating force of mankind, developing, with little concern for the consequences, into the out-of-balance (excessive) me-phenomenon of today. In various guises, "me" is a human phenomenon on a planetary scale disrupting not only local social systems but, more ominously, national and continental ways of life. In a word, "me" has set cultures into conflict with one another. The problem has escalated rapidly in the last hundred years as liberalism spawned self-determination in those who are not equipped to deal with the consequences of free expression. Leaders of the world have seemed powerless to deal with the problem. They are mostly seen as self-serving themselves, lacking in vision and moral courage to seek the collaborations needed among the great world movements and ideologies (democratic capitalism, socialism/communism and religion), to address the problems.

Sustainable development might best be achieved by creating new social models based on reexamining and reconstructing, from today's vantage point, the ways in which early families and village communities survived and advanced through acquisition of the skills needed to guarantee their water and food supply, the provision

[97] Lund, H. Chapter 6, p. 253 in reference 85(c): Practical Problems in Electrosynthesis.

of shelter, the availability of energy sources, and the organizations they needed in their own battles for self-preservation. Early life developed into larger, more fractious societies, enabling scientific and other discoveries, leading to the industrial revolution and the wartime disasters of the 20th century continuing! Going back and remodeling history, *by integrating and addressing the major consequences of the process of human development, ignored at the time*, may enable modern man to determine better ways of utilizing water and other finite natural resources, as well as creating sustainable social systems, continually educating the population into more of a selfless development mode, evolving leadership and still accommodating individual creativity in a way that harmonises with the evolution of a steady state. Basically, creativity has generated the wealth that sustains us all. But it is mostly the excesses resulting from creativity, such as the abuse of power and profiteering, which have produced the ignored consequences. The issue thus becomes how to fashion more "WE phenomenon" while still preserving individual creativity.

Such modeling may identify how an ideal planetary world may evolve, but it will undoubtedly be unimaginably difficult to reformulate the present-day human condition at a time when the "me" world is irreversibly consumed by its accelerating, consequence-ignoring, out-of-control growth. It hardly seems possible that modern man can be persuaded to adopt a long-term holistic approach to life without first precipitating some remorseless, unstoppable cataclysmic event with a catastrophic loss of planetary life, leading to new foundations.

Everyone prepared to think about how to find ways of avoiding or minimising the impact of a cataclysmic event quickly realizes that possible solutions have already been identified. For me, pursuing the goal means more vigorously addressing only three core matters. These are conservation, especially of energy use, much wider education, especially enabling the have-not third-world countries achieve greater health and wealth, and population stabilization, especially gained through education.

Energy conservation is only a minor component of the relatively small-scale operations in the pharmaceutical industry. Nevertheless, it needs to be addressed. In regard to the very large scale, those using organic chemical-based transport systems need to be urgently obliged to become much more efficient consumers of fossil fuels. To the chemist, seeing the world's organic chemical feedstock so wastefully converted to carbon dioxide is almost a crime, whether or not you believe carbon dioxide also contributes to global warming. The use of biologically derived ethanol and other biofuels—preferably produced from abundant cellulosic raw materials, and even biogas from animal slurry waste and manure[98]—is only a stopgap activity. Wind, waves, tides, and sea current sources of electricity are being developed. They are not as limited as hydroelectric power (available only from rivers and reservoirs), but they need more research and development, including in better battery technology, to become more mainstream. Solar power is better established and geothermal energy sources could and will be increasingly harnessed as research and development improves their contribution. These technologies are all likely to be only supplementary sources of electricity for the near future. Fossil fuels, with greatly improved pollution controls in

[98] Doubtless, human foul waste could also be used as a source of biogas, especially if it could be concentrated by separating it from general domestic sewage in an economical way.

the case of coal, will be the major sources of energy, especially electricity, over the next several decades. Only nuclear energy, despite its fearful waste and terrorism baggage, will become the major source of electricity for the foreseeable future.[99] Much more research and development is being undertaken, especially in waste recycle and also in the cleaner nuclear fusion alternative, which will undoubtedly improve the already quite favorable economics. Terror threats might be expected to decline given more education. It would thus appear to this writer that electricity will become man's long-term source of clean energy, leaving fossil fuels for more specialist uses and, particularly, for the world's chemical industry.

