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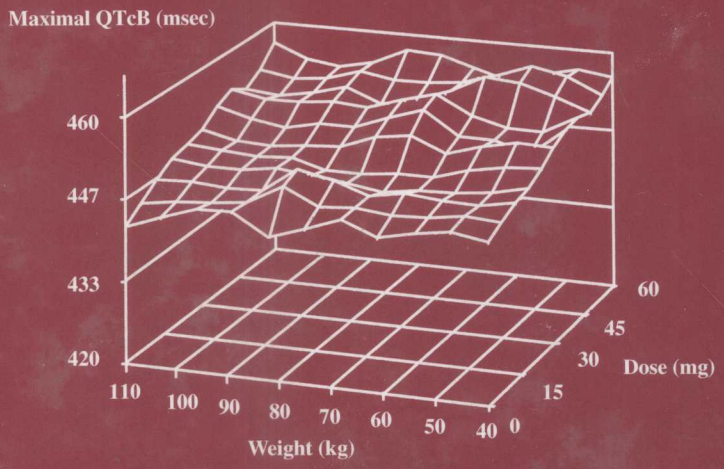
Simulation for Designing Clinical Trials

A Pharmacokinetic-Pharmacodynamic Modeling Perspective



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A Pharmacokinetic-Pharmacodynamic Modeling Perspective

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Simulation for Designing Clinical Trials

DRUGS AND THE PHARMACEUTICAL SCIENCES

To Dennis, Edwin, Jason & Aynsley, and Ella & Holly

Foreword

Computer simulations of clinical trials, employing realistic virtual subjects and typical trial conditions, based on both experimentally informed disease progress and drug intervention models, originated within the last decade. Previously, clinical trials were designed using ad hoc empirical approaches, unaided by a systematic clinical pharmacology orientation or a quantitative pharmacokinetic-pharmacodynamic framework, leading to highly inefficient drug development programs. Stimulated by research and educational contributions from academia, and encouragement from regulatory agencies, expert simulation teams have recently deployed hundreds of clinical trial simulation projects. The advent of modern clinical trial simulation is transforming clinical drug development from naïve empiricism to a mechanistic scientific discipline.

The editors and contributors have provided more than just a comprehensive history, critical vocabulary, insightful compilation of motivations, and clear explanation of the state of the art of modern clinical trial simulation. This book advances a rigorous framework for employing simulation as an experiment, according to a predefined simulation plan that reflects good simulation practices.* We describe attributes of the multidisciplinary simulation team that position it to achieve benefits of enhanced communication and collaboration during the development and employment of the simulation.

* Holford NHG, Hale M, Ko, HC, Steimer J-L, Sheiner LB, Peck CC. Simulation in Drug Development: Good Practices, 1999. http://cdds.georgetown.edu/SDDGP.html.

While the far future of scientific drug development is difficult to predict, successful advancement and integration of clinical trial simulation lead to a daring prediction: in the not so distant future, most clinical trials will be virtual—only a few actual trials will be undertaken. These few human trials will be designed to inform simulation models and to confirm model predictions. The academic, pharmaceutical, and regulatory scientists who have articulated the state of the art of clinical trial simulations in this book provide the first comprehensive description of a breakthrough technology that is enabling this bold departure from inefficient past practices.

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Preface

Simulation has been used widely in various disciplines such as engineering, physics, and economics to support the development and testing of the performance of systems. Some of the most notable examples arise from the wealth of experience in the aerospace industry, in which over the past 30 years it has become routine practice to simulate the performance of aircraft before production and launch. The use of simulations in these industries has been shown to reduce costs and shorten development time. Some of the experience gained from these highly technical systems has pervaded the highly stochastic area of biological systems. Within the pharmaceutical industry, this has culminated in the growth of modeling and simulation in the drug development process, where computer simulation is gaining popularity as a tool for the design of clinical trials.

