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# Drug Metabolism Prediction

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# Drug Metabolism Prediction

WILEY-VCH
Verlag GmbH & Co. KGaA

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**Library of Congress Card No.:** applied for

**British Library Cataloguing-in-Publication Data**

A catalogue record for this book is available from the British Library.

**Bibliographic information published by the Deutsche Nationalbibliothek**

The Deutsche Nationalbibliothek lists this publication in the Deutsche Nationalbibliografie; detailed bibliographic data are available on the Internet at http://dnb.d-nb.de.



**Print ISBN:** 978-3-527-33566-4
**ePDF ISBN:** 978-3-527-67299-8
**ePub ISBN:** 978-3-527-67301-8
**Mobi ISBN:** 978-3-527-67300-1
**oBook ISBN:** 978-3-527-67326-1

**Cover Design:** Grafik-Design Schulz, Fußgönheim
**Typesetting:** Thomson Digital, Noida, India
**Printing and Binding:** Markono Print Media Pte Ltd, Singapore

Printed on acid-free paper

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# Preface

In addition to mediating cell metabolism, the metabolic system developed in animals and humans for the chemical conversion of xenobiotics. Over millions of years, a plethora of oxidizing, hydrolyzing, conjugating, and other enzymes were optimized by evolution. Modification, degradation, and/or conjugation, in many cases to polar products, enable a safe elimination from the organism. Whereas many plant products are toxic, there are only rare examples that the metabolic system converts harmless natural substances into toxic entities. The situation changed about two centuries ago, after the advent of synthetic organic compounds: many of them contain structural features that the metabolic system cannot handle in the same manner as natural products. In only a few generations, evolution did not have enough time to optimize the enzymes for this new challenge. Of course, also potential drug candidates offer such a challenge to the metabolic system. The development of many compounds must be discontinued because of severe side effects of some toxic metabolites, most often chemically reactive compounds [1]. Some metabolites, even formed in only minor amounts, may cause idiosyncratic toxicity, rarely observed but with fatal consequences for the individual.

Chemical features that are easily metabolized are responsible for short biological half-life of some potential drug candidates; on the other hand, lack of such moieties might cause a half-life that is too long for safe use of the drug. In addition, such compounds as well as highly lipophilic analogs have a higher risk to form toxic metabolites. Thus, it is most important to understand metabolic pathways and to have tools to predict which compounds might be generated. This necessity applies especially for the common oxidation of xenobiotics by various cytochrome P450s (CYPs). Three approaches are suited to achieve this task: theoretical treatment, by calculating the accessibility and chemical reactivity of the chemical features of the compound; molecular modeling, especially pharmacophore searches and docking, using 3D structures of the cytochrome binding pockets; and empirical approaches, using the large databases of known metabolic pathways. All these methods have their pros and cons, and none of them seems to be perfect. Especially species selectivity, to conclude from animal results to humans, and the relative amount of certain metabolites are difficult or even impossible to predict.

The introduction of this book provides an overview of the role of metabolism in drug development, followed by a part on software and databases for the study of metabolism. The next part discusses computational approaches for the study of the most important metabolic enzymes, the cytochrome P450 enzymes. 3D structures, substrate recognition and binding, and theoretical and experimental methods for the study of ligand–protein interactions are discussed in this part. The chapters of the next part go into more detail with respect to the sites and products of metabolism, using either molecular interaction fields or structure-, reactivity-, and knowledge-based approaches. The important aspect of enzyme inhibition and induction is discussed in the next chapters, using quantitative structure–activity relationships and pharmacophore-based methods; separate chapters discuss the role of P-gp-mediated disposition and the prediction of toxic effects of metabolites. Last but not least, three chapters describe experimental approaches, that is, *in vitro* models for the study of metabolism and drug–drug interactions and experimental metabolite detection and profiling.

We are very grateful to Johannes Kirchmair for having accepted our invitation to edit this book, which will be of great importance and practical value for all scientists involved in drug research. Our thanks also go to all chapter authors for their valuable contributions, as well as to Frank Weinreich and Heike Nöthe at Wiley-VCH for their engagement in this project and in our entire book series "Methods and Principles in Medicinal Chemistry."

Düsseldorf — *Raimund Mannhold*
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June 2014

## Reference

1 Kalgutkar, A.S., Dalvie, D., Obach, R.S., and Smith, D.A. (eds) (2012) *Reactive Drug Metabolites, Methods and Principles in Medicinal Chemistry*, vol. 55 (series eds R. Mannhold, H. Kubinyi, and G. Folkers), Wiley-VCH Verlag GmbH, Weinheim.

## A Personal Foreword

Metabolism is a decisive factor for the safety and performance of drugs, cosmetics, food bioactives, and agrochemicals. Methods for analyzing and predicting the metabolic fate of small molecules have become a thriving field of research during the past few years. The allure of predictive metabolism arises from its multidisciplinary nature, bringing together scientists from diverse backgrounds. The research of predictive metabolism also brought me to Cambridge, where I had the privilege to work with Robert Glen and our metabolism team, an inspiring group of a dozen scientists including bioinformaticians, chemists, computer scientists, mathematicians, pharmacists, and physicists, on new methods for predictive metabolism. Unilever and other companies supported us with the necessary funding, a platform for scientific interactions, and, most importantly, experimental data to play with. This has been a truly enlightening, collaborative environment for research and led me to further pursue this work, now together with Bayer Pharma AG at ETH Zurich.

Today a broad range of computational tools and knowledge bases for drug metabolism research are available. The vast majority of these resources are accessible to nonexpert users. With this book, we intend to provide more than a comprehensive overview of these methods and their underlying principles. Our aim is to convey expert knowledge distilled from years – decades – of experience in drug metabolism and our fascination for this field of research.