As for education and population stabilization, the world only needs to watch and, as requested, discretely help India, which seems to contain all the world's problems in "microcosm." India, with its 700 million rural people in 600,000 villages, and its educated class of more than 300 million, is already working, if painfully slowly, to modernize its social and economic systems to raise itself to the level of the most developed nations. Its success could provide a model for all the third-world nations. However, as already mentioned, the so-called developed world needs, itself, to do far, far more to educate and transform itself away from its excessive, me-phenomenon obsession into a we-phenomenon state, providing an example for the underdeveloped world.

Education is the key requirement for all to undertake. It is probably too much to ask all but a few to subscribe to Darwin's view.[100] But there is much to be said for re-educating those populations, excessively given to seeking pleasure in unhealthful diversions, to use their resources in more worthy social pursuits. The needs were no doubt apparent before Roman times but were well expressed by John of Salisbury in 1159.[101]

Sustainable Chemical Process Development in the Pharmaceutical Industry

As in all fields of endeavor, the pursuit of excellence in education and re-education, in any discipline, and particularly in the integration of disciplines that need to work together is the prime requirement for progress and success. Specialization is inevitable, but overspecialization and overfocus on narrow areas of endeavor (whether in a single science discipline or, in general, obsessing on a single diversionary pleasure) leads to narrow programming of the human mind. Excessive narrowing inhibits the

[99]The cost of uranium makes up between 5 and 10 percent of the total cost of electricity production in a nuclear power plant. Strikingly, 5 g of uranium corresponds to 700 kg of coal, which also emits up to 1.7 tonnes of CO_2! Vatanen, A. *The Scotsman*, March 9, 2007, p. 34.

[100]"A man who dares to waste one hour of life has not discovered the value of life."

[101]He railed against people wasting their time enjoying performers (jugglers, musicians, actors, etc.): "tedium steals upon unoccupied minds and they are not able to endure their own company unless they are pampered by the solace of some pleasure. Therefore spectacles and the countless hosts of vanities by which they who cannot endure to be entirely idle are occupied, but to their greater harm. Better it had been for them to have idled away their time than to have busied themselves to their own ruin. . ." from John of Salisbury's work, "Policraticus." What would he have said had he seen the excessive diversions that consume today's world.

ability to deal with the unexpected.[102] Managements in any field therefore need to ensure that the general philosophy in undertaking interdisciplinary work is founded on preservation of the freedom and climate to enable their educated creative scientists to express themselves in every collaboration.[103] Working in this way, managements in the chemical process development field create the best chance of discovering and developing the best[104] and most sustainable API manufacturing processes.

In terms of chemical process development, such a philosophy is not apparent today. In my experience, most new commercial processes for API manufacture are substantially suboptimal and therefore higher in cost than they should be. Generally, progress toward better processes has been compromised by the overly zealous compliance with regulatory guidance resulting from timid managements having succumbed to excessive misinterpretation of regulatory intent. Rightly the regulatory agencies (safety, environment, and FDA regulatory affairs) are continually striving to ensure that the public is protected from harm. A major regulatory objective is to prevent those entrepreneurs who have little regard for the consequences of their self-serving activities from inflicting harm.[105] Another objective is to raise standards to prevent those with inadequate knowledge (which might trigger an adverse event) from making mistakes. It is usually individuals and sometimes companies who are excessively focused on personal and corporate profit who, neglecting or ignoring consequences, spoil the field for the many reputable companies and individuals who take the care to accommodate consequences and to protect public health.

One possible solution, enabling chemists and engineers to create optimal processes, has been outlined in the earlier essay on Bureaucracy Reduction (q.v.).[106] The proposed solution allows for high-integrity people and companies to become qualified with special freedom to keep innovation going in practice throughout the whole exercise of developing a chemical process for use in API manufacture. Such an approach is in concert with the other great need, to raise education to a war footing.

