Chapter 15. Bioavailability and Bioequivalence >

Study Submission and Drug Review Process

The contents of New Drug Applications (NDAs) and Abbreviated New Drug Applications (ANDAs) are similar in terms of the quality of manufacture (). The submission for a NDA must contain safety and efficacy study as provided by animal toxicology studies, clinical efficacy studies, and pharmacokinetic/bioavailability studies. For the generic drug manufacturer, the bioequivalence study is the pivotal study in the ANDA that replaces the animal, clinical, and pharmacokinetic studies.

Table 15.8 NDA versus ANDA Review Process

Brand–Name Drug NDA Requirements	**Generic Drug ANDA Requirements**
1. Chemistry	1. Chemistry
2. Manufacturing	2. Manufacturing
3. Controls	3. Controls
4. Labeling	4. Labeling
5. Testing	5. Testing
6. Animal studies	6. Bioequivalence
7. Clinical studies	
8. Bioavailability	

Source: Center for Drug Evaluation & Research, U.S. Food & Drug Administration.

An outline for the submission of a completed bioavailability study for submission to the FDA is shown in . The investigator should be sure that the study has been properly designed, the objectives are clearly defined, and the method of analysis has been validated (ie, shown to measure precisely and accurately the plasma drug concentration). The results are analyzed both statistically and pharmacokinetically. These results, along with case reports and various data supporting the validity of the analytical method, are included in the submission. The FDA reviews the study in detail according to the outline presented in . If necessary, an FDA investigator may inspect both the clinical and analytical facilities used in the study and audit the raw data used in support of the bioavailability study. For ANDA applications, the FDA Office of Generic Drugs reviews the entire ANDA as shown in . If the application is incomplete, the FDA will not review the submission and the sponsor will receive a Refusal to File letter.

Table 15.9 Proposed Format and Contents of an *In-Vivo* Bioequivalence Study Submission and Accompanying *In-Vitro* Data

Title page
Study title
Name of sponsor
Name and address of clinical laboratory
Name of principal investigator(s)
Name of clinical investigator
Name of analytical laboratory
Dates of clinical study (start, completion)
Signature of principal investigator (and date)
Signature of clinical investigator (and date)
Table of contents
I. Study Résumé
Product information
Summary of bioequivalence study

Summary of bioequivalence data
Plasma
Urinary excretion
Figure of mean plasma concentration–time profile
Figure of mean cumulative urinary excretion
Figure of mean urinary excretion rates
II. Protocol and Approvals
Protocol
Letter of acceptance of protocol from FDA
Informed consent form
Letter of approval of Institutional Review Board
List of members of Institutional Review Board
III. Clinical Study
Summary of the study
Details of the study
Demographic characteristics of the subjects
Subject assignment in the study
Mean physical characteristics of subjects arranged by sequence
Details of clinical activity
Deviations from protocol
Vital signs of subjects
Adverse reactions report
IV. Assay Methodology and Validation
Assay method description
Validation procedure
Summary of validation
Data on linearity of standard samples
Data on interday precision and accuracy
Data on intraday precision and accuracy
Figure for standard curve(s) for low/high ranges
Chromatograms of standard and quality control samples
Sample calculation
V. Pharmacokinetic Parameters and Tests
Definition and calculations
Statistical tests
Drug levels at each sampling time and pharmacokinetic parameters
Figure of mean plasma concentration–time profile
Figures of individual subject plasma concentration–time profiles
Figure of mean cumulative urinary excretion
Figures of individual subject cumulative urinary excretion
Figure of mean urinary excretion rates
Figures of individual subject urinary excretion rates

Tables of individual subject data arranged by drug, drug/period, drug/sequence
VI. Statistical Analyses
Statistical considerations
Summary of statistical significance
Summary of statistical parameters
Analysis of variance, least squares estimates and least-squares means
Assessment of sequence, period, and treatment effects
90% Confidence intervals for the difference between Test and Reference products for the log-normal-transformed parameters of AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} should be within 80% and 125%
VII. Appendices
Randomization schedule
Sample identification codes
Analytical raw data
Chromatograms of at least 20% of subjects
Medical record and clinical reports
Clinical facilities description
Analytical facilities description
Curricula vitae of the investigators
VIII. *In-Vitro* Testing
Dissolution testing
Dissolution assay methodology
Content uniformity testing
Potency determination
IX. Batch Size and Formulation
Batch record
Quantitative formulation

Modified from Dighe and Adams (1991), with permission.

