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Pharmacokinetic Optimization in Drug Research

Edited by Bernard Testa, Han van de Waterbeemd, Gerd Folkers and Richard Guy, Wiley-Vch, 2001. Price £95, 655 pages in hardback and CDROM)
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The pharmaceutical industry has revolutionized its approach to drug discovery over the past four or five years. The technological advances that are now occurring early in the drug discovery process have enabled lead identification groups to deliver large numbers of compounds to teams responsible for lead optimization and candidate selection. Furthermore, the wisdom of selecting a lead scaffold that offers value in terms of pharmacokinetics, as well as potency and selectivity, is now recognized.

As a consequence, the scientists involved in pharmacokinetic evaluation and optimization have had to deal with larger numbers of compounds. This has necessitated the development of *in silico* models along with high-throughput *in vitro* and *in vivo* tools, which on incorporation into project screening strategies, has enabled pharmacokinetic considerations to be addressed earlier and more effectively within drug discovery.

The book under review addresses many of these pharmacokinetic issues that are now at the forefront of drug discovery. It is based on *LogP2000 – The Second Lipophilicity Symposium*, held in Lausanne, Switzerland on 5–9 March 2000. Of the 33 chapters, 23 originate from the invited lecturers at that symposium, and a further 10 chapters have been added to widen the scope of the book. The authors are all highly respected scientists in their fields of expertise, and are drawn from both academia and industry. Overall, the book provides a valuable resource (both direct and through numerous references) for drug metabolism and pharmacokinetics scientists in drug discovery. However, a book of this title would have benefited from greater emphasis on the objective evaluation of the use of these tools in the pharmaceutical industry today. Also, greater coverage of the link between pharmacokinetics and pharmacodynamics, and the prediction of clinical outcome from the use of preclinical tools, would have been useful.

The text is divided into six sections, each focusing on a different aspect of pharmacokinetic optimization in drug research. The first section provides an overview of drug discovery in the modern pharmaceutical industry, from lead optimization to clinical trials. This introduces the reader to the techniques discussed in the following chapters, and their relevance.

The second section is entitled '*Molecular and Biological Background*', and summarizes some of the issues concerning absorption and metabolism of drugs. The current difficulties in predicting metabolic vulnerability are clearly elucidated, although the challenge in designing successful prodrugs was perhaps underestimated.

The third section provides details of many of the *in vitro* tools that are currently available. Of particular note are the detailed reviews of the use of cell culture to study membrane permeation through the skin, gastrointestinal tract and the blood–brain barrier. All the details needed to establish these techniques are here, from basic cell-culture methods to studies of transporters such as P-gp, and the interpretation of the complex data that can be generated. *In vitro* metabolic techniques are also reviewed, with an emphasis on the relevance of microsomal and hepatocyte systems. Screening methods for evaluating toxic potential are covered adequately. However, the opportunity to discuss the relevance, or otherwise, of protein binding to drug interactions, an issue of relevance when progressing a candidate to a medicine, has been missed.

The section on *Physicochemical Strategies* focuses on partitioning and solubility and is particularly rewarding as it ranges from in-depth physical chemistry for those designing and implementing *in vitro* and *in silico* models, to technical details of measuring physicochemical parameters, and finally to the use and relevance of these tools to the DMPK scientist involved in lead optimization. The developing knowledge in the field of transporters, in contrast to passive transport, is discussed later in the book.

The final section looks at *Computational Strategies*. It both highlights the difficulties in the predictive use of current disposition models in diverse chemical series, and discusses some of the novel approaches now being explored to rectify this shortcoming. The book concludes with a critique of the current paradigm in lead optimization, thankfully recognizing that, despite the increased use of automation and new technologies, the intelligence of the scientist is still central to a successful drug R&D programme.

Overall, this book is an excellent reference work for DMPK scientists, but others in drug discovery would also benefit from many of its chapters.

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