In terms of creating sustainability, enhancing education and reducing bureaucracy need leadership and commitments from the most senior company executives. Such

[102] As an example, take the excessive use of the eyes only to tune manual dexterity to operate a computer game as fast as possible. An addiction to such excess may have the adverse effect of stunting other senses. As a result, language skills, people interactions, broad problem-solving abilities, general curiosity for the natural world, personal health, and so on, may be affected to the point of eventually impacting on survival.

[103] This is not a carte blanche freedom but envisaged as one needing to gain the support of visionary people, not bureaucrats. See comments on leadership in Chapter 2.

[104] Best in being the safest and most environmentally sound (including in waste minimization and recycling), with superior economics (in labor, equipment, and materials useage). Best is, of course, a relative term since frequently, even better processes emerge from ongoing research and development.

[105] Sadly, practices and laws that should be universal (not all laws should be) do not become so. It is astonishing that following the 1938, FDA-driven outlawing of the use of diethylene glycol in medicinal formulations (see Chapter 6), several countries have reported deaths caused by medicines contaminated with diethylene glycol; most recently, 88 children died in Haiti (1995/1996), 33 children died in India (1998), and more than 22 people died in Panama (2006).

[106] I can again challenge readers of this book to offer other practical alternatives to the chromatography-based system proposed.

support is essential but will need better internal company structures than now exist. An internal structure, which separates research and development from the time driven systems currently in place everywhere, is essential for the sustainable discovery of APIs and the development of processes to produce them. The current pressures for faster progress usually result in incomplete and short-term thinking. Financial investors and analysts play a large part in promoting company business strategies. They are often seen as asking companies "What have you done for me lately." They seek quarterly reports from an industry that moves only slowly. Such attitudes can play havoc with the selection and progression of a drug through the FDA approval process.

Excessive speed and disregard of the consequences of going very fast greatly increase the chance of making mistakes and missing API opportunities, as well as reducing costs. Despite this, stockholders and executives prefer to go for the best chance. Powering those APIs (which look likely to be approved by the FDA) through the system as fast as possible makes money for investors at the fastest possible rate. But speed is at the mercy of the clinical data. Unexpected clinical findings, with no clear understanding of the reasons, can greatly retard progression of an API through the FDA approval process.[107] Speed was also undoubtedly a factor in missing the opportunity to patent a metabolite of Schering–Plough's anti-androgen, Flutamide, thereby limiting the drug's market potential (see Chapter 6).

In chemical process development programs, discontinuities in introducing new processes, due to regulatory constraints, frequently cause the selection of suboptimal processes for development. Once established in manufacturing, even suboptimal processes can be difficult to replace (see earlier essay on Bureaucracy Reduction). Other agendas have also to be considered, as evidenced in our efforts to develop a new process for albuterol manufacture (see Chapter 5). In another case, lack of time, and perhaps also a lack of faith in the future market potential of Temozolomide, were major factors retarding the development of new processes for the manufacture of this API (see Case Study 2).

In the effort to pursue profit as rapidly as possible, short-term thinking is the ascendant philosophy. Today it is speed from the discovery phase to the market that is the accepted driving force of any pharmaceutical company. I know of no studies that might challenge this philosophy. But it may well not be true for those APIs where speed has caused potentially new APIs (e.g., metabolites) to be missed. And again, developing suboptimal processes is not only expensive in its own right, but later changing to a more efficient lower-cost process can take years at great expense (see Bureaucracy Reduction). As a result of all the turbulence associated with developing an API to the marketplace, including dealing with all the inhibitions to introducing optimal processes for API manufacture, it is clear that achieving sustainable development will be a difficult task. There is an urgent need for more enlightened

[107]The finding of cataracts in the clinical trials of Schering–Plough's anti-inflammatory drug, Flunixin, delayed the drug's approval. It took years to resolve the issue by which time the patent was near expiry. This led to Flunixin being marketed only as a lower profit animal health drug. Schering–Plough's nonsedating antihistamine, Loratadine also suffered long delays in gaining FDA approval due to being caught up in a liver enzyme induction issue raised by the FDA.

thinking on the structural changes needed to enable all of the research and development components in any endeavor, including industrial, university, and government components, to work together. Education, exploration, and experiment are all needed to determine how the earth's limited physical resources, from which all wealth is drawn, can be harvested by individual stable populations for the benefit of all life coexisting in a symbiotic way with the physical world. It seems, from the perspective of today's world scene, almost impossible to imagine sustainable development in a slowly evolving steady state world, managed by a reformed mankind. A stepwise progression is all we can promote starting with education, conservation, and population stabilization.