Table 15.10 General Elements of a Biopharmaceutics Review	
Introduction	Summary and analysis of data
Study design	Comments
Study objective(s)	Deficiencies
Assay description and validation	Recommendation
Assay for individual samples checked	

Figure 15-10.
Generic drug review process. *Source:* Office of Generic Drugs, Center for Drug Evaluation & Research, U.S. Food & Drug Administration.

Waivers of *In-Vivo* Bioequivalence Studies (Biowaivers)

In some cases, *in-vitro* dissolution testing may be used in lieu of *in-vivo* bioequivalence studies. When the drug product is in the same dosage form but in different strengths, and is proportionally similar in active and inactive ingredients, an *in-vivo* bioequivalence study of one or more lower strengths can be waived based on the dissolution tests and an *in-vivo* bioequivalence study on the highest strength. Ideally, if there is a strong correlation between

dissolution of the drug and the bioavailability of the drug, then the comparative dissolution tests comparing the test product to the reference product should be sufficient to demonstrate bioequivalence. For most drug products, especially immediate-release tablets and capsules, no strong correlation exists, and the FDA requires an *in-vivo* bioequivalence study. For oral solid dosage forms, an *in-vivo* bioequivalence study may be required to support at least one dose strength of the product. Usually, an *in-vivo* bioequivalence study is required for the highest dose strength. If the lower-dose-strength test product is substantially similar in active and inactive ingredients, then only a comparison *in-vitro* dissolution between the test and brand-name formulations may be used.
For example, an immediate-release tablet is available in 200-mg, 100-mg, and 50-mg strengths. The 100- and 50-mg-strength tablets are made the same way as the highest-strength tablet. A human bioequivalence study is performed on the highest or 200-mg strength. Comparative *in-vitro* dissolution studies are performed on the 100-mg and 50-mg dose strengths. If these drug products have no known bioavailability problems, are well absorbed systemically, are well correlated with *in-vitro* dissolution, and have a large margin of safety, then arguments for not performing an *in-vivo* bioavailability study may be valid. Methods for correlation of *in-vitro* dissolution of the drug with *in-vivo* drug bioavailability are discussed in and . The manufacturer does not need to perform additional *in-vivo* bioequivalence studies on the lower-strength products if the products meet all *in-vitro* criteria.
Dissolution Profile Comparison
Comparative dissolution profiles are used as (1) the basis for formulation development of bioequivalent drug products and proceeding to the pivotal *in-vivo* bioequivalence study; (2) comparative dissolution profiles are used for demonstrating the equivalence of a change in the formulation of a drug product after the drug product has been approved for marketing (see SUPAC in); and (3) the basis of a biowaiver of a lower-strength drug product that is dose proportional in active and inactive ingredients to the higher-strength drug product.
A model-independent mathematical method was developed by to compare dissolution profiles using two factors, f_1 and f_2. The factor f_2, known as the *similarity factor*, measures the closeness between the two profiles:

where n is the number of time points, R_1 is the dissolution value of the Reference product at time t, and T_1 is the dissolution value of the Test product batch at time t.
The Reference may be the original drug product before a formulation change (prechange) and the Test may be the drug product after the formulation was changed (postchange). Alternatively, the Reference may be the higher-strength drug product and the Test may be the lower-strength drug product. The f_2 comparison is the focus of several FDA guidances and is of regulatory interest in knowing the similarity of the two dissolution curves. When the two profiles are identical, $f_2 = 100$. An average difference of 10% at all measured time points results in a f_2 value of 50. The FDA has set a public standard for f_2 value between 50 and 100 to indicate similarity between two dissolution profiles.
In some cases, two generic drug products may have dissimilar dissolution profiles and still be bioequivalent *in-vivo*. For example, have shown that slow-, medium-, and fast-dissolving formulations of metoprolol tartrate tablets were bioequivalent. Furthermore, bioequivalent modified-release drug products may have different drug release mechanisms and therefore different dissolution profiles. For example, for theophylline extended-release capsules, the *United States Pharmacopeia* (USP) lists 10 individual drug release tests for products labeled for dosing every 12 hours. However, only generic drug products that are FDA approved as bioequivalent drug products and listed in the current edition of the *Orange Book* may be substituted for each other.
The Biopharmaceutics Classification System (BCS)
A theoretical basis for correlating *in-vitro* drug dissolution with *in-vivo* bioavailability was developed by . This approach is based on the aqueous solubility of the drug and the permeation of the drug through the gastrointestinal tract. The classification system is based on Fick's first law applied to a membrane:

