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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 integrated to create and develop a chemical process to meet all the needs.

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

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

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

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

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

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

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

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

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

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

The chapters in this book started out as handouts for a series of talks prepared for students of chemistry interested in the possibilities of a career in the chemical process development field. Some were also presented to my manufacturing colleagues at Schering–Plough. The chapters are based on the work carried out during my employment at several pharmaceutical companies (Arapahoe Chemicals/Syntex, Glaxo, Bristol–Myers, and Schering–Plough) in both the R&D and manufacturing areas. This diversity of experience enabled me to appreciate the need to accommodate the different objectives and philosophies that drive each company, and frequently divisions within companies. Add to this the iterative nature of the drug development field and one soon understands the need for flexibility in progressing the work of any organization. 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

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(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.