FANTASY

Introduction

I intend, in invoking fantasy, to provoke the wildest dreams and actions in those who can make a difference. There are many enormous "chemistry" problems to solve, with the human condition (the "chemistry" of the human brain, including brain diseases) providing the greatest challenges. Over the millennia the human condition has spawned many, many problems that grow larger with human development. Yet the consequences of human development seem to attract, proportionately, diminishing attention. Knowledge, to deal with consequences, is gathered only slowly and, sad to say, no bold visionaries are emerging with the power to lead the proactive and painful crusades required to restore balance. Of the many, many problems, educating people enabling them to become socially responsible is surely the core endeavor on the planet recognizing that education needs to be integrated with the reformulation of family and social (including religious) agendas to create and implement new action plans—in short an interdisciplinary endeavor. Unfortunately, problems increase as the planet becomes bogged down by overly self-serving activities, plagued by intolerance and befuddled by bureaucracy, leaving only a small-mindedness and a level of thinking about the future which is far, far too trivial.

There are two major, seemingly insoluble, problems in the world today. The first is the millennia old problem of population growth leading to organisations of people creating dominating social systems. The second is the "spaceship earth" problem, which is a major consequence of the first. Millennia ago, small consequences did not matter.

The first problem developed as barbarism, tyranny, empires, monarchs, religious zealots, and, more recently and more damaging, the ruling ideologies based on Socialism/Communism and Capitalism/Democracy, all even more reliant on the tools of power, gained dominance. Earlier, power was based on the ability to organize, in many cases aided by the marshaling forces of religious doctrines. The major driving forces resulted from the growth of populations leading to the take over of any fertile lands they could reach and hold to promote their prosperity. This evolved as the science-based creation of weaponry developed to sustain the ideologies euphemistically referred to as "modern civilizations." The development of the "spaceship earth" problem, dealing with human physical emissions, from both the developed and

developing populations, adds greatly to the pressure on civilization to reform. World leaders appear to recognize that the consequence of present expanding energy demands, and particularly the seemingly mindless conversion of the world's organic feedstock into carbon dioxide, even if much of it could be captured by plants and microorganisms to produce carbohydrates, is detrimental to the global environment (and, not incidentally, to the organic chemical industry of future centuries).

The time for implementing vigorous global solutions is on us. The consequences of power-imposed dominance and associated energy development have been neglected. In reality, governments of the Western world are only a political mindset away from overcoming the neglect of consequences. In the energy case, dominating narrow economic arguments (although now tempered by environmental issues) have impeded efforts to aggressively enhance investment in science/engineering to effect the wider use of solar, wind, wave, tide, hydroelectric (from glacial melting?), geothermal, and nuclear sources of energy (given greater efforts to deal with nuclear wastes). And although the narrow applications of science/engineering have enabled the powerful to create their dominations, the powerful are now recognizing that scientists and engineers need to be given a far more important role in determining the future of the planet—better brains beget better behavior.

The Pharmaceutical Industry

Greater understanding of the chemistry and functions of the brain and its central nervous system is perhaps the most challenging field of endeavor for scientists and engineers in the 21st century. It is a field of endeavor involving the major disciplines already integrated into pharmaceutical industry research and also into some university operations.

At the genetic level, vigorous work programs are already in place (for instance, on diseases such as Alzheimer's) to find and map and thus gain knowledge of all the genes involved in a disease with the expectation that this will provide a fundamental basis for drug design.

At the molecular level the chemical sciences are already involved in the mechanistic aspects and particularly in the analysis of brain processes in collaboration with many other disciplines. And although the chemical process development field has no direct link with chemical processes in the brain, except through the adaptation and application of those exquisite analytical techniques, such as NMR and MS, so vital to understanding chemical processes, the link is enough to provoke fantasies addressing one of the major brain problems the world faces, namely how to deal with illegal drugs.

