Book Reviews

Drug Metabolism Databases and High-Throughput Testing During Drug Design and Development. Edited by Paul W. Ehrhardt. International Union of Pure and Applied Chemistry, Blackwell Science, Ltd., Malden, MA. 1999. 340 pp. 19 x 25 cm. ISBN 0-632-05342-9. $60.00.

This book is the result of deliberations of a Working Party of the IUPAC, assembled to consider the topic Metabolism Databases and Their Potential Utility in the Development of New Drugs. Paul Ehrhardt, the technical editor for this volume, was the chair of the Working Party. His introduction provides a historical perspective and highlights some of the biological considerations that contribute to poor predictability of drug metabolism in humans. The book is arranged in three sections. The first contains several historical case studies describing the use of metabolism expert systems or databases in the pharmaceutical industry. The middle section contains monographs on various techniques for high-throughput screening of drug candidates, descriptions of ex vivo models of drug metabolism, and chapters on the use of metabolism databases in drug design. The final section of the book, entitled Emerging Products, contains contributions from vendors of commercial products. Expert systems and metabolism databases are described briefly. The appendix contains tables of commercially available drug metabolism databases and contract research organizations that conduct high-throughput screening. A glossary is also provided.

The first section of the book, Case Studies, is well-balanced and provides thought provoking and entertaining examples of the utility of various databases available from 1985−1995. Several evaluations of the effectiveness of expert systems to predict drug metabolism are presented. Specific drug examples from industrial scientists illustrate the difficulty of prediction and indicate the difficulties in quantitative prediction with "expert" systems. Descriptions of searchable metabolism databases used at Parke-Davis, Eli Lilly, and Baeyer provide clear examples of what information should be included in these databases. However, a chapter submitted from Daiichi Pharmaceutical consists almost entirely of metabolic schemes for two drugs and a discussion is missing. The section ends with a chapter on the design and development of two prodrugs, esmolol and imidazolone, but this seems out of place with the previous chapters.

The organization of the middle section of the book is disjointed. The first chapter describes the determination of drug permeability of the Caco-2 colon cell line for prediction of gastrointestinal absorption and would have been more logically placed with the other chapters on high-throughput screening. Unfortunately, the use of the Caco-2 system to study the role of intestinal transporters and efflux pumps such as P-glycoprotein in drug absorption is not included in this chapter. This section includes a chapter on preclinical drug metabolism screening, screening for inhibition of P-450 metabolism, and pharmacokinetic screening by the N-in-one (cassette dosing) technique. These chapters are well-written, and they critically evaluate the techniques and problems arising from high-throughput screening.

The second chapter in the section the contains a lengthy introduction on the cytochrome P450 system. This may be useful to novices in the drug metabolism field, but the rest of the book appears to be targeted to a more knowledgeable audience. The second half of the chapter describes the administration of a drug cocktail consisting of several individual P450 enzyme substrates to predict the clearance of drugs in an individual through a “handprint strategy”. This material does not relate to either high-throughput screening or ex vivo models of drug metabolism. A commentary on the importance of developing databases of drug interactions (by using antiepileptic drug examples) would have been more logically placed after the high-throughput screening chapters. Three short chapters on model systems to predict P450-mediated metabolism are located between chapters on high-throughput screening of drug metabolism. Chapters on the use of microorganisms as model systems of drug metabolism and synthetic metalloporphyrins as P450-like catalysts highlight other experimental techniques for ex vivo prediction of oxidative metabolism.

An interesting chapter describes the use of a database called the Encyclopedia of *E. coli* Genes and Metabolism (EcoCyc) used to identify novel targets for antimicrobial drug discovery. The section ends with more traditional discussions of the use of metabolism databases to design prodrugs and codrugs and the design of soft drugs.

The final section of the book was written by several commercial vendors (not associated with the IUPAC Working Group) and describes products such as MetabpolExpert, META, and Metabolite. Descriptions of two metabolic databases from Synopsys and LHASA UK, Ltd. are included. These chapters are brief and descriptive in nature, but along with the appendix will be useful for those in the pharmaceutical industry who are interested in a general overview of the currently available products.

The potential audience for this book lies primarily in the pharmaceutical industry. This compendium would be a very useful starting point for those involved in data management of drug metabolism results, although a chapter or two from experts in bioinformatics might have been an interesting addition to the book. The individual monographs are not highly detailed and individuals involved in programming and database management will use the book primarily as a source for reference citations. Academic libraries that support groups of researchers in drug metabolism or drug discovery may wish to obtain this volume of the IUPAC series, but the book should not be considered as a

reference text in drug metabolism, nor can this reviewer foresee its use as a textbook. The volume is well-edited and contains very few typographical errors. This volume achieves its goal as a broadly based introduction to the application of drug metabolism databases to drug discovery.

Rory P. Remmel

Department of Medicinal Chemistry
University of Minnesota
Minneapolis, Minnesota 55455

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