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Book Reviews

Pharmaceutical Substances, Syntheses, Patents, Applications, 5th ed. by A. Kleeman, J. Engel, B. Kutscher and D. Reichert. Thieme: Stuttgart, 2009. ISBN 978-3-13-558405-8. Hardback. pp 1722 (including indices).

The fourth edition of *Pharmaceutical Substances* was printed in 2001, and in the intervening time the authors note there have been significant changes in the pharmaceutical sector with once well-known vendors having disappeared or changed names. In addition, a vast number of brand names have disappeared or changed, drugs have been withdrawn or sold to another vendor, and many drugs have become generic after their patents expired. The authors also make the point that there is an electronic version (which I have previously reviewed), and although that version is constantly updated (for instance, version 3.0, updated in June 2007, was the seventh update since its launch in November 2003), many users approached the authors and publishers to request an updated printed version. In response, this new edition is now available with 165 new monograph entries, revisions to existing entries, and countless changes to vendor and trade names. This edition contains about 1300 active pharmaceutical ingredients (APIs) with a very useful alphabetical list of monographs in the opening section wherein those included in the printed version are highlighted in bold-face print and additional entries in the electronic version are included in light-face print. This is a very helpful means to show the contents and illustrate the two sources of information available to users.

The following information is given in each monograph: chemical structure, synthetic route, intermediates, nomenclature (INN standard, trivial names, synonyms), CAS registry number, ATC codes, medical applications/therapeutic category, toxicological data, patent information (number, origin, holder and application date), commercial information such as trade names.

To the rear of the book is a second very useful set of indices. The first lists trade names of the contained APIs, and thus complements the previously mentioned API names index. A second index I've found very useful is a list of intermediates, giving the drugs in which they are used. Finally, the index of substance classes can also be very helpful.

I have used this specific edition of the text consistently for a couple of months now, and it is on the basis of this continual use that I have compiled this review. Overall, it is an excellent text full of useful information which is very readily accessed. It can be used on its own or in concert with the electronic version where more general searching can be performed using keywords. Thank you to the authors and publishers for this updated printed version which I use as the first point of reference to very quickly check information about an API whose name I know.

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Organic Reactions. S. E. Denmark, Ed. Wiley: Hoboken NJ. 2008. Vol. 72. 704 + ix pages. £93.50. ISBN 978-0-470-42374-5.

Organic Reactions (OR) reviews are intended for the practical synthetic chemist, enabling the practioner not only to quickly assimilate the history of a particular transformation and its substrate tolerance but also to get to grips with how the changes in experimental conditions affect the yield and byproduct formation. As such, the mandatory section or "scope and limitations" is possibly the most valuable, along with the experimental summaries.

The latest volume begins with a review of "Electrophilic Amination of Carbanions" by Engelbert Ciganek, who has already contributed to several chapters of OR. This first review involves displacement of N−X bonds and additions to N═Y bonds to produce more functionalised amines. These are useful reactions, particularly the first type; the second require further transformation of the intermediate to reveal the amine, and the review does not, unfortunately, discuss this aspect (although details are given in the experimental). Surely the "deprotection" is an integral part of the amination procedure when considering a synthetic strategy! As usual, this review is otherwise of a high standard, with the emphasis on practical issues, rather than mechanisms. Literature coverage is to 2007.

Sulfones are increasingly used in organic synthetic procedures but are not often desired in the final molecule and thus need to be removed. The second and final chapter in this latest volume of OR is on "Desulfonylation Reactions" by Diego Alonso and Carmen Nájera from the University of Alicante, Spain. In this chapter, in addition to covering the practical aspects, there is a lot more mechanistic discussion of the intermediates generated by the different reducing agents and how this affects the stereochemistry of the products. Deuterisation studies are useful in this context.

Some of the procedures in this review are very environmentally unfriendly − particularly the use of mercury salts and amalgams. The authors have pointed out some of the hazards of these, and other reagents, and have provided methods by which to trap the mercury. In general the safety warnings in this chapter are highly commendable.

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In conclusion, this latest volume of *Organic Reactions* lives up to the high standard of previous volumes, and the series fills a gap not provided by journals and other monographs. Long may it continue!

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Validation of Pharmaceutical Processes, 3rd ed. By J. Agalloco and F. J. Carleton. Informa Healthcare: New York. 2008. 737 + xvi pages. ISBN 978-0-8493-7055-7. £165.

For the 3rd edition of this well-produced compendium, written by approximately 20 experts in the field, one would think that a suitable subtitle should be "All you need to know about process validation". If you are involved in sterile product manufacture, sterilisation, sanitization and sterility assurance, then this may well be appropriate.

