Preface

During the seven years following the inaugural publication of *Simulation for Designing Clinical Trials: A Pharmacokinetic-Pharmacodynamic Modeling Perspective*, acceptance and application of clinical trials modeling and simulation (M&S) in drug development and regulation have greatly expanded. Biopharmaceutical companies have employed M&S in all phases of drug development to achieve greater efficiency and dosage optimization. The Food and Drug Administration’s (FDA) visionary 2004 Critical Path Initiative highlighted clinical trial simulations (CTS) in “model based drug development” to facilitate efficient development. In the meantime, FDA and the European Medicines Agency have encouraged use of CTS via regulatory guidances, and have employed M&S for labeling and approval decisions. On the backdrop of these developments, the title of this edition has been chosen to reflect how CTS is being employed in drug development and regulation, and trends for expanded applications in the future.

This edition includes updates, new uses, and issues concerning CTS, along with case studies on how clinical trial simulations are being applied in various therapeutic and application areas. Importantly, the book expands on the use of CTS for informing decisions during drug development and regulatory review. Each chapter author was selected on the basis of demonstrated expertise in state-of-the-art application of CTS.

Editors’ opinions on advances and impactful trends of CTS in model-based drug development and regulation are introduced (Chap. 1). Regulatory agencies have been proactive in promoting use of CTS, and Chaps. 2 and 3 present the perspectives and experiences of FDA and European regulatory agencies by the authors working in these agencies.

Methods to facilitate decision making in drug development are discussed by pointing out the importance of assessing uncertainty of predicted trial performance and outcomes in planning of prospective trials (Chap. 4). For quantitative decision-making, constructing clinical utility curves (Chap. 5) can be useful. Adaptive trial design has gained attention as a method for more efficient and informative drug development, and its current status is reviewed in Chap. 6. Chapter 7 illustrates an M&S application case where personnel from biostatistics, clinical research and clinical PK-PD could collaborate to make better informed decisions on trial designs.
throughout a clinical development. Chapter 8 illustrates how preclinical data can be
integrated in a model-based drug development program to optimize early stage
development, using CTS to simulate a first-in-human study.

Many successful cases employing CTS in guiding drug development decisions
have been published in the literature and presented at conferences. Representative
cases in selected therapeutic areas provide a general background on how to beneficially employ CTS, followed by the authors’ experiences. Applications of CTS in eight therapeutic areas (Chaps. 9–16) are covered: diabetes, cardiovascular diseases, viral infections, antimicrobial chemotherapy, cancer, hematology, anxiety disorder, and epilepsy.

Chapter 17 discusses how CTS can be used in therapeutic biologics development. Designing ethical and informative pediatric studies requires integrating all available information, while gaining pediatric specific knowledge from a limited number of observations. The factors to consider in using CTS for pediatrics studies are described in Chap. 18.

The final section of the book includes chapters that describe evolving methodologies in CTS. The importance of incorporation of disease progression elements in CTS models is emphasized, especially when the evolution of disease during a trial is considered in evaluating treatment effects attributable to the drug (Chap. 19). The systems biology approach incorporates high resolution mechanistic models, involving fundamental dynamics of cells and biological signaling systems. Using such models, predictions of clinical responses may ultimately be made by simulations (Chap. 20). Recent advances in *in vitro, ex vivo, and in silico* methods to provide input variable information have significantly increased the applicability of the traditional whole-body physiology-based pharmacokinetic modeling approach, and its practical implementation is reviewed in the Chap. 21. Simulating drug responses in a virtual patient population and how to collect and utilize datasets for construction of covariate distribution models are presented (Chap. 22).

The target audience for this volume, *Clinical Trial Simulations* includes researchers and scientists who wish to consider use of simulations in the design, analysis, or regulatory review and guidance of clinical trials. This book does not embrace all aspects of trial design, nor is it intended as a complete recipe for using computers to design trials. Rather, it is an information source that enables the reader to gain understanding of essential background and knowledge for practical applications of simulation for clinical trial design and analysis. It is assumed that the reader has a working understanding of pharmacokinetics and pharmacodynamics, modeling, pharmacometric analyses, and the drug development and regulatory processes.

We express our sincere gratitude to all the authors who have contributed to this book. Many thanks go to the Springer publication team. Lastly, on behalf of all the contributors of this book, we appreciate the reader’s interest in the application of clinical trial simulations in order to improve the way we develop useful drugs.

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