The developed, science-based nations spend billions of dollars worldwide to try to eliminate their addicted populations' use of narcotics, hallucinogens, hypnotics, "controlled" analgesics, stimulants, and sedatives.[108] The education, monitoring, and rehabilitation of drug users has been going on for centuries and will undoubtedly grow with increased investment in education generally. On the supply side, drug dealers

[108]Plant-based ones include Morphine ex *Papaver somniferum*, Cocaine ex *Erythroxylon coca*, Hashish ex *cannabis sative*, Mescaline ex *Lophophora Williamsii* (source of peyote).

and transporters will continue to be pursued. Growers in Asia and South America will continue to live with ongoing eradication of their crops. Efforts will continue to provide incentives for growers to grow legitimate crops.

The ethical pharmaceutical industry will continue to look for profit in developing pharmacotherapies against addiction. The use of nature's basic plant structures as a route into legitimate ethical drugs has yielded a few useful commercial products in the case of the morphine alkaloids.[109] There have so far been no major successes along the line of the series of drugs produced from plant-derived steroid raw material where an astonishing variety of biological activities has been created.[110] This area may be worthy of further investment but may be limited to new approaches to creating anti-depression or other mood-altering and cognition–altering drugs. The ability of addictive, narcotic biological drugs to cross the blood–brain barrier might be harnessed by providing a handle for delivering, for example, anti-cancer drugs to the brain, though their usefulness may also be compromised if the new combination drugs lock onto brain receptors at their original principal locking sites.

The gravity and immense size of the world's drug addiction problem continues to attract enormous investment in the whole field of "brain chemistry," especially in the pharmaceutical industry, in universities, and by governments. Very large programs of research and development are going on covering the whole field of addiction, such as to alcohol, smoking, and illegal drugs.[111] These programs only maintain a status quo—larger programs might progress solutions.

The difficulties in treating addiction in general are compounded by the addict's willful lust for a short-term "fix," leading to difficulties in ensuring treatment compliance, and the all-too-frequent relapse and drop-out rates.

Currently, there are no options with guaranteed success for eliminating drug addiction, only hope and the determination to create a "universal cure" which will, no doubt, eventually happen, just as the world's accessible oil resource will, eventually, run out.[112] In the meantime, one can only offer partial solutions to slowing down the "drug trade." This is happening on several fronts already, with restrictions on the purchase and transport of certain chemicals used in making chemical drugs. For example, intermediates used for manufacturing the hazardous methamphetamine, such as pseudoephedrine (which illegal manufacturers extract from decongestion medications) and methyl phenyl ketone (still available, with restrictions, from one supply house), are being controlled, and in the first case replaced by other decongestants, where possible. There is also a case for governments to direct some of the massive and growing funding for combating drugs into selected existing programs such as

[109] A number of narcotic antagonists based on the morphinan structure have been marketed—for example, Buprenorphine, Naloxone, Naltrexone, and Nalorfine. Nalmefene is being pursued for the treatment of alcohol abuse. Oxycodone, and its precursor Codeine, are marketed, with restrictions, as analgesics.

[110] See Chapter 9, Table 3.

[111] For a good overview of these efforts see Thayer A. *Chemical and Engineering News*, 2006, September 25, pages 21–44.

[112] One draconian analogy lies in Aldous Huxley's *Brave New World*: His imagined society promoted immunization, at birth, of those who would serve in areas of the world where particular diseases are prevalent! The complexity of gene functions in the brain may preclude altering genes, though it may be possible to permanently alter particular cell types to affect gene activity.

some of those outlined in the Thayer overview (see footnote 111). A few of these programs might be evaluated and funded through oversight by the National Institutes of Health (NIH), say, initially, along the lines of support for orphan drug programs. Other ideas should be solicited for review by panels of experts in the diverse fields which one might expect to apply. I will offer a couple "starter" thoughts for the botanically based illegal drug field—one for the chemical/pharmaceutical industry and one for the biotechnology industry, specifically the seed industry.

