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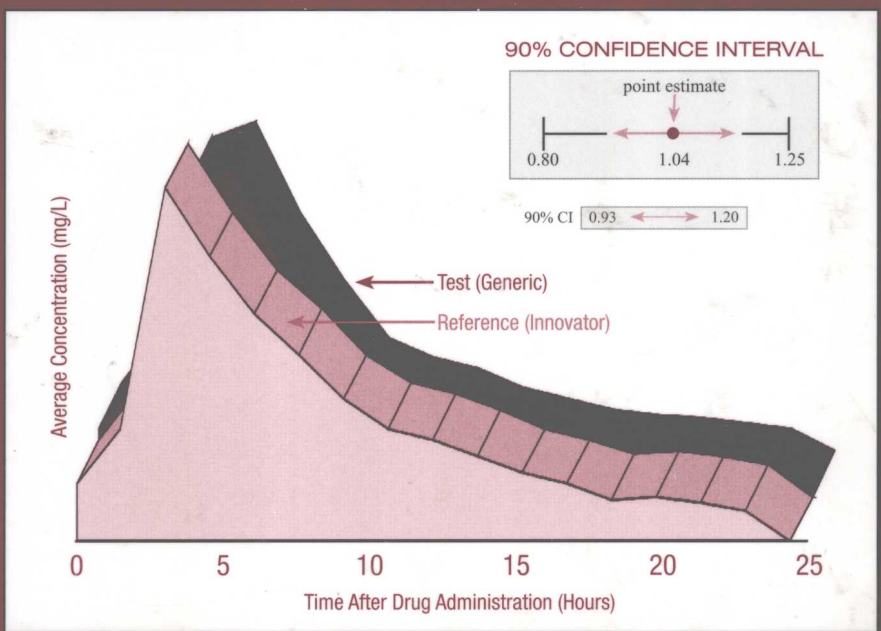
Generic Drug Product Development

Bioequivalence Issues



Isadore Kanfer Leon Shargel

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Bioequivalence Issues

Isadore Kanfer
Rhodes University
Grahamstown, South Africa

Leon Shargel
Applied Biopharmaceutics
Raleigh, North Carolina, USA

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healthcare

New York London

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Preface

This book is the second volume in a series of books on Generic Drug Product Development. The objective of the first book, *Generic Drug Product Development – Solid Oral Dosage Forms*, was to describe from concept to market approval the development of therapeutic equivalent generic drug products, including regulatory and legal challenges. This second volume, *Generic Drug Product Development – Bioequivalence Issues* focuses on current problems concerning the scientific demonstration of bioequivalence of two drug products.

Bioequivalence studies are very expensive, time consuming, and always have the possibility of failure. Failure to demonstrate bioequivalence of a proposed generic drug product results not only in a loss of money and time, but also may lead to a management decision not to pursue further development of this product.

Bioequivalance can be established for a large number of oral drug products that are intended for systemic drug absorption in which the drug and/or metabolites can be measured in biological fluid such as blood, plasma, serum, etc. For these drug products, the worldwide regulatory agencies and the scientific community are in agreement as to the design of a bioequivalence study and the statistical analyses of the results. For many other drug products, such as drugs intended for locally acting effects, highly variable drugs, and drugs with long elimination half-life bioequivalence can be very difficult to demonstrate.

Methods for the assessment of the bioequivalence of oral drug products that are intended for systemic drug absorption are well-documented and the approaches for such studies are described in guidances issued by many regulatory authorities throughout the world. While in general, the bioequivalence requirements of most regulatory bodies have much in common, in various instances specific issues and approaches may differ.

The objective of this volume is to discuss and explore various approaches for the demonstration of bioequivalence of drug products in which the regulatory agencies and the scientific community are not in agreement. These are usually related to drug products that have biopharmaceutical, bioavailability, pharmacokinetic, and pharmacodynamic properties that preclude the use of standard approaches that are outlined in published regulatory guidelines. The chapters in this volume

address those largely unresolved bioequivalence issues for the specific purpose of establishing therapeutically equivalent multisource (generic) drug products which will lead to regulatory approval and which can be confidently substituted for their brand-name counterparts.

Chapter 1 provides an introduction to the scientific principles underlying the assessment of bioequivalence, including various relevant definitions. The application of bioequivalence methodology and the approaches used to assess bioequivalence including statistical considerations and acceptance criteria are discussed.

The official position of the United States Food and Drug Administration, relevant to bioequivalence and therapeutic equivalence, is emphasized in Chapter 2. Approval of a generic drug product implies that such a product is a therapeutic equivalent to the brand product and may be safely substituted. This chapter will assist the reader in understanding the Food and Drug Administration position and what is required for generic drug approval.

Chapter 3 discusses pharmaceutical alternatives such as different salts and/or different dosage forms (e.g., capsule or tablet) that contain the same active pharmaceutical ingredient. This chapter examines whether pharmaceutical alternatives can be considered as therapeutic equivalents and interchangeable.