where J_w is the drug flux (mass/area/time) through the intestinal wall at any position and time, P_w is the permeability of the membrane, and C_w is the drug concentration at the intestinal membrane surface.
This approach assumes that no other components in the formulation affect the membrane permeability and/or intestinal transport. Using this approach, studied the solubility and permeability characteristics of various representative drugs and obtained a biopharmaceutic drug classification () for predicting the *in-vitro* drug dissolution of immediate-release solid oral drug products with *in-vivo* absorption.

Table 15.11 Biopharmaceutics Classification System

Class	Solubility	Permeability	Comments
Class 1	High	High	Drug dissolves rapidly and is well absorbed. Bioavailability problem is not expected for immediate release drug products.

Class 2	Low	High	Drug is dissolution limited and well absorbed. Bioavailability is controlled by the dosage form and rate of release of the drug substance.
Class 3	High	Low	Drug is permeability limited. Bioavailability may be incomplete if drug is not released and dissolved within absorption window.
Class 4	Low	Low	Difficulty in formulating a drug product that will deliver consistent drug bioavailability. An alternate route of administration may be needed.

From *FDA Guidance for Industry: Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate Release Solid Oral Dosage Forms Containing Certain Active Moieties/Active Ingredients Based on a Biopharmaceutics Classification System* (2000), and .

The FDA may waive the requirement for performing an *in-vivo* bioavailability or bioequivalence study for certain immediate-release solid oral drug products that meet very specific criteria, namely, the permeability, solubility, and dissolution of the drug. These characteristics include the *in-vitro* dissolution, of the drug product in various media, drug permeability information, and assuming ideal behavior of the drug product, drug dissolution, and absorption in the GI tract. For regulatory purpose, drugs are classified according to the Biopharmaceutics Classification System (BCS) in accordance the solubility, permeability, and dissolution characteristics of the drug (*FDA Guidance for Industry*, 2000;).

Solubility

An objective of the BCS approach is to determine the equilibrium solubility of a drug under approximate physiologic conditions. For this purpose, determination of pH–solubility profiles over a pH range of 1–8 is suggested. The solubility class is determined by calculating what volume of an aqueous medium is sufficient to dissolve the highest anticipated dose strength. A drug substance is considered highly soluble when the highest dose strength is soluble in 250 mL or less of aqueous medium over the pH range 1–8. The volume estimate of 250 mL is derived from typical bioequivalence study protocols that prescribe administration of a drug product to fasting human volunteers with a glass (8 ounces) of water.

Permeability

Studies of the extent of absorption in humans, or intestinal permeability methods, can be used to determine the permeability class membership of a drug. To be classified as highly permeable, a test drug should have an extent of absorption > 90% in humans. Supportive information on permeability characteristics of the drug substance should also be derived from its physical-chemical properties (eg, octanol: water partition coefficient).

Some methods to determine the permeability of a drug from the gastrointestinal tract include: (1) *in-vivo* intestinal perfusion studies in humans; (2) *in-vivo* or *in-situ* intestinal perfusion studies in animals; (3) *in-vitro* permeation experiments using excised human or animal intestinal tissues; and (4) *in-vitro* permeation experiments across a monolayer of cultured human intestinal cells. When using these methods, the experimental permeability data should correlate with the known extent-of-absorption data in humans.

Dissolution

The dissolution class is based on the *in-vitro* dissolution rate of an immediate-release drug product under specified test conditions and is intended to indicate rapid *in-vivo* dissolution in relation to the average rate of gastric emptying in humans under fasting conditions. An immediate-release drug product is considered rapidly dissolving when not less than 85% of the label amount of drug substance dissolves within 30 minutes using USP Apparatus I (see) at 100 rpm or Apparatus II at 50 rpm in a volume of 900 mL or less in each of the following media: (1) acidic media such as 0.1 N HCl or Simulated Gastric Fluid USP without enzymes, (2) a pH 4.5 buffer, and (3) a pH 6.8 buffer or Simulated Intestinal Fluid USP without enzymes.