The chemistry starter has two components. The first would ask for expert reviews to assess whether the illegal botanicals (see footnote 108) might conceivably be structurally manipulated to provide new activities, different from their controlled substance role, along the lines of the successes realized in the steroid field (see footnote 110). The second, which could be related to the first by providing new structures, would involve a search for chemical reactions (e.g., ozonolysis) that would radically alter the structure of the controlled substance, making it useful for a variety of other uses—say, as resolving agents or chiral induction agents for chiral synthesis, or as intermediates for agricultural applications (pesticides, herbicides, etc.), specialty polymers, antioxidants, chelating agents, and so on.

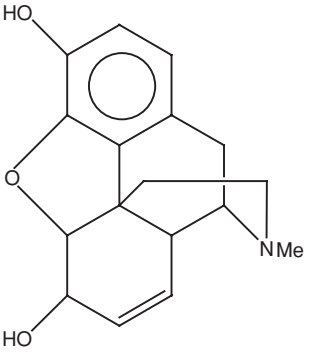
The chemical drugs, such as methamphetamine, present somewhat more of a problem since successes in dealing with the botanical illegal drugs seems likely to drive the addict to switch to the chemical ones. It may take many years of relentless education and constant public relations work, as in the case of tobacco addiction, to enable addicts to recognize, and react to, the severe life and health impacts of chemical drugs—sadly it seems unlikely that we will reform them all.

Finally, going back to the botanical illegal drugs, one has mostly to recognize that the principal drugs, the morphine alkaloids, cocaine, and to some extent marijuana, are mostly produced by people in alien cultures, where values and traditions differ and where the illegal drug industry is often a major contributor to the country's economy. It will always be difficult to persuade the farmers in these poor countries to switch to other crops when the drug lords offer so much more to the farmers for growing illegal crops. It appears that even the security gained through a lower income from a legal crop is not enough to offset losses in some years from government eradication programs.

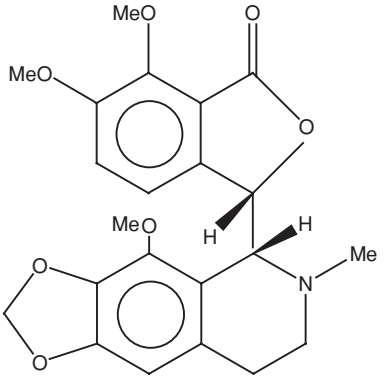
An action that might have a better chance of encouraging farmers to switch would be to offer a higher price for a legal crop coupled with a threat to implement an eradication program that would, forever, kill the illegal crop's ability to produce the offending addictive substance—much as the smallpox virus has been wiped out worldwide—if the farmer does not accept the offer.

Others working in the botanical world must have made the same suggestion years ago, from which it must be concluded that altering an offending plants genetics, cellular or enzyme systems to achieve such an objective must be difficult.

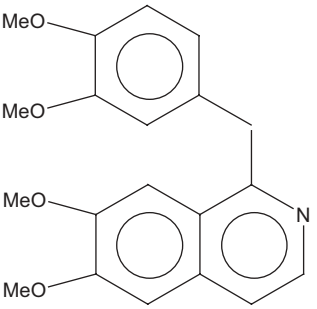
Nevertheless, in view of the gravity of the illegal drug problem, it may be worth re-appraising the idea from the platform of modern science. Take the poppy plant, Papaver somniferum, as an example. The plant produces opium, which is the air-dried milky exudate collected from incised unripe poppy-seed capsules. Opium contains a mixture of about 20 alkaloids which amount to ca 25% by weight of the opium. Of these 20 alkaloids the main ones are:



