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.

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!

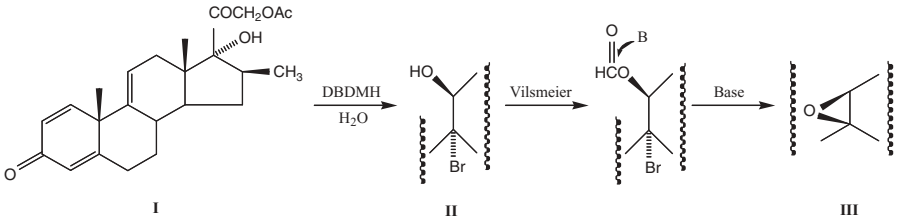
Bruce Shutts, like his supervisor at Bristol, Walt Williams, was born and raised in Pittsfield, Massachusetts, and was schooled in chemical engineering at Cornell University, New York. The Cornell chemical engineering program provides a comprehensive chemistry training as well as an excellent training 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.

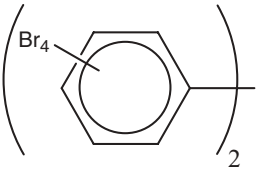
Chou had brominated steroid I with 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) to give the bromohydrin, II, which in turn was formylated (Vilsmeier reagent) and treated with base to give epoxide III:



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 . . .?