Metabolizing enzymes show a distinguished level of promiscuity for the binding of small molecules and complex and diverse reaction mechanisms. This makes assay design, readout, and interpretation extremely challenging. The importance of understanding assay and analytical technologies cannot be overemphasized. Thus, in addition to the systematic overview of prediction-based methods, in this volume four dedicated chapters will provide expert accounts of state-of-the-art experimental approaches for investigating drug metabolism, pointing out the most important caveats and common errors to consider when working with experimental data.

It was a great pleasure for me to contribute to this book with such a distinguished team of experts. I would like to take the opportunity to thank the series editors, Raimund Mannhold, Hugo Kubinyi, and Gerd Folkers, and Frank Weinreich and Heike Nöthe at Wiley-VCH for their continuous support during the

preparation of this book. I am very grateful to all contributors for their excellent work and communication.

Drug metabolism is a captivating and challenging playground for experimentalists and theoreticians alike, and there are so much more questions and challenges ahead to resolve! Thus, I hope that this book will inspire and encourage young scientists and established experts in metabolism research to further contribute to this exciting field.

On behalf of all contributors, I wish you an enjoyable and informative read.

Zurich
June 2014

*Johannes Kirchmair*

# Part One
# Introduction

*Drug Metabolism Prediction*, First Edition. Edited by Johannes Kirchmair.

# 1
# Metabolism in Drug Development

*Bernard Testa*

## 1.1
## What? An Introduction

Drug metabolism, and more generally xenobiotic metabolism, has become a major pharmacological and pharmaceutical science with particular relevance to biology, therapeutics, and toxicology, as abundantly explained and illustrated in a number of recent books [1–8] and reviews [9–18]. As such, drug metabolism is also of great importance in medicinal chemistry and clinical pharmacology because it influences the deactivation, activation, detoxification, and toxification of most drugs [19–22]. This broader pharmacological context will be considered in Section 1.2. There, I shall address the "Why?" question, namely "Why does drug metabolism deserve so much attention?"

Given the major impact of biotransformation reactions and resulting metabolites on the preclinical and clinical success or failure of drug candidates, it comes as no surprise that huge efforts are being deployed toward developing ever earlier and faster biological tools. Here, the objective is to assess as rapidly as possible the viability of such candidates. This brings us to the "How?" question (Section 1.3), namely "How to obtain useful data and predictions on the metabolism of candidates?" Although an overview of modern analytical technologies is provided in Chapter 19 of this book, a first focus here will be on the many factors affecting the fate of a drug. Having gathered many sound if narrow experimental results, drug researchers need to make sense of them. In other words, they seek the help of artificial intelligence to extract reliable information from experimental data and transform it into valuable knowledge permitting extrapolative predictions to new molecules. This, as the reader knows, is the focus of this multi-authored book, the present chapter serving as a bird's eye view of the field.

As much as we live in an artificial world of hardware and software, human beings, so we believe and hope, must remain masters of the game by defining objectives, being cognizant of limits, and interpreting as wisely as possible the predictions generated by machines. The point made in Section 1.4 will thus be a "Who?" question and conclusion, namely "Who among scientists are best able to assess the soundness and reliability of drug metabolism predictions?" Should

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these be software specialists, chemists, biologists, or physicians? This section will end with a plea to pool competences and create teams whose total expertise will be greater than the sum of individual expertise.

## 1.2 Why? Metabolism in Drug Development

### 1.2.1 The Pharmacological Context

To put the present book in a global context, it appears useful to ponder the fate of medicines in the body and, more specifically, in the human body. The upper part of Figure 1.1 illustrates in schematic form the two aspects of the interactions between a xenobiotic and a biological system [15,23]. Note that a "biological system" is defined here very broadly and includes functional proteins (e.g., receptors), monocellular organisms and cells isolated from multicellular organisms, isolated tissues and organs, multicellular organisms, and even populations of individuals, be they uni- or multicellular. As for the interactions between a drug (or any xenobiotic) and a biological system, they may be simplified to

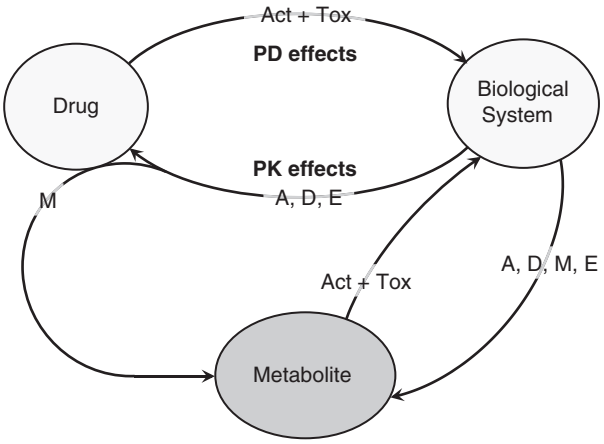


**Figure 1.1** The upper part of this scheme illustrates the interaction between a drug (or any xenobiotic) and the organism (or any biological system). The salient point is the interdependence between pharmacodynamic processes ("what the drug does to the body," namely activity (Act) and toxicity (Tox)) and pharmacokinetic processes ("what the body does to the drug," namely absorption (A), distribution (D), metabolism (M = biotransformation), and excretion (E)). The lower part of the scheme is meant to make explicit the potential role of metabolites in the PD effects of a drug. It emphasizes that a metabolite, once formed, will also be involved in PK processes. More important, the figure highlights the fact that metabolite(s) may also play PD roles. Such roles are two, namely pharmacological activity and/or toxic effects (modified from Ref. [23]).