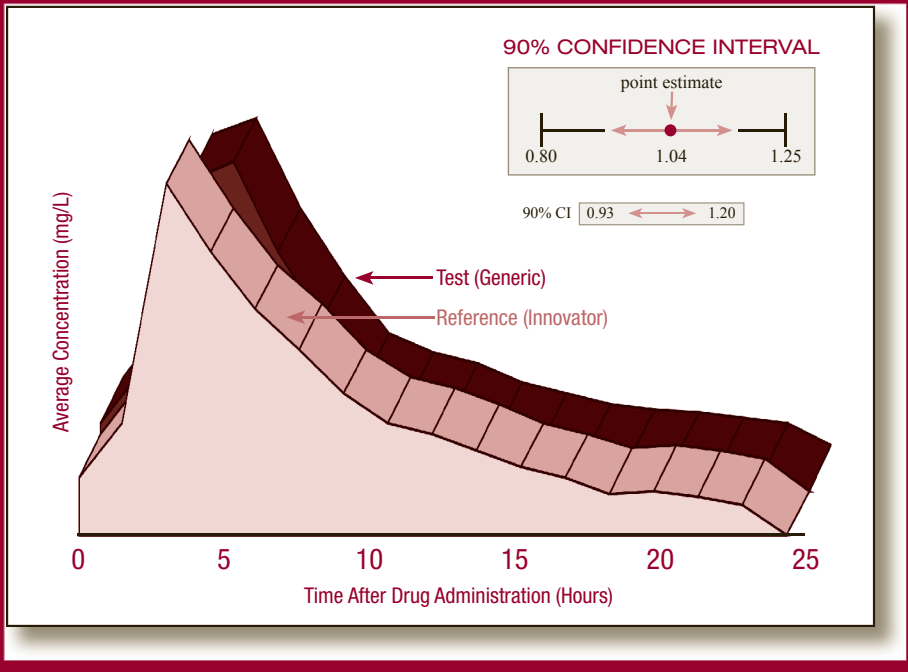
DRUGS AND THE PHARMACEUTICAL SCIENCES VOLUME 180

Generic Drug Product Development

Bioequivalence Issues



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Bioequivalence Issues

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Generic Drug Product Development

Bioequivalence Issues

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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*

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1

Introduction—Bioequivalence Issues

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GENERIC DRUG PRODUCT SUBSTITUTION AND THERAPEUTIC EQUIVALENCE

Generic drug products, also referred to as multi-source medicines, are drug products containing the same active pharmaceutical drug ingredient (API) in the same dosage form as that marketed by the innovator (brand) company. Generic drug products that meet national regulatory requirements for therapeutic equivalence and are approved by a regulatory agency can be substituted for their brand name counterparts with the full expectation that the generic drug product will produce the same clinical effect and safety profile as the prescribed product.

In the United States as in many other countries, a generic drug product is considered a *therapeutic equivalent* to the innovator (brand) drug product if it meets the regulatory requirements for therapeutic equivalence. To be classified as a therapeutic equivalent, generic drug products must meet the following general criteria as defined in the Orange Book (1):

1. They are approved as safe and effective
2. They are pharmaceutical equivalents in that they
   (a) contain identical amounts of the same API in the same dosage form and are intended to be administered by the same route of administration, and

(b) meet compendial or other applicable standards of strength, quality, purity, and identity and exert essentially the same effects with respect to both efficacy and safety.

3. They are bioequivalent in that
   (a) they do not present a known or potential bioequivalence problem, and they meet an acceptable in vitro standard, or
   (b) if they do present such a known or potential problem, they are shown to meet an appropriate bioequivalence standard.
4. They are adequately labeled
5. They are manufactured in compliance with Current Good Manufacturing Practice regulations.