For readers of *Org. Process Res. Dev.* (OPRD) who may be more interested in primary manufacture of nonsterile bulk pharmaceutical chemicals (to use an older term constantly used in this book) rather than active pharmacutical ingredient (API), there are only a few chapters which will interest them specifically, apart from the introductory chapters such as "Organising for Validation and Facility Design".

Section VI is devoted to Primary Manufacturing and begins with Validation of Bulk Pharmaceutical Chemicals (12 pp) − this is far too short to do justice to this important topic and is a rather dated approach − the key concepts of critical process parameters and proven acceptable ranges are not covered. Perhaps a clue to the chapter is in the references in that none date after 2000; it is almost as if this chapter has not been updated from the previous edition! Of more application to process chemists are chapters on "Validation of Recovery and Purification Processes" and "Validation of Process Chromatography" even though the latter focuses on biopharmaceuticals.

Section VII covers Manufacturing Related Activities and begins with an excellent overview of cleaning validation (28 pp) which includes much practical advice. Process chemists will also value chapters related to outsourcing, such as "Vendor Qualification and Validation" and "Validation and Contract Manufacturing". The latter contains some useful tables and checklists.

A brief overview of "Validation and Six Sigma" mentions DOE and the importance of use of statistical methods in validation, although DOE (Design of Experiments) and factorial design are terms which all fail to get indexed. The concept of the risk-based approach using process understanding rarely gets a mention in the book, and then only in passing.

"PAT and Validation" is an excellent chapter which lists methods used, the attribute analysed, and whether on-line, in-line or at-line; there are even references to OPRD articles. In fact this is one of the best chapters for having comprehensive and up-to-date references (121), whereas most chapters have only a few.

This reflects on the book as a whole; those chapters with few references tend to be of a more general nature without specific examples. For the process chemists, it is the examples which highlight what needs to be done in validating a process, and these are the chapters which make recommended reading, as I have highlighted.

Thus, in a volume of over 700 pages, there will be only 100−150 pages which will interest the process chemist and engineer involved in API development and manufacture. For those involved in secondary manufacturing, there are more chapters of interest. Thus, I can only give a partial recommendation.

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Modern Pharmaceutics, 5th ed. Edited by Alexander T. Florence and Juergen Siepmann. Informa Healthcare: London. 2009. £215. 2 Volumes. ISBN 978-142006566-4 and 978-142006564-0.

The fifth edition of *Modern Pharmaceutics* is long overdue. Now in two volumes covering Basic Principles and Systems (Vol. 1) and Applications and Advances (Vol. 2), it covers everything you need to know about this important subject. New additions and contributions have enhanced an excellent pair of volumes.

For readers of *Organic Process Research & Development* (OPRD), for whom pharmaceutics may be of more peripheral interest, there is an excellent chapter by Alastair Florence (University of Strathclyde) on the Solid State - almost 50 pages covering issues such as polymorphism and solvation. The coverage is up-to-date with lots of references including some from OPRD.

For those chemists and engineers wishing to learn about the different dosage forms and their applications, this is an excellent book. A minor criticism would be that the contributors are mostly from academia, apart from two specialist chapters on Ophthalmic and Veterinary products. So there is a lack of discussion of pharmaceutics issues related to scale-up, manufacture, and storage.

For this reason, nonspecialists may prefer the recently published second edition of *Pharmaceutical Preformulation and Formulation*, (edited by Mark Gibson of AstraZeneca, from the same publisher) which is more limited in scope, but much more industrially focussed.

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Polymorphism in Pharmaceutical Solids, 2nd ed. Edited by Harry G. Brittain. Informa Healthcare: London, New York. 2009: 640+ xi pages. £150. ISBN 978-142007321-8.

The second edition of *Polymorphism in Pharmaceutical Solids* - last published about 10 years ago - is most welcome.

The editor, who has also contributed several chapters, has recruited some new chapter authors, including some British experts to expand the scope from the original edition. All chapters have been updated, and coverage of the literature is up to 2008.

The volume is divided into six sections beginning with Thermodynamic and Theoretical Issues. In this section a new chapter on Computational Methodologies: Towards Crystal Structure Prediction by one of the experts in the field, Sally Price, describes the considerable advances that have been made in the field in the last 10 years.

Of perhaps more direct interest to process chemists is part II, entitled "Preparative Methods for Polymorphs and Solvatomorphs" (solvates and hydrates to the practicing chemist!). This section is geared more towards screening and preparing all forms of a substance for analysis, rather than a single form for manufacture. Two new contributors, Peter Cains (Avantium) and Alistair Florence (University of Strathclyde), each contribute chapters, the latter focussing on High Throughput Screening Methods.

