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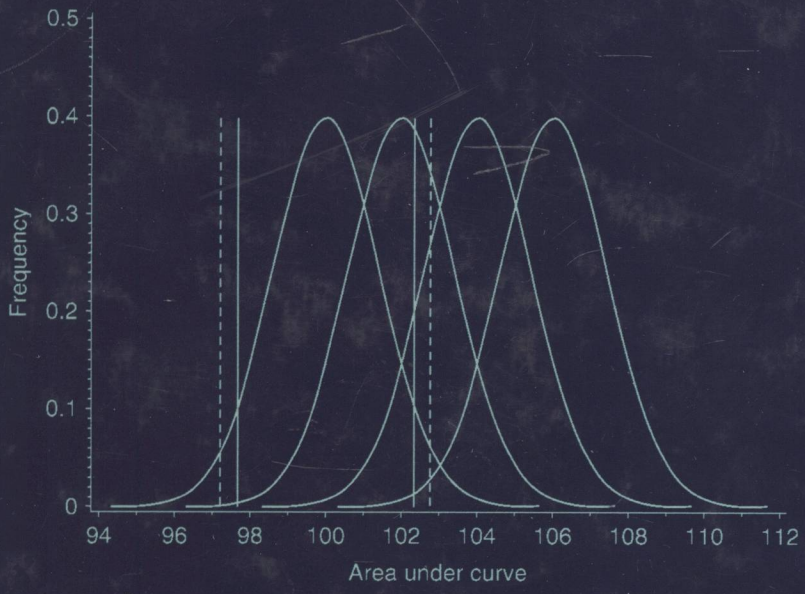
Design and Analysis of Bioavailability and Bioequivalence Studies

Third Edition



Shein-Chung Chow

Jen-pei Liu

CRC Press
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A CHAPMAN & HALL BOOK

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Preface

As the first decade of the twenty-first century draws to an end, the arena of bioavailability and bioequivalence has generated a lot of scientific, statistical, and regulatory activities and issues from the pharmaceutical industry, health authorities, as well as academia, since the publication of the second edition of our book in 2000. In particular, a series of regulatory guidelines or guidances were issued by different health authorities in the world. In January 2001, the U.S. Food and Drug Administration (FDA) issued the guidance on *Statistical Approaches to Establishing Bioequivalence*. Six months later, in July 2001, the European Agency for the Evaluation of Medicinal Products (EMEA) issued the *Note for Guidance on the Investigation of Bioavailability and Bioequivalence*. In March 2003, the U.S. FDA released the guidance on *Bioavailability and Bioequivalence Studies for Orally Administrated Drug Products—General Considerations*. Later, the World Health Organization, in 2005, issued the draft revision of the guidelines on *Multisource (Generic) Pharmaceutical Products: Registration Requirements to Establish Interchangeability*. On the other hand, tremendous opportunities as well as challenges still lie ahead for bioavailability and bioequivalence in the twenty-first century because of breakthroughs in biotechnology and methodological research in medicine, pharmacokinetics, and statistics. In response to the challenges, upon the invitation of Professor R.B.D'Agostino, one of the co-editors of *Statistics in Medicine*, we were invited as guest editors for a special issue of 13 papers on individual bioequivalence that was published on October 30, 2000. In addition, the U.S. FDA issued a document on *Critical Path Opportunities for Generic Products* on May 1, 2007 to address emerging challenges and opportunities for generic drug products. The issues on the regulations and scientific issues of biosimilar products or follow-on biologics still remain unresolved. Consequently, there is an urgent need for the third edition of this book to provide a complete and overall presentation of the latest development of activities and results in bioavailability and bioequivalence on regulatory requirements, scientific and practical issues, and statistical methodology.

