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# *Book Reviews* *

**Polymorphism in the Pharmaceutical Industry.** Edited by R. Hilfiker. Wiley-VCH: Weinheim. 2006. 414 + xix pp. £105. ISBN 3-527-31146-7.

Organic process chemists and engineers will welcome the appearance of another book devoted to the increasingly important topic of polymorphism. Of course polymorphism is not only important in the pharmaceutical industry but in other areas also (dyestuffs and pigments, explosives, etc.), but the major impact is in pharmaceuticals. This multi-author work covers not only polymorphism, but all aspects of production and analysis of crystal forms, including hydrates/solvates, salt selection, and the amorphous state.

After a brief, but useful, introduction from the editor and his colleagues at Solvias, the thermodynamics of polymorphs is discussed by S. Lohani and D. J. W. Grant. This is followed by chapters on various techniques used to characterise polymorphs and polymorphic systems such as thermal analysis (37 pp), solid-state NMR (13 pp), vibrational spectroscopy (44 pp), crystallography (38 pp), and microscopy (33 pp).

Chapters on "The Importance of Solvates", "Characterisation of Hygroscopicity", and "Polymorphism Screening" are of much more interest to the process chemist than the earlier analytical chapters, and this continues with chapters on "Salt Selection", in which excellent unpublished case studies from Novartis are presented, and "Processing Induced Phase Transformations" where the implications for product quality are discussed.

The quality of the chapters is high, although I would have liked to see more real-life examples of modern pharmaceuticals evaluated rather than the "old favourites" such as carbamazepine. Perhaps more industrial authors would have helped on this.

A major omission is the absence of discussion of polymorphism from the generic manufacturing viewpoint, where, to avoid infringement the generic company may have to produce the less stable polymorph in bulk and to show, by appropriate analytical methods, that they are not infringing patents. This is a challenging area and could have included sections on seeding issues, filtration, and drying (with the importance of choice of equipment for control of polymorph/solvate form). Particle size control and size reduction methods often have an impact on control of polymorphs, amorphicity, and product stability, and I felt these issues could have been included in more depth, from a scale-up and manufacturing viewpoint.

The penultimate chapter by Joel Bernstein on "Polymorphs and Patents from a Chemist's Point of View" is an updated version of his summary in his own monograph "Polymorphism in Molecular Crystals" (Oxford University Press, 2002). As well as discussion of the Raintidine Hydrochloride and Cefadroxil cases, this new account includes Paroxetine Hydrochloride cases, especially GSK versus Apotex. He also has a section on the importance of seeding—i.e., intentional seeding. Overall, this chapter is a very readable, if short, summary of the controversies that arise in patent litigation involved with the nature, identity, production, analysis, and quantification of crystal forms.

Finally, the editor has persuaded three scientists from the FDA to contribute an extremely interesting chapter on "Scientific Consideration of Pharmaceutical Solid Polymorphism on Regulatory Applications" which discusses effects on bioavailability and bioequivalence of drug substance and product stability and manufacturing issues, as well as control and acceptance criteria. In the final section there is a brief introduction to process analytical technology in drug substance and product.

The compilation is highly recommended reading for all in process R&D and manufacture. Those who are actively involved in polymorphism research and development, or analytics will wish to have a personal copy.

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**Fundamentals of Early Clinical Drug Development: From Synthesis Design to Formulation.** Edited by A. F. Abdel-Magid and S. Caron. Wiley: New Jersey. 2006. 323 pp. £58.95. ISBN 0-471-69278-6.

The editors are to be congratulated on persuading many process chemists and engineers to contribute chapters to this new book, which looks at case studies in process R&D, as well as other aspects of drug development. The book arose from a symposium of the same name in 2003; the editors, however, should probably have changed the name of the book to reflect the contents, which are mainly of interest to process R&D chemists.

The main chapters comprise case studies of process R&D and scale-up and indicate where problems have arisen and describe the solutions to the problem. An advantage of the book format, compared to that of a research paper, is that the philosophy behind the chosen approach can be discussed in more detail and this provides the reader with more insight on strategies in process R&D as well as technical aspects.

All the early chapters provide excellent case studies so it is difficult to choose those to exemplify in this review. The chapter by John Ragan from Pfizer on heterocyclic cross-coupling discusses the reasons for the lack of reproducibility in scale-up of a Negichi coupling. This resulted in Pfizer choosing a Stille coupling to generate early supplies, and the scale-up of this process is also discussed.