The United States Food and Drug Administration (FDA) considers drug products to be therapeutically equivalent if they meet the criteria outlined above, even though they may differ in certain other characteristics such as shape, scoring configuration, packaging, excipients (including colors, flavors, preservatives), expiration date/time and minor aspects of labeling (e.g., the presence of specific pharmacokinetic information) and storage

It should, however, be emphasized that the concept of therapeutic equivalence does not encompass a comparison of different therapeutic agents used for the same condition (e.g., propoxyphene hydrochloride *vs.* pentazocine hydrochloride for the treatment of pain). Whereas initially bioequivalence was only applicable to pharmaceutically equivalent products, in some countries this is no longer a requirement (2–5). In these countries, products that are not pharmaceutical equivalents as defined by the Orange Book, may be considered therapeutic equivalents, and as such, substitutable. In those countries, therapeutic equivalence has been extended to include pharmaceutical alternatives. According to the European Agency for the Evaluation of Medicinal Products (2), "Medicinal products are pharmaceutical alternatives if they contain the same active moiety but differ in chemical form (salt, ester, etc.) of that moiety or in the dosage form or strength." Furthermore, the term, pharmaceutical alternatives has also been included in their definition of bioequivalence, viz. "Two medicinal products are bioequivalent if they are pharmaceutically equivalent or pharmaceutical alternatives and if their bioavailabilities after administration in the same molar dose are similar to such degree that their effects, with respect to both efficacy and safety, will be essentially the same." Similarly, WHO (3) has defined pharmaceutical alternatives as: "Products are pharmaceutical alternative(s) if they contain the same molar amount of the same active pharmaceutical moeity(s) but differ in dosage form (e.g., tablets versus capsules), and/or chemical form (e.g., different salts, different esters)." Pharmaceutical alternatives deliver the same active moiety by the same route of administration but are otherwise not pharmaceutically equivalent. They may or may not be bioequivalent or therapeutically equivalent with the comparator product.

According to the FDA (4), drug products are considered pharmaceutical alternatives if they contain the same therapeutic moiety, but are different salts, esters, or complexes of that moiety, or are different dosage forms or strengths (e.g., tetracycline hydrochloride, 250 mg capsules *vs.* tetracycline phosphate complex, 250 mg capsules, 250 mg capsules; quinidine sulfate, 200 mg tablets vs.quinidine sulfate, 200 mg capsules). In addition, FDA considers different dosage forms and strengths within a product line by a single manufacturer as pharmaceutical alternatives, as are extended-release products when compared with immediate-release or standard-release formulations of the same active ingredient. However, FDA does not at this time consider tablet and capsule formulations as a therapeutic equivalents even if they have been shown to be bioequivalent.

The reader is referred to Chapter 3 in this book that is devoted to a comprehensive discussion on pharmaceutical alternatives.

BIOAVAILABILITY

Bioavailability is defined as the *rate* and *extent* to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action (1). Bioavailability studies are important part of new drug development to establish a *systemic exposure* profile obtained by measuring the concentration of drug and/or metabolite concentration in the systemic circulation over time (4). Bioavailability data provides an estimate of the fraction of drug absorbed as well as drug distribution and elimination. Bioavailability studies are also used to develop a therapeutic dosage regimen. In generic drug development, bioequivalence studies are used to determine bioequivalence.

The most common approach for the determination of bioavailability is the in vivo measurement of active moiety or moieties in biologic fluid (e.g., plasma, urine). After a drug product is administered to a volunteer or patient, a plasma drug concentration curve versus time profile is obtained (Fig. 1). The major parameters representing the rate and extent of drug absorption are:

1. C_{max}. The peak plasma drug concentration, C_{max} is used as a measurement for the rate of drug bioavailability. C_{max} has the units of mass/volume.
2. AUC. The area under the plasma level–time curve, AUC, is a measurement of the extent of drug bioavailability.
3. T_{max}. The time of peak plasma concentration, T_{max}, corresponds to the time required to reach maximum drug concentration after drug administration.