Drug Products for Which Bioavailability or Bioequivalence May Be Self-Evident

The best measure of a drug product's performance is to determine the *in-vivo* bioavailability of the drug. For some well-characterized drug products and for certain drug products in which bioavailability is self-evident (eg, sterile solutions for injection), *in-vivo* bioavailability studies may be unnecessary or unimportant to the achievement of the product's intended purposes. The FDA will waive the requirement for submission of *in-vivo* evidence demonstrating the bioavailability of the drug product if the product meets one of the following criteria (U.S. Code of Federal Regulations, 21 CFR 320.22). However, there may be specific requirements for certain drug products, and the appropriate FDA division should be consulted.

1. The drug product (a) is a solution intended solely for intravenous administration and (b) contains an active drug ingredient or therapeutic moiety combined with the same solvent and in the same concentration as in an intravenous solution that is the subject of an approved, full, New Drug Application.

2. The drug product is a topically applied preparation (eg, a cream, ointment, or gel intended for local therapeutic effect). The FDA has released guidances for the performance of bioequivalence studies on topical corticosteroids and antifungal agents. The FDA is also considering performing dermatopharmacokinetic (DPK) studies on other topical drug products. In addition, *in-vitro* drug release and diffusion studies may be required.

3. The drug product is in an oral dosage form that is not intended to be absorbed (eg, an antacid or a radiopaque medium). Specific *in-vitro* bioequivalence studies may be required by the FDA. For example, the bioequivalence of cholestyramine resin is demonstrated *in-vitro* by the binding of bile acids to the resin.
4. The drug product meets both of the following conditions:
a. It is administered by inhalation as a gas or vapor (eg, as a medicinal or as an inhalation anesthetic).
b. It contains an active drug ingredient or therapeutic moiety in the same dosage form as a drug product that is the subject of an approved, full, New Drug Application(NDA).
5. The drug product meets all of the following conditions:
a. It is an oral solution, elixir, syrup, tincture, or similar other solubilized form.
b. It contains an active drug ingredient or therapeutic moiety in the same concentration as a drug product that is the subject of an approved, full, New Drug Application.
c. It contains no inactive ingredient that is known to significantly affect absorption of the active drug ingredient or therapeutic moiety.

Generic Biologics

Biologics, in contrast to drugs that are chemically synthesized, are derived from living sources such as human, animal, or microorganisms. Many biologics are complex mixtures that are not easily identified or characterized and are manufactured by biotechnology. Other biological drugs, such as insulin and growth hormone, are proteins derived by biotechnology and have been well characterized.

Presently, there is no FDA regulatory pathway to establish the bioequivalence of a biotechnology-derived drug product. Scientifically, there are advocates for and against the feasibility for the manufacture of generic biotechnology-derived drug products (generic biologics) that are bioequivalent to the innovator or brand-drug product.

Those opposed to the development of generic biologics have claimed that generic manufacturers do not have the ability to fully characterize the active ingredient(s), that immunogenicity-related impurities may be present in the product, and that the manufacture of a biologic drug product is process dependent.

Many biologic drug products are given parenterally. The efficacy of the biologic may be affected by the development of antibodies to the active ingredient or to product-related impurities. The degree of immunogenicity and subsequent antibody formation to a foreign peptide or protein will alter the efficacy of the drug. Antibodies can increase bioavailability if they are not neutralizing, which would result in higher drug levels in the body. In contrast, antibodies can decrease bioavailability of the biologic drug by forming an antibody–protein complex that results in a change in drug distribution and a change in clearance.

Advocates for the manufacture of generic biologics argue that bioequivalent biotechnology-derived drug products can be made on a case-by-case basis. Currently, manufacturers of marketed biotechnology drugs may seek to make changes in the manufacturing process used to make a particular product for a variety of reasons, including improvement of product quality, yield, and manufacturing efficiency. These manufacturers have developed improvements in production methods, process and control test methods, and test methods for product characterization.