The third edition is different from the first and second editions in four aspects. First, we have revised and updated each section to reflect recent developments in statistical methodology in the design and analysis of bioavailability and bioequivalence studies. For example, the third edition provides a complete update of the status of regulations on bioavailability and bioequivalence, especially, the guidelines issued by the U.S. FDA, EMEA, and WHO. Second, the third edition is expanded to 20 chapters, 4 chapters more than the second edition and 8 chapters more than

the first. The third edition includes four new chapters as well as some new sections to present a complete account of the new developments in bioavailability and bioequivalence studies. The four new chapters include "Population Pharmacokinetics" (Chapter 17), "Other Pharmacokinetic Studies" (Chapter 18), "Review of Regulatory Guidances on Bioequivalence" (Chapter 19), and "Frequently Asked Questions and Future Challenges" (Chapter 20). Third, to deliver an effective presentation of the material, we modified the configurations of the 20 chapters into 5 parts: "Preliminaries," "Average Bioequivalence," "Population and Individual Bioequivalence," "*In Vitro* and Alternative Evaluation of Bioequivalence," and "Other Bioequivalence Studies." Part I, "Preliminaries", describes the regulatory history of bioavailability and bioequivalence, design of bioavailability studies, and statistical inference for the standard 2×2 crossover design. Part II, "Average Bioequivalence," reviews the methods for evaluation of average bioequivalence, power and sample size determination, transformation and assessment of intra- and inter-subject variabilities, outlier detection, and higher-order designs for evaluation of average bioequivalence. Part III, "Population and Individual Bioequivalence," gives an update of the methods for the design and analysis of population and individual bioequivalence. Part IV, "*In Vitro* and Alternative Evaluation of Bioequivalence," includes assessment of average bioequivalence with negligible plasma levels, *in vitro* bioequivalence studies, and *in vitro* dissolution profile comparison. Part V, "Other Bioequivalence Studies," consists of meta-analysis for bioequivalence review, population pharmacokinetics, other pharmacokinetic studies, review of regulatory guidance, and future challenges. Finally, the third edition has 120 new references from the bioavailability and bioequivalence literature.

Similar to the first two editions, the third edition is also entirely devoted to the design and analysis of bioavailability and bioequivalence studies. It covers all of the statistical issues that may occur in the various stages of design and data analysis in bioavailability and bioequivalence studies. We strongly believe that this new, updated and much expanded third edition not only is an extremely useful reference book for pharmaceutical scientists and researchers, regulatory reviewers, clinicians, and biostatisticians in the academia, regulatory agencies, and pharmaceutical industry but also serves as an advanced textbook for graduate courses dealing with the topics of bioavailability and bioequivalence in the areas of pharmacokinetics, clinical pharmacology, and biostatistics. It is also our intent that this book will serve as a bridge among the pharmaceutical industry, government regulatory agencies, and academia.

Although the information, material, and presentation configuration of the third edition are different from the first two editions, the third edition still focuses on concepts rather than technical details. The mathematics and statistics dealt in the book are still fundamental. We have received many positive and constructive feedbacks and comments from scientists and researchers in academia, regulatory agencies, including the FDA, and pharmaceutical industry. Therefore, we have maintained our intuitive writing style as well as the emphasis on concepts through numerous examples and illustrations.

We would like to thank Jessica Vakili and David Grubbs of Taylor & Francis for their administrative assistance and support. We are deeply indebted to the Duke

University School of Medicine (especially, Rob Califf, MD, Robert Harrington, MD, Ralph Corey, MD, John McHutchison, MD, and Wesley Burks, MD) and the National Taiwan University for their encouragement and support. We also want to express our sincere gratitude to many pharmaceutical scientists, researchers, and biostatisticians for their feedbacks, support, and encouragement. Chow wishes to thank his fiancée Annpey Pong, PhD, for her constant encouragement and support during the preparation of this edition. Liu wishes to express his appreciation to his wife, Professor Wei-Chu Chie, MD, PhD, and daughter, Angela, for their patience, endurance, understanding, and support during the preparation of this edition.

Finally, we are fully responsible for any errors remaining in the book. The views expressed in this book are those of the authors and are not necessarily those of the Duke University School of Medicine, the National Taiwan University, or the National Health Research Institutes of Taiwan.