The integration of modeling and simulation into drug development has been a gradual process in spite of the long-term use of stochastic simulations by biostatisticians for exploration and analyses of data and deterministic simulations by pharmacologists for descriptive purposes. However, simulation has considerable potential for design of trials as evidenced by the rapid growth in discussion groups, conferences, and publications. The basis of the use of simulation lies in the argument that if, in theory, a virtual trial could be constructed that incorporated all relevant influences (controllable and uncontrollable, and deterministic and stochastic) and their related outcomes, the researcher could then explore the influence of changes in the design on the performance of the trial. If this theoretical construct were a reality, then it is equally conceivable that trial designs could be selected based on their probability for success. While this seems a straightfor-

ward task, albeit computationally intensive, its introduction has been at the mercy of the availability of powerful computing. Since fast computing machines are now available on almost every office desk, it is no surprise that both the design of trials and the necessary knowledge and understanding of the time course of drug effects that underpins the design process have shown a dramatic upsurge. The parallel development of more complex and mechanistic models for drug effects and design of trials is not coincidental, since an understanding of the effects of drugs is paramount for design of trials and the more complex models themselves rely heavily on computational methods for their solution.

This book describes the background and lays the foundation for simulation as a tool for the design of clinical trials. The target audience is any researcher or practitioner who is involved in the design, implementation, analysis, or regulatory decisions concerning clinical trials. This book does not embrace all aspects of trial design, nor is it intended as a recipe for using computers to design trials. Rather, it is a source of information that enables the reader to gain a better understanding of the theoretical background and knowledge of the practical applications of simulation for design. It is assumed that the reader has a working understanding of pharmacokinetics and pharmacodynamics, modeling, and the drug development process. In addition, some knowledge of types and practicalities of designs commonly used for clinical trials is assumed.

The book is divided into parts that describe model development, model evaluation, execution of simulation, choice of design, and applications. It is useful to partition the simulation model into submodels (e.g., input-output model, covariate distribution model, execution model) in order to describe specific aspects of the process. The input-output model (Chapter 2) describes the relationship between dosing schedule and response in an explanatory manner for any given patient. This model itself usually comprises a number of submodels: the pharmacokinetic and pharmacodynamic models, disease progression models, and (patho)physiological models of homeostatic systems in the body. The covariate distribution model (Chapter 3) describes the characteristics of the virtual patient that affect the input-output models and execution models. The execution model (Chapter 4) describes the deviation from the nominal design, thereby mimicking the actual trial conduct.

Details of model evaluation methods are provided in Chapter 5. The mechanics required for simulation of a trial, including replications, random number generation, and the implementation of numerical integration are outlined in Chapter 6. Analysis of replicates of the subsequent virtual trial is discussed in Chapter 7. Chapter 8 addresses the important issue of the sensitivity of the trial design to assumptions in the development of the models that underpin the response of the virtual patient. Finally, in this section discussion is raised about how a sufficient design might be selected from all possible designs (Chapter 9).

While simulation as an investigation tool has proven conceptually to be

straightforward, complete acceptance by regulatory authorities and the pharmaceutical industry remains elusive. Details of perspectives by regulatory authorities, academia, and the pharmaceutical industry are provided by Chapters 10, 11, and 12, respectively. In addition to these perspectives, an overview and history of mechanism-based model development for physiological/pharmacological processes are presented in Chapter 13.

We have also included a part devoted to applications of simulation for trial design and evaluation (Chapters 14 to 18). These include a wide range of practical applications, including optimization of sampling strategies, dose selection, integration of optimal design with simulation, prediction of efficacy, and side effects.

We accept that our current knowledge of predicting clinical responses for the individual patient pales beside that imagined by science fiction writers. Our way of exploring the nature of drug activity is limited to conducting clinical trials in the hope of learning about clinical responses and confirming these findings using methods that are often empirical. Since it is recognized that the analysis of data is dependent on the quality of the data, and the quality of the data dependent on the quality of the study design, we are dependent on adequately designed clinical trials to pave the way for better treatments. In due course, it is expected that methods that promote more informative and rigorous designs such as those based on modeling and simulation will provide the same benefits for drug development that have been seen in other industries.

We thank the authors of the chapters and Marcel Dekker, Inc., for providing the opportunity to publish this book.

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