Based on the above, the rate (C_{max}) and extent (AUC) to which the active ingredient is absorbed and becomes available from similar

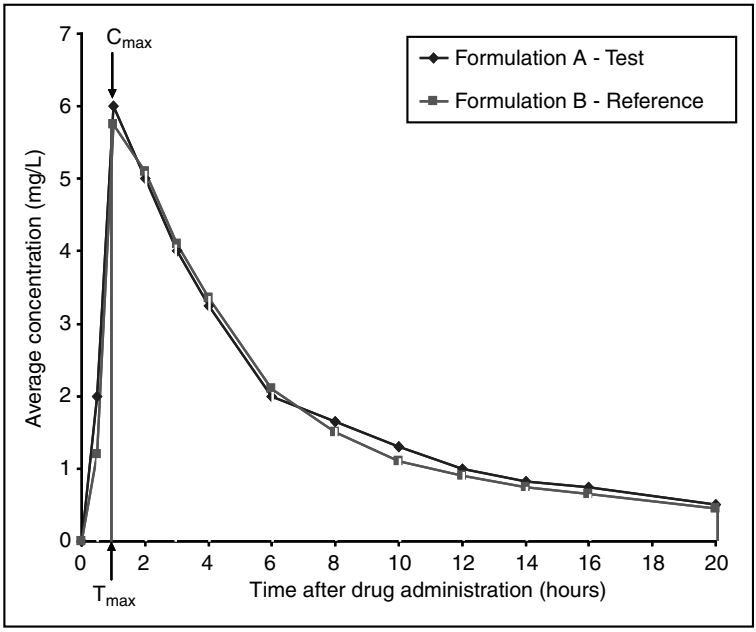

Figure 1 Bioequivalence of test and reference drug products.

formulations can readily be compared. As such these variables are thus used as surrogate measures of safety (C_{max}) and efficacy (AUC). Hence, when different formulations of the same drug in identical dosage forms are compared on the basis of their bioavailabilities, and are found to be bioequivalent, it can reasonably be expected that they will exhibit essentially similar therapeutic and safety/toxicity profiles following administration to patients. It is, however, important that such products should be neither better nor worse relative to each other since they can only be equivalent or inequivalent.

For drug products that are not intended to be absorbed into the bloodstream, bioavailability may be assessed by measurements intended to reflect the rate and extent to which the active ingredient or active moiety becomes available at the site of action. Other methods for assessing bioavailability use endpoints such as acute pharmacodynamic effect, clinical observations or in vitro studies.

BIOEQUIVALENCE

Bioequivalent drug products are pharmaceutical equivalent or pharmaceutical alternative products that display comparable bioavailability to a reference drug product when studied under similar experimental conditions (1). The test drug product (usually the generic product) is considered

bioequivalent to the reference drug product (usually the brand product) if the rate and extent of absorption of the test drug does not show a significant difference from the rate and extent of absorption of the reference drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions. Both bioequivalence and bioavailability studies focus on the release of a drug substance from a drug product and subsequent absorption into the systemic circulation. For this reason, similar approaches to measuring bioavailability are used to assess bioequivalence.

The objective of a bioequivalence study is to compare formulation performance, between two or more drug products and is demonstrated by equivalent bioavailability.

Formulation performance is defined as the release of the drug substance from the drug product leading to bioavailability of the drug substance and eventually leading to one or more pharmacologic effects, both desirable and undesirable (6). Bioequivalence is a measure of formulation performance. After a drug product has been approved for marketing, a major change in the formulation (e.g., postapproval change) that affects components and composition, scale-up, site change, and manufacturing process or equipment changes may require an in vivo bioequivalence study (7,8). The postapproval bioequivalence study is necessary to demonstrate that the new formulation, manufacturing process, etc. and the performance of the new drug product is not different than the performance or the original drug product. Bioequivalence studies may also be used as "bridging" studies during new drug development when the innovator drug manufacturer changes the original clinical formulation of the drug used in the safety and efficacy studies to the final formulation to be marketed as the drug product.

Table 1 Approaches to Determining Bioequivalence

Method	Example
In vivo measurement of active moiety or moieties in biologic fluid (e.g., plasma, urine)	Oral drug products intended for systemic drug absorption
In vivo pharmacodynamic comparison	FEV_1—Albuterol Blanching Study—Topical Corticosteroids
In vivo limited clinical comparison	Nonsteroidal and other topical drug products not intended for absorption into the systemic circulation
In vitro comparisons	Comparative dissolution profiles
Any other approach deemed appropriate by FDA	Cholestyramine binding to bile acids

Various approaches for the determination of bioequivalence are listed in Table 1. The measurement of the active drug in a biologic fluid is the most direct approach and generally has the least variability. The use of clinical endpoints to establish bioequivalence is generally the most variable in vivo approach and is least sensitive to small changes in drug bioavailability (see Chapter 5).

