

Preface

Drug discovery and development is a long, costly, and high-risk process. It starts with the identification and validation of a disease target and the generation and optimization of compounds that potentially have some important effect on the target. This is followed by a battery of in vitro and in vivo (animal) studies to characterize the safety profile and finally clinical testing on human beings. Only then can a new drug filing be made to regulatory agencies such as the FDA and the EMA to secure the legal right to market a drug product. In parallel, a manufacturing process and associated analytical methods are developed and validated to produce drug product in the appropriate dosage form of consistent quality in the appropriate dosage form for the many required clinical studies and then post-approval marketing. This is a concerted collaboration involving many scientific disciplines and organizations against the backdrop of a heavily regulated industry.

Moving from the early discovery phase to the marketing of a drug is a high-risk proposition. Less than 1/5,000 compounds make it through the development pipeline to successful marketing. So it is no surprise that pharmaceutical companies strive to establish an ample pipeline of therapeutically important compounds with significant activity and a good safety profile. These compounds can only come from basic discovery experiments, preclinical safety studies, and formulation and manufacturing process studies employing good quality control methods. In these nonclinical areas, discovery, preclinical development, and chemistry, manufacturing, and controls (CMC), variability is the norm and most decisions are data driven. Statistics plays a significant role in moving drug candidates through the drug development pipeline, in decision making and assessing risks, and in directly improving the efficiency of the drug development process.

The novice statistician just entering this exciting and rich field of nonclinical statistical applications, however, lacks good reference books describing important statistical tools necessary for their work and professional development. In the literature, the authors are only aware of two reference books covering selected topics in nonclinical statistics. One is *Pharmaceutical Statistics Using SAS: A Practical Guide* (Dmitrienko, Chuang-Stein, and D'Agostino 2007), with four out of 14 chapters discussing nonclinical topics. The other is *Statistics in Drug*

Research: Methodologies and Recent Developments (Chow and Shao 2002), with three out of ten chapters discussing topics in the CMC area. Many important references to nonclinical statistical applications are scattered throughout numerous scientific and statistical journals, industry standards, and regulatory documents. So clearly there is a need for a reference book that collects and summarizes the wide diversity of nonclinical topics into a single volume. With this in mind, we are proud to present the first book that is completely dedicated to the diverse range of nonclinical topics, bringing together relevant discussions of statistical methods in all three nonclinical areas: discovery, nonclinical development, and CMC.

The book is intended to be a reference book for scientists and statisticians in the pharmaceutical and biotechnology industries, as well as in regulatory agencies. It can also serve as a textbook for a statistical consulting course for a statistics graduate program. Our aim is to also provide an excellent resource for academic researchers to understand the current challenges within nonclinical statistics and direct research in this area. It is also the authors' hope that this book will inspire professional statisticians to write additional reference books so as to build a library of reference materials for nonclinical statistics, matching the level of reference materials available to clinical statisticians.

This book is divided into four parts. Part I introduces the book with three chapters. Chapter 1 defines nonclinical statistics, discusses the nonclinical statistical profession, and points out pathways to making it a discipline. Chapter 2 surveys current nonclinical statistical contributions in regulatory agencies with a focus on the US FDA. Chapter 3 gives a roadmap on how to become a good nonclinical statistician.

Part II of the book, including Chaps. 4–8, focuses on the statistical and scientific problems in early drug discovery. This is a broad field; Chap. 4 is a broad overview that introduces this section of the discovery pipeline. The other chapters in the second part focus on target discovery using genetic markers, compound screening via high-throughput screening (HTS), compound optimization, early safety screening, and computational chemistry models.

Part III, including Chaps. 9–14, addresses the statistical challenges associated with working in nonclinical safety assessment and drug development. It is designed to be a clear and accessible presentation of up-to-date technical material combined with practical insight into its application. Experts working in the field share their insights covering six related areas: an overview of the statistician's role and contribution within nonclinical drug safety assessment; statistical aspects of key regulatory safety studies; clinical assay development for biological macromolecules; regulatory perspectives on design and interpretation of carcinogenicity studies, including new research on statistical methods; design and evaluation of drug combination studies; and the increasingly important role of biomarkers in pharmaceutical discovery and development.

Part IV, including Chaps. 15–26, is dedicated to important topics concerning the chemistry, manufacturing, and controls (CMC) aspects of drug development, covering both large molecules (biologics) and small molecules. These follow on the heels of the discovery phase of drug development touched on above. Numerous

formulation studies are carried out that combine the API with other substances, known as excipients, to produce the drug product that possesses desirable properties of appearance, shelf stability, and bioavailability. The scientific studies required to produce the final drug product also involve analytical method development studies. These are comprised of studies that develop analytical methods to characterize the physical and chemical properties of the drug product. All of these activities in the CMC area are governed by considerable regulatory oversight in the form of US Code of Federal Regulations sections, or their European and international requirements as well as numerous guidance documents pertaining to pharmaceutical product development. Given this brief description, Part IV covers a broad array of topics that expand and elucidate the regulatory and statistical aspects of these broad areas of CMC studies briefly described above. The topics covered are analytical method validation, lifecycle approach to bioassay, quality by design, process validation, process capability and statistical process control, stability modeling, in vitro dissolution, content uniformity, acceptance sampling, chemometrics and predictive modeling, and comparability studies. Each chapter focuses on a key aspect of analytical method development, formulation development, or associated statistical considerations in manufacturing.

While these 26 chapters include cross-referenced material, they can be read as individual contributions. Collectively they represent a rich source of current information, good practice, practical advice, and guidance with examples.

The editors are grateful to all the contributors who took time to write the chapters of this book. They are leaders and top experts in the field. Their broad view on the topic, in-depth discussion, and stimulating advice for future directions make this book an invaluable reference for practicing statisticians and scientists, academic researchers, and regulatory reviewers. We are indebted to numerous reviewers who helped to edit and improve the chapters. We thank Jonathan Gurstelle who helped to initiate this project before he left Springer. We are indebted to Matthew Amboy and Christine Crigler of Springer Sciences for their professional help in guiding us from the preparation of manuscripts through the production of the book. Our sincere gratitude goes to our families for their patience and support.

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Nonclinical Statistics for Pharmaceutical and
Biotechnology Industries

Zhang, L. (Ed.)

2016, XXII, 698 p. 144 illus., 113 illus. in color.,

Hardcover

ISBN: 978-3-319-23557-8