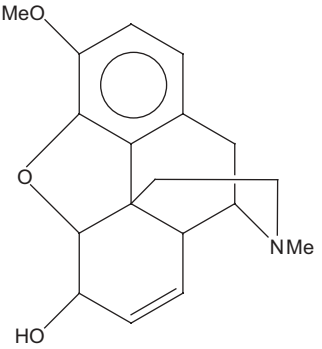
Morphine ~10–16%



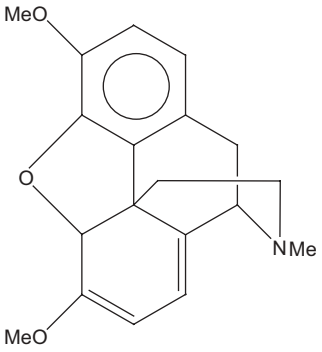
Noscapine ~ca 4–8%



Papaverine ~0.5–2.5%



Codeine ~0.8–2.5%



Thebaine ~0.5–2%

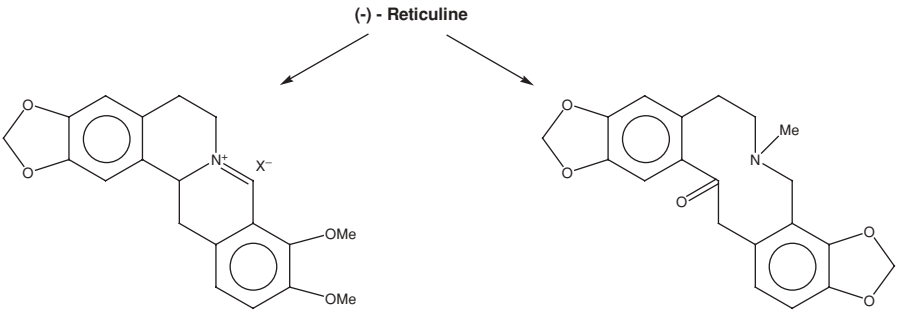
The amounts of these alkaloids in opium vary greatly with growing conditions and regions. Of the above, only noscapine and papaverine have no narcotic properties. Papaverine has found some medicinal use as an antispasmodic and cerebral vasodilator, and noscapine found use a few decades ago in antitussive preparations.

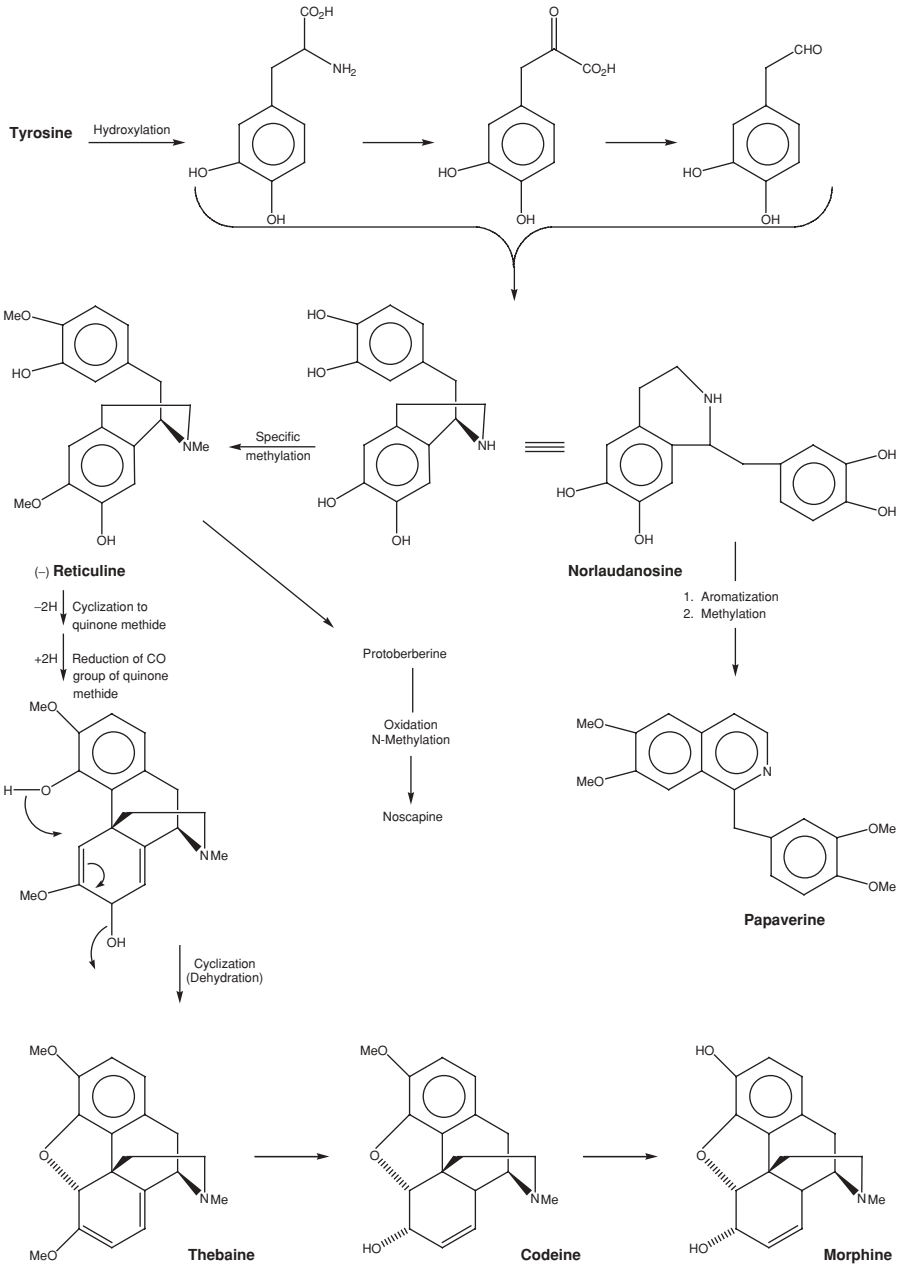
No doubt plant breeding programs, even in countries such as Afghanistan, by selection of seeds from high morphinan-producing plants, have enabled growers to significantly increase their production of the narcotic components. The questions thus arise, Can the biosynthesis of the morphinans be disrupted by interfering with the biochemical synthesis steps, and could seeds be generated with the property of guiding the biosynthesis of morphinans into useless products? The ultimate questions then become, Could seeds so derived be grown in massive quantities for aerial distribution over the growing fields of countries responsible for the heroin (diacetate of morphine) trade? Then, would such seeds provide plants and flowers to dilute or destroy the morphine-producing capability of plants already growing?