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Scientists from GSK describe the synthetic routes to a complex HIV protease inhibitor, with emphasis on identifying impurities in intermediates and final products. The strategy discussed is that knowledge of key impurities allows subsequent later-stage changes in the synthetic route to be monitored carefully so that they do not impact the overall impurity profile of the API. Such a strategy allows for more flexibility in synthetic route design.

In developing an asymmetric synthesis of an anti-cancer agent, workers from Abbott developed an organozinc addition to an α-keto menthyl ester. Key issues in the scale-up of this reaction including the method of generation of the organozinc reagent, agitation rate, and order/rate of addition of the reagent are discussed in detail.

The book also contains additional chapters which are not related to synthetic chemistry but are, nevertheless, of great interest to the synthetic chemist. Additional chapters include "Outsourcing − the Challenge of Science, Speed and Quality", "Automation and the Changing Face of Process Research . . .", "Large-Scale Synthesis − an Engineering Perspective", and "Selection of the Drug Form in Exploratory Development".

"Strategies to Achieve Particle Size of APIs" is a short chapter by scientists from Pfizer which discusses the advantages and disadvantages of control of particle size by direct crystallisation methods (e.g., impinging jet crystallisation), by wet milling, and also by the various dry milling approaches. In each case the implications for scale-up and the types of equipment available are evaluated. A strategy for selection of the appropriate particle size reduction method is then presented.

The following chapter "Challenges in Early Formulation: Turning Drug Substance into Drug Product" describes GSK's experiences in this area and is a useful guide for development chemists on preformulation and the art of the formulation.

The final chapter on "Intellectual Property and Early Development" by Maria Schuka from J&J covers key issues including process patents and patents on salts, polymorphs, solvates, etc. The latter discussion would have benefited from a recent example (e.g., paroxetine or ranitidine) and could have mentioned the critical issue of disappearing polymorphs. But other than this minor criticism, this is a valuable summary of patent issues for development chemists, and something which is not available elsewhere. Thus, this chapter has no references.

Overall, this is an excellent book which adds to the increasing literature on process R&D. It is highly recommended to all scientists involved in developing new processes for APIs.

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**Handbook of Industrial Biocatalysis.** Edited by Ching T. Hou. CRC/Taylor & Francis: Boca Raton, FL. 2005. 557 pp + xv. $179.95. ISBN 0824724232.

The title of the book fails to specify that the focus of the book is towards the oils and fats and food industry, with only one chapter—that by Ramesh Patel of Bristol Myers Squibb (Synthesis of Chiral Intermediates for Pharmaceuticals)—of interest to the majority of *Org. Process Res. Dev.* readers.

However, the book covers an area that has not been covered earlier, and those interested in industrial biocatalysis—and in green chemistry—will learn a lot from many of the chapters. I particularly enjoyed "Carbohydrate Active Enzymes for the Production of Oligosaccharides" by H. Taniguchi. In the introduction to the chapter, he informs us that the total production of oligosaccharides in Japan amounts to 60,000 tonnes with a value of 15 trillion yen in 2001. He lists 13 major products with the price of the biocatalyst and the Japanese manufacturer. He also lists the sources of the biocatalysts—mostly from starches and sugars, of course. The rest of the chapter focuses on the production processes for the manufacture of several oligosaccharides, mostly for use as sweeteners in the food industry.

Another chapter of interest to chemists and engineers will be "Enzymatic Production of Diacylglycerol . . ." by authors from Kao Corporation in Japan. The early part of this chapter concentrates on the choice of reaction type for industrial processing and the advantages and disadvantages of each type.

Scientists from the fine chemicals and pharmaceuticals industries will also enjoy reading about "Biocatalysts for the Epoxidation and Hydroxylation of Fatty Acids and Fatty Alcohols" where the focus is on P450 mono-oxygenases. The authors, from the University of Stuttgart, speculate that these biocatalysts, which can catalyse dehydrogenation as well as hydroxylation and epoxidation, should be more widely used in organic synthesis.

In conclusion, for those scientists working in the oils and fats industries, or in cosmetics, food, and related areas, this compilation of 29 chapters will be an invaluable source of information, particularly from Japanese literature sources. A criticism could be that for a work devoted to Industrial Biocatalysis, very few of the chapter authors are actually from industry.

For those in fine chemicals and pharmaceuticals, there are some interesting chapters, which I have highlighted, but these probably warrant borrowing the book from a library rather than individual purchase.

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