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Book Reviews *

Process Chemistry in the Pharmaceutical Industry. Edited by Kumar G. Gadamasetti. Marcel Dekker: New York, Basel. 1999. 473 pp. $195.00. ISBN 0-8247-1981-6

Readers of *Organic Process Research and Development* will need little reminding of the central value of innovative process chemistry to the long-term success of projects in the fine chemical industries, or of the intellectual satisfaction which can be gained by overcoming the numerous challenges and frustrations encountered in this area. Chemical development as a subject has traditionally been neglected in universities, and in comparison with most other areas of chemistry the literature is still relatively sparse. That situation is gradually being rectified; a number of excellent books on the subject have appeared during the past few years, and this latest example represents a very worthy addition to the canon.

Kumar Gadamasetti's book aims to give the reader an understanding of the basic principles involved in the development of the active ingredients of potential drugs. Its 23 chapters have been contributed by experts working within major pharmaceutical companies. Roughly half of the chapters present a specific case study, dealing with one or more target molecules which have reached an advanced level of clinical research, and in some cases commercialisation. A very wide range of molecular complexity, length of synthesis, and manufacturing scale is encompassed. While each case study emphasises its own particular problems in the degree to which they were encountered, the main theme of each is the evolution of the original drug discovery chemistry into a practical process for large scale operation. In describing these efforts, the authors have drawn attention to the multifaceted nature of process research. Masame Okabe (Hoffmann-La Roche), discussing the production of the steroid hormone calcitriol, describes efforts to understand the origin of a novel homologue impurity. Hans-Jürgen Federsel and Edip Jakupovik (Astra Production Chemicals) emphasise the importance of identifying a suitable intermediate which can be contracted out to toll manufacturers. This considerably simplified their process for the bronchodilator enprofylline. Derek Walker (Schering-Plough), in his chapter on the development of the beta-blocker dilevalol—an example of a racemate-to-enantiomer switch—reminds us that reactions with the highest enantiomeric excess do not necessarily translate into the most efficient processes in terms of cost and/or throughput. Other chapters emphasise the cost and availability of raw materials and the most efficient use of them to provide a competitive process. This involves strategic selection of synthetic routes, consideration of solvent and reagent recovery—particularly of expensive chiral auxiliaries, minimisation of unit operations, efficient use of reactor space, ease of handling of materials, avoidance of highly toxic reagents, and the control of potentially dangerous exotherms. To reconcile all these demands there is often a need to develop genuinely innovative chemistry, to say nothing of the increasingly narrow time frames in which this is to be accomplished.

Most of these case studies have been previously presented, at least in part, at process development or scale-up conferences. A few have even appeared as papers in this journal. This in no way detracts from the value of the book, as this format allows the authors to take a more wide-ranging overview of the subject and allows the reader to consider the chemistry at leisure—freed from the time constraints of a conference presentation. Copious literature references are provided in each case.

To complement the case studies the remaining chapters concentrate on particular recurrent themes. For example, Christopher Cimarusti (Bristol-Myers Squibb) discusses company strategies for the effective deployment of research resources to meet the challenge of accelerated process development—getting the candidate drug to market as quickly as possible. Other chapters focus on enzymatic intervention, the use of phase transfer catalysis technology, the development of the drug substance solid form, the assessment of thermal process safety, the use of statistical experimental design for process optimisation, and the increasing importance of laboratory automation for the rapid generation of process information. The pre-eminence of enantiopure drugs in the modern marketplace is reflected in the fact that three chapters are devoted to asymmetric synthesis and related topics. These special topic chapters enunciate the general principles and illustrate them with examples—mostly drawn from the contributor's own company, although in some cases a more wide-ranging review is provided.

I personally would have liked to see an additional chapter dedicated to the influence of regulatory considerations on the development of the process; this is a curious omission, given the book's focus on the pharmaceutical industry. Some of the case studies do deal with drug substance purity and the evolution of specifications both for raw materials and the final drug substance, but there is little about strategies for defining critical process parameters and nothing about process validation. Some general discussion of these areas would, I am sure, have been widely welcomed.

That aside, this volume gives a thorough overview of the challenges facing the modern development chemist in the pharmaceutical industry. It can be recommended to any graduates or post-graduates considering a career in this fascinating field, and even old hands will find much stimulating chemistry in the case studies.