The task may not be such an easy one, although developments by commercial agricultural and seed companies like Monsanto suggest that, given the "seed money" to fund such an endeavor, seeds carrying the desired characteristics might be engineered. Monsanto's success with genetically modified soybean and tomato plants, to name just two, would augur well for such a venture. In addition, continuing with the poppy example, the known mechanism by which poppies biosynthesize the morphinans suggests several possibilities for inhibiting narcotic formation.

There would appear, from Scheme 4, to be many opportunities to modify the genetic material that creates the enzymes responsible for the biosynthesis of the morphinans. Blocking the specific methylation of norlaudanosine to (−) retuciline would be one worthwhile target, perhaps coupled with promoting the aromatization and methylation sequences leading from norlaudanosine to papaverine.

Even given that the formation of (−) reticuline cannot be blocked, there may be opportunities to block the biochemical sequences leading to thebaine, or even to splice in mechanisms leading to nonaddictive alkaloids produced from (−) reticuline by other plants—for example, berberine ex *Hydrastis canadensis* or protopine ex *Fumaria officinalis*.





SCHEME 4. The biosynthesis of the morphinans, papaverine and noscapine.

Conclusion

Aldous Huxley's proactive solution apart, it may ultimately be recognized that the addictive behaviors of some people cannot be dealt with by any of the ingenious means that can be imagined today. In the end, some horrific alternative to chemical pleasure stimulation might need to be supported, perhaps a science-fiction-type implantation of such as electrodes into addicted brains that can be coupled to stimulating inputs supervised in some government-organized pleasure center— equivalent to Aldous Huxley "Brave New World" feelies. Such "warehousing," coupled with an education process, may enable addicts to also take on a function in life which is satisfying to them and, preferably, useful.

I can conclude this fantasy by paraphrasing Einstein's statement at the beginning of this chapter: The problem of satisfying the pleasure requirements of the brain will only be resolved when we have gained the understandings needed to invent processes for dealing with them.

The bottom line, and the finale for this book, is that the world needs to fund more interdisciplinary science, at the same time as figuring out how to deal with the perceived consequences of all we have done and all we invent.

AUTHOR INDEX

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SUBJECT INDEX

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