The use of pharmacodynamic measurements in lieu of plasma drug concentrations to assess bioequivalence is discussed in Chapter 4. The chapter discusses how the Emax model is used to relate changes in the pharmacodynamic response to changes in drug bioavailability.

The determination of bioequivalence using clinical endpoints is discussed in Chapter 5. Clinical endpoint bioequivalence studies are often used for locally acting drug products that are not intended for systemic absorption. Examples include topical anti-infective drugs, drugs given by inhalation, orally administered, non-absorbed drugs, ophthalmic, and otic drug products. The design and assessment of bioequivalence using clinical outcomes is also discussed.

Chapter 6 presents an overview of statistical considerations including alternate designs and approaches for bioequivalence assessments. Parallel study designs such as those needed for drugs with very long half-lives where a crossover study may be impractical are discussed as are the issues of outliers, studies performed in groups, and interim analyses. The vexing problem of the evaluation of highly variable drugs is discussed in Chapter 7. The problem of assessing the bioequivalence of these products and the implications of the usual regulatory conditions together with proposed solutions to resolve these issues are presented. The scaled average bioequivalence approach for highly variable drug products is presented together with the necessary computational procedures, limits and metrics, and associated statistical issues and recommendations.

Chapter 8 provides readers with a comprehensive account of population pharmacokinetic approaches to assessing bioequivalence, which includes compartmental versus non-compartmental pharmacokinetic approaches for bioequivalence. Mixed-effect modelling such as NONMEM and ITS2 are discussed and the advantages and disadvantages of the various methods and approaches are presented using case studies.

The role of metabolites in bioequivalence assessment is examined in Chapter 9. Presently, there is a lack of regulatory harmony regarding whether to monitor the parent drug and/or metabolite(s). An account of the formation of metabolites and associated implications for the assessment of bioequivalence is also provided.

Chirality and stereochemical considerations in bioequivalence are discussed in Chapter 10. This chapter provides a useful background with relevant definitions and associated terms. Reference is made to regulatory guidelines of the U.S.A., Canada, Europe, and Japan, and the limitations of these guidelines with respect to the implications of chirality for the assessment of bioequivalence are discussed. The effect of stereoselectivity on the pharmacodynamics and pharmacokinetics of chiral drugs and their formulation is discussed along with analytical methodology.

Food, including the quality and quantity, has been known to affect drug bioavailability, but not always in a predictable manner. It is sometimes not clear when to undertake a food effect bioequivalence study. Chapter 11 examines the effect of food on bioavailability and the use of a food-effect study in the assessment of bioequivalence.

The final Chapter, 12, discusses the role of endogenous drug substances in the determination of bioequivalence of drug products containing drugs that also occur naturally in the body. Potassium chloride and progesterone are used as examples. The chapter describes the pharmacokinetic and statistical assessment of endogenous substances administered exogenously including approaches in determining the endogenous drug concentration baseline and the factors affecting baseline stability.

The audience for this book includes undergraduate and graduate pharmacy students, pharmacy faculty, and drug manufacturers and regulators in the pharmaceutical industry who are interested in generic drug development and need more information concerning the current issues in bioequivalence assessment. The book discusses specific unresolved issues that are troubling to the scientific community and regulatory agencies and provides information on how to deal with such problems. Emphasis is on practical information for the development of protocols and the design and conduct of studies for the assessment of bioequivalence of generic drug products.

Isadore Kanfer *Leon Shargel*

Contributors

Sanford Bolton University of Arizona, Tucson, Arizona, U.S.A.

Charles Bon Biostudy Solutions LLC, Wilmington, North Carolina, U.S.A.

Philippe Colucci Faculté de Pharmacie, University of Montreal, Montreal, Quebec, Canada

Kim Dalhoff Clinical Pharmacologic Unit, Bispebjerg Hospital, Copenhagen, Denmark

Murray P. Ducharme Cetero Research, Cary, North Carolina, U.S.A. and Faculté de Pharmacie, University of Montreal, Montreal, Quebec, Canada

Laszlo Endrenyi Department of Pharmacology, University of Toronto, Toronto, Ontario, Canada

Loren Gelber RRI Consulting Inc., Lake Wylie, South Carolina, U.S.A.

Christopher Hendy Novum Pharmaceutical Research Services, Pittsburgh, Pennsylvania, U.S.A.

Manish Issar Watson Laboratories, Inc., Corona, California, U.S.A.

André Jackson Food and Drug Administration, Office of Clinical Pharmacology, Silver Spring, Maryland, U.S.A.

Fakhreddin Jamali Faculty of Pharmacy, University of Alberta, Edmonton, Alberta, Canada

Isadore Kanfer Faculty of Pharmacy, Rhodes University, Grahamstown, South Africa

Jean-Francois Marier Pharsight Corporation, Mountain View, California, U.S.A.

Reza Mehvar School of Pharmacy, Texas Tech University Health Sciences Center, Amarillo, Texas, U.S.A.

Marika Pasternyk-Di Marco Pharmacokinetics and Pharmacodynamics, MDS Pharma Services, Montreal, Quebec, Canada

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