Bioequivalence may sometimes be demonstrated using an in vitro bioequivalence standard, especially when such an in vitro test has been correlated with human in vivo bioavailability data. In other situations, bioequivalence may sometimes be demonstrated through comparative clinical trials or pharmacodynamic studies. Where these above methods are not applicable (e.g., for drug products that are not intended to be absorbed into the bloodstream), other in vivo or in vitro test methods to demonstrate bioequivalence may be appropriate.

STATISTICAL CRITERIA FOR BIOEQUIVALENCE

Since different products containing the same active ingredient, or even the same product administered to the same subject on two separate occasions, rarely exhibit completely identical and superimposable profiles, some degree of difference must be considered acceptable to assure safety and efficacy without compromising therapeutic performance. Although, the substitution of a bioequivalent product necessitates that the therapeutic outcomes must be the same, hence sound scientific decision rules must be used for the declaration of bioequivalence. Such rules have been formulated using appropriate statistical criteria.

Study Designs

The most common design for a bioequivalence study that compares the test product to the reference product is a conventional nonreplicated design, such as the standard two-formulation, two-period, two-sequence crossover design. The crossover study is used most frequently for estimating bioequivalence of two or more drug products. The bioequivalence study is usually performed in a limited number of healthy volunteers, over 18 years of age or older and capable of giving informed consent. Generally, bioequivalence studies are conducted in subjects representative of the general population, taking into account age, sex, and race. Other subject populations may be used due to safety considerations. The assumptions in a crossover study are that drug clearance, volume of distribution, and absorption, as determined by physiological variables (e.g., gastric emptying, motility, pH), are assumed to have less inter-occasion variability compared to the variability arising from formulation performance. Therefore, differences between two products because of formulation factors can be

determined. Under certain circumstances, parallel designs can also be used (4). Other study designs may be used and are discussed in this book and elsewhere (9).

Reference Drug Product

FDA designates a reference-listed drug (RLD) as the standard to which all generic versions must be shown to be bioequivalent. The RLD is generally the brand-name drug that has been approved following the filing of a full new drug application. For US marketed drug products, the RLD is listed in the Orange Book (1). FDA hopes to avoid possible significant variations among generic drugs and their brand name counterpart. Such variations could result if generic drugs were compared to different reference drug products.

Statistical Considerations

The statistical methodology for analyzing these bioequivalence studies is called the two one-sided test procedure (9,10). Two situations are tested with this statistical methodology. The first of the two one-sided tests determines whether a generic product (test), when substituted for a brand-name product (reference) is significantly less bioavailable. The second of the two one-sided tests determines whether a brand-name product when substituted for a generic product is significantly less bioavailable.

Based on historical pharmacodynamic data and FDA medical experts, a significant difference in a clinical effect is not observed when a difference in plasma drug concentrations following administration of a test and reference product are less than 20%.

By convention, all bioequivalence data are expressed as a ratio of the average response (AUC and C_{max}) for Test/Reference. The statistical criteria for acceptance of a generic product (test) are based on 90% confidence intervals (CIs) and not based upon differences in average values for AUC and C_{max}. The 90% CIs for the Test product must fall within 80% to 120% of the Reference product based on nonlog transformed data. The use of log-transformed data tends to normalize the statistical distribution of the data. Therefore, based on log-transformed data, the 90% CIs for the test product must fall within 80% to 125% of the Reference product. The determination of the 90% CIs is performed by using two one-sided *t*-tests (9,10). These tests decide whether the response values (AUC and C_{max}) for the test product is significantly greater or significantly less than those for the Reference product.

All data are thus log-transformed prior to conducting statistical testing. In practice, these statistical tests are carried out using an analysis of variance (ANOVA) procedure and calculating a 90% CI for each pharmacokinetic parameter (C_{max} and AUC). A 90% CI is used since it allows a 5% statistical error at both the upper and lower limits which translates into a 10% total