

AAPS Advances in the Pharmaceutical Sciences Series 14

Stephan Schmidt
Hartmut Derendorf
Editors

Applied Pharmacometrics

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AAPS Advances in the Pharmaceutical Sciences Series

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Editors

Applied Pharmacometrics



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Preface

Modeling and simulation tools have long been used in engineering and aerospace industries to develop products that would be prohibitively expensive to optimize through iterative improvement of prototypes. Modern drug development is now adapting and integrating analogous tools based on information from all phases of the development process. This integrative approach is now recognized as the discipline of pharmacometrics. With the increased regulatory burden and high expectations from prescribers and patients, it is neither cost-effective nor time-efficient to tackle all open questions experimentally. An increasing number of decisions are now based on appropriate modeling and simulation, which allows integration of all available knowledge in a quantitative and objective way.

This book provides an update on the current state of pharmacometrics in drug development. After an introduction of the basic and underlying pharmacokinetic and pharmacodynamic concepts of pharmacometrics in drug development, the book presents numerous specific applications as examples that utilize pharmacometrics with modeling and simulations over a variety of therapeutic areas. These chapters were contributed and written by leading scientists from academia, the pharmaceutical industry, and regulatory agencies. The examples illustrate how results from all phases of drug development can be integrated in a more timely and cost-effective process. The process of applying pharmacometric decision tools during drug development can allow data-based objective decision making. At the same time, the process can identify redundant or unnecessary experiments as well as some costly clinical trials that can be avoided. In addition to cost savings by the expedited development of successful drug candidates, pharmacometrics has an important economic impact in drug product selection. Unsuccessful drug candidates can be identified early and discontinued without expending efforts required for additional studies and allocating limited resources. Hence, pharmacometric modeling and simulation has become a powerful tool to bring new and better medications to the patients at a faster pace and with greater probability of success. We hope that this book will help to spread modeling and simulation activities in drug development and that it will initiate many more applications in the future.

We thank all of our colleagues who contributed to this book and were most generous in devoting their time and effort to make this envisioned project a reality. We

deeply appreciate the priority given to this project by these leaders in their field who have numerous demands on their professional expertise. Prof. Daan Crommelin provided the initial seed for this book and deserves a special thanks. We also thank the team at Springer Science+Business Media for the pleasant, professional, and uncomplicated collaboration on this project. And finally, we thank our families for their patience and understanding.

Orlando, FL, USA
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Chapter 1

Introduction to Pharmacometrics and Quantitative Pharmacology with an Emphasis on Physiologically Based Pharmacokinetics

Sherwin K. B. Sy, Xiaofeng Wang and Hartmut Derendorf

1.1 Introduction

Pharmacometrics has become a term that encompasses modeling and simulation for pharmacokinetics (PK), exposure–response relationship, and disease progression. Mechanistic models that describe the biochemical processes involved in a physiological system have become more utilized in drug development. The models of complex systems are generally classified as systems pharmacology. A quote from William Jusko describes the role of pharmacometrics in drug development: “Pharmacometrics lies at the heart of what drug companies do: collecting data from animals, normal volunteers, and patients; quantifying it, and then being able to determine what that data mean for optimizing drug efficacy and minimizing toxicity” (Nielsen and Friberg 2013). Pharmaceutical and biotech companies have invested heavily in establishing pharmacometrics expertise to utilize the preclinical, clinical, as well as human genomic data to understand the disease progression, the drug behavior, and its effect on individual patients and to personalize medicine to specific groups of patient population. The purpose of this chapter is to provide an overview of different approaches that were used in pharmacometrics in the context of pharmaceutical drug development.

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