Shein-Chung Chow
Jen-pei Liu

Authors

Shein-Chung Chow, PhD is currently a professor in the Department of Biostatistics and Bioinformatics, Duke University School of Medicine, Durham, North Carolina. Before joining Duke University, he was the director of the Taiwan Cooperative Oncology Group Statistical Center and the executive director of National Clinical Trial Network Coordination Center of Taiwan. Dr. Chow has also held various positions in the pharmaceutical industry including vice president. He has worked in the areas of biostatistics and data management, and as a medical writer at Millennium Pharmaceuticals, Inc., Cambridge, Massachusetts. He had also been executive director, statistics and clinical programming, at Covance, Inc. Princeton, New Jersey; director and department head at Bristol-Myers Squibb, Plainsboro, New Jersey; senior statistician at Parke-Davis Pharmaceutical Division, Warner-Lambert Company, Ann Arbor, Michigan; and research statistician at Wyeth-Ayerst Laboratories, Rouses Point, New York. Through these positions, Dr. Chow provided technical supervision and guidance to project teams on statistical issues and made presentations for partners, regulatory agencies, or scientific bodies, defending the appropriateness of statistical methods used in clinical trial design, data analyses, and the validity of reported statistical inferences. Dr. Chow has identified best statistical and data management practices, organized and led working parties for the development of statistical design, analyses, and presentation applications, and has participated on many data safety monitoring boards.

Dr. Chow's professional activities include playing key roles in many professional organizations such as officer, board of directors member, advisory committee member, and executive committee member. He has served as program chair, session chair/moderator, panelist, and instructor/faculty at many professional conferences, symposia, workshops, tutorials, and short courses. He is the editor-in-chief of the *Journal of Biopharmaceutical Statistics*. Dr. Chow is also the editor-in-chief of the CRC Press biostatistics series. He was elected fellow of the American Statistical Association in 1995 and was elected member of the International Statistical Institute in 1999. He was the recipient of the DIA Outstanding Service Award (1996), the ICSA Extraordinary Achievement Award (1996), and the Chapter Service Recognition Award of the American Statistical Association (1998). Dr. Chow was scientific advisor to the Department of Health, Taiwan, Republic of China during 1999–2001 and from 2006 till date. Dr. Chow was president of the International Chinese Statistical Association, chair of the advisory committee on Chinese pharmaceutical affairs, and a member of the advisory committee on statistics of the DIA.

Dr. Chow has authored/co-authored over 170 methodology papers and 14 books, which include *Advanced Linear Models*, *Design and Analysis of Bioavailability and Bioequivalence Studies* (first and second editions), *Statistical Design and Analysis in Pharmaceutical Science*, *Design and Analysis of Clinical Trials* (first and second editions), *Design and Analysis of Animal Studies in Pharmaceutical Development*, *Encyclopedia of Biopharmaceutical Statistics* (first and second editions), *Sample Size Calculations in Clinical Research*, *Adaptive Design Methods in Clinical Trials*, and *Statistical Design and Analysis of Stability Studies*.

Dr. Chow received a BS in mathematics from the National Taiwan University, Taipei, Taiwan and a PhD in Statistics from the University of Wisconsin, Madison.

Jen-pei Liu, PhD is currently the director of Statistical Education Center, Nationa Taiwan University, the director of Consulting Center for Statistics and Bioinformatics, National Taiwan University, and a Professor of Statistics, Division of Biometry, Department of Agronomy, National Taiwan University, Taipei, Taiwan. Professor Liu is a clinical biostatistician with more than 20 years experience, and has been involved with all phases of clinical trials in a wide spectrum of therapeutic areas. He also has extensive publications. His publication includes five reference books in statistical methods for the biopharmaceutical industry (Marcel Dekker) and *Design and Analysis of Clinical Trials* (co-authored with S.C. Chow; John Wiley & Sons), over 120 articles in peer-reviewed statistical journals, and over 20 invited book chapters in the *Encyclopedia of Biostatistics* and *Encyclopedia of Biopharmaceutical Statistics*. His papers were cited in the 2001 FDA guidance on *Statistical Approach to Establishing Bioequivalence* and in the 2005 WHO guideline on multisource drug products. He is an associate editor for the *Journal of Biopharmaceutical Statistics*, an associate editor for the *Taiwan Journal of Public Health* (since January 2002), and a member of the advisory committee on *Statistics in Biosciences* (since January 2008). He is one of the editors for the CRC Press biostatistics series. He serves as a referee for many international statistics journals. Currently, he is on the Drug Consultation Committee, the Committee for Medical Devices, and the Committee for the Chinese Drug and Pharmacy, all for the Department of Health, Taiwan. Dr. Liu received his BS in agronomy and MS in biometry from the National Taiwan University, Taipei, Taiwan and his MS and PhD in Statistics from the University of Kentucky, Lexington.

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