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*Unsigned book reviews are by the Editor.

Analysis, Synthesis and Design of Chemical Processes. by R. Turton, R. C. Bailie, W. B. Whiting, and J. A. Shaeiwitz. Prentice Hall: New Jersey, 1999. 814 pp. ISBN 0-13-570565-70. £66.

The inspiring title of the book and a brief glance at the contents pages, where there are five sections (economic analysis, technical analysis, system performance analysis, optimisation, and the engineer, the environment, and communications) filled me with optimism as I began to read this book, which arose from teaching experience by the authors at West Virginia University in the Chemical Engineering Department. I was hoping for a chemical engineering text that was appropriate for both chemists and chemical engineers in the batch/semibatch fine chemical industries. The book, however, is still focused on the petrochemical/bulk chemical industries and the examples refer mostly to the design of processes for the manufacture of commodity chemicals such as dimethyl ether, acetone, acrylic acid, heptenes, allyl chloride, etc.

There is much to admire in this comprehensive volume—the chapters on flow diagrams, cost estimation and profitability analysis, understanding process conditions, regulating process conditions, process trouble shooting, and process optimisation all make interesting reading. The section on ethics and professionalism is unusual in a technical text, and its inclusion, whilst admirable, says much about our present society. Health, safety, and environmental issues are also covered, but not enough attention is given to toxicity hazards and reactive chemical hazards. A chapter on written and oral communications emphasises that the book arose from a university course (a report writing case study is also provided but seems inappropriate here). There are useful appendices relating to capital cost estimation, information for the design of four chemical processes, and design projects such as increasing the production of allyl chloride in a 20,000 t/a facility or scale down of phthalic anhydride production and design of a 100,000 t/a cumene production facility.

In summary, the focus of the book is on design—analysis and synthesis mean different things to the chemist and the engineer. For example, quality control issues are hardly mentioned, and chemical synthesis is not mentioned at all. The book is well produced and a good value; a minor criticism is that the subject index is poor (five pages)—it is easier to find what you need by using the 11 detailed contents pages than by using the index. In conclusion, this volume is well worth exploring, given the limitations of scope mentioned earlier.

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Hydrolases in Organic Synthesis. . by U. T. Bornscheuer and R. J. Kaslauskas. Wiley-VCH: Weinheim, 1999. 336 pp. ISBN 3-527-30104-6.

This an excellent book by two highly qualified experts in the field. Bornscheuer and Kaslauskas have set out, and succeeded, in producing a definitive manual on hydrolytic enzymes (especially lipases, esterases, and proteases) for organic chemists. The book opens with a short introduction followed by an excellent account of the structure and availability of lipases, esterases, and proteases. In view of the important contributions made by Kaslauskas to our understanding of lipase structure and mechanism, this chapter is authoritatively written and contains much useful information distilled from the literature. The chapter concludes with an interesting section on directed evolution, an area of research that promises much for the optimisation of enzyme activity and stability. Chapters 3 and 4 deal with the practical aspects of using hydrolytic enzymes in the laboratory, followed by two excellent chapters, 5 and 6, which give numerous examples of the range of chiral intermediates that can be prepared using lipases. These two chapters are organised in a way that will be appealing to organic chemists since the authors make use of high quality diagrams to illustrate the complementary specificity of the different enzymes. Chapters 7, 8, and 9 continue in the same vein, covering phospholipases, proteases, and esterases, respectively. The only minor criticism by this reviewer is that chapters 10, 11, and 12, which conclude the survey of hydrolytic enzymes by covering epoxide hydrolases, nitrile hydrolases, and glycosidases, respectively, do not do complete justice to the volume of literature associated with these enzymes. The book concludes with a 100-page section devoted to references which represents an invaluable resource. Remarkably this book, which arrived on my desk in late May, contains some 1999 citations, a tribute to the efficiency and hard work of both the authors and publishers.

This is quite simply the best book of its type and can be unreservedly recommended to organic chemists who have an interest in using hydrolytic enzymes in synthesis. In view of the continuing increase in the use of biocatalysis for organic synthesis, I suspect that this book will become a classic before too long.

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