The main body of the book is on structural and analytical aspects, to assist characterisation, and sections III and IV cover these areas in depth. Cocrystals are covered in a new chapter. The characterisation section is divided neatly into Thermoanalytical and Crystallographic Methods, Vibrational Spectroscopy, and Solid State NMR, with a final excellent chapter on Solubility and Dissolution Rate - how this is affected by polymorphism and solvation.

Part V covers interconversion of forms, with the editor supplying his eighth chapter (a magnificent effort!) on solid-state transformations, as well as a chapter of great relevance and interest to chemists/engineers in industry entitled "Effects of Pharmaceutical Processing on the Solid Form of Drug and Excipient Materials.

Finally in part VI there are chapters on Structural Aspects of Molecular Dissymmetry (the editor again!) and a welcome finale on Amorphous Solids.

Overall, this is an excellent book which is highly recommended to all who work in this field, whether in pharmaceuticals, fine chemicals, pigments, chemicals for electronics, etc. Despite the title referring to pharmaceuticals, there are many examples from fine chemicals, and the theoretical, structural, and characterisation sections are relevant across many industries. The editor is to be commended not only for contributing to nine chapters himself but also for gathering such an excellent team to contribute and complement his leadership.

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Thermal Safety of Chemical Processes: Risk Assessment and Process Design. By Francis Stoessel. Wiley-VCH: Weinheim. 2008. 374pp. Euro 99.00. ISBN: 978-3-527-31712-7.

This book should be essential reading for anyone entering process safety and is also highly recommended for anyone involved in chemical process development, scale up or production. It contains 13 chapters organised into 3 sections, which are entitled "General Aspects of Thermal Safety", Mastering Exothermal Reactions", and "Avoiding Secondary Reactions". In this way it covers all the relevant and necessary aspects of process safety, covering topics such as Risk Analysis, Fundamentals of Process Safety, Assessment of Thermal Risks, Experimental Techniques, Genral Aspects of Reactor Safety, Batch Reactors, Semibatch Reactors, Continuous Reactors, Technical Aspects of Reactor Safety, Risk Reducing Measures, Thermal Stability, Autocatalytic Reactions, and Heat Confinement.

Each chapter starts with a short case history illustrating a problem relevant to the forthcoming chapter. The event is discussed in terms of the lessons that can be learnt or how better decisions could have been made either by making better use of the existing data or by obtaining more data. There are also a large number of worked examples in all chapters, except for the introduction, which help to illustrate the concepts and ideas being presented. These examples illustrate how various worst-case scenarios and safety measures can be assessed and the data and equations that need to be used and how to use them. At this point it is worth warning synthetic organic chemists that the book does contain a significant number of mathematical equations, but these are explained well and are, of course, essential for the manipulation, interrogation, and understanding of the data.

Many different reaction types are considered along with secondary reactions and runaways, and even here different runaway types are discussed. Similarly all the main reactor types, batch, semibatch and various continuous reactors, such as continuous stirred tank reactors (single and cascades), tubular reactors, and microreactors are covered. Many of the ideas discussed will not be new to experienced workers in the area, but this book is nevertheless a very welcome addition to the library of process chemistry and engineering. Strongly recommended.

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Theilheimer's Synthetic Methods of Organic Chemistry. Edited by G. Tozer-Hotchkiss. Karger Publishing: Basel, Switzerland. 2009. Volume 74. 457+ xix pages. $790.00. ISBN 978-3805-59235-2.

I make no bones about it - I am a great fan of the Theilheimer series and have been for decades. The latest volume covers the synthetic chemistry literature up to December 2008. I particularly enjoy the opening section on "Trends and Developments in Synthetic Organic Chemistry 2009". In these 6 pages (43 references), the essence of the

previous year's research is distilled into useful fractions/paragraphs; references are up to May 2009.

As always, the focus is on practicality, with experimental procedures highlighted and scope of reactions discussed. Of course, readers will eventually want to access the original paper, but use of Theilheimer makes discovery of that important paper more likely.

But, to my mind, Theilheimer would not be as useful without the comprehensive 55-page index, which not only lists subjects but also relates them to syntheses (e.g., Azides, starting materials for amines; amines from azides). Excellent cross-referencing makes this the most useful compilation.

There is also a comprehensive listing of review articles (15 pp) divided into sections (e.g., Heterocyclic Chemistry, Transition Metal Catalysis, Name Reactions, Multicomponent Synthesis). This listing covers reviews from Nov 2008−April 2009. It is a commendable achievement to be so up-to-date.

In summary, this latest volume of Theilheimer is, despite its high price, good value and is highly recommended to synthetic chemists in industry and academia.

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