For example, a biologics manufacturer institutes a change in its manufacturing process, before FDA approval of its product but after completion of a pivotal clinical study. The FDA may not require the manufacturer to perform additional clinical studies to demonstrate that the resulting product is still safe, pure, and potent. Such manufacturing process changes, implemented before or after product approval, have included changes implemented during expansion from pilot-scale to full-scale production, the move of production facilities from one legal entity to another legal entity, and the implementation of changes in different stages of the manufacturing process such as fermentation, purification, and formulation. The manufacturer may be able to demonstrate product comparability between a biological product made after a manufacturing change ("new" product) and a product made before implementation of the change ("old" product) through different types of analytical and functional testing, with or without preclinical animal testing. The FDA may determine that two products are comparable if the results of the comparability testing demonstrate that the manufacturing change does not affect safety, identity, purity, or potency (*FDA Guidance Concerning Demonstration of Comparability of Human Biological Products, Including Therapeutic Biotechnology-Derived Products*, 1996). The FDA currently requires that manufacturers should carefully assess manufacturing changes and evaluate the product resulting from these changes for comparability to the preexisting product. Determinations of product comparability may be based on chemical, physical, and biological assays and, in some cases, other nonclinical data.

It is important to note that the FDA uses such terms as *comparable* and *similar* for approval of manufacturing changes of biologic drug products (*FDA Guidance,* 1996). In contrast, the FDA uses the term *bioequivalence* for approval of manufacturing changes of drug products that contain chemically derived active ingredients. Advocates for the manufacturer of generic biologics feel that the science and technology for the manufacture of certain bioequivalent biologic drug products are already available. Moreover, if the innovator manufacturer of a marketed biologic drug product can perform a manufacturing change and demonstrate the comparability of the "new" to the

"old" marketed biologic drug product, then a generic manufacturer should be able to use similar techniques to demonstrate bioequivalence of the generic drug product.

Clinical Significance of Bioequivalence Studies

Bioequivalence of different formulations of the same drug substance involves equivalence with respect to rate and extent of systemic drug absorption. Clinical interpretation is important in evaluating the results of a bioequivalence study. A small difference between drug products, even if statistically significant, may produce very little difference in therapeutic response. Generally, two formulations whose rate and extent of absorption differ by 20% or less are considered bioequivalent. The considered that differences of less than 20% in AUC and C_{max} between drug products are "unlikely to be clinically significant in patients." The Task Force further stated that "clinical studies of effectiveness have difficulty detecting differences in doses of even 50–100%." Therefore, normal variation is observed in medical practice and plasma drug levels may vary among individuals greater than 20%.

According to , a small, statistically significant difference in drug bioavailability from two or more dosage forms may be detected if the study is well controlled and the number of subjects is sufficiently large. When the therapeutic objectives of the drug are considered, an equivalent clinical response should be obtained from the comparison dosage forms if the plasma drug concentrations remain above the minimum effective concentration (MEC) for an appropriate interval and do not reach the minimum toxic concentration (MTC). Therefore, the investigator must consider whether any statistical difference in bioavailability would alter clinical efficiency.

Special populations, such as the elderly or patients on drug therapy, are generally not used for bioequivalence studies. Normal, healthy volunteers are preferred for bioequivalence studies, because these subjects are less at risk and may more easily endure the discomforts of the study, such as blood sampling. Furthermore, the objective of these studies is to evaluate the bioavailability of the drug from the dosage form, and use of healthy subjects should minimize both inter- and intrasubject variability. It is theoretically possible that the excipients in one of the dosage forms tested may pose a problem in a patient who uses the generic dosage form.

For the manufacture of a dosage form, specifications are set to provide uniformity of dosage forms. With proper specifications, quality control procedures should minimize product-to-product variability by different manufacturers and lot-to-lot variability with a single manufacturer (see).

Special Concerns in Bioavailability and Bioequivalence Studies

The general bioequivalence study designs and evaluation, such as the comparison of AUC, C_{max}, and t_{max}, may be used for systemically absorbed drugs and conventional oral dosage forms. However, for certain drugs and dosage forms, systemic bioavailability and bioequivalence are difficult to ascertain (). Drugs and drug products (eg, cyclosporine, chlorpromazine, verapamil, isosorbide dinitrate, sulindac) are considered to be highly variable if the intrasubject variability in bioavailability parameters is greater than 30% by analysis of variance coefficient of variation (). The number of subjects required to demonstrate bioequivalence for these drug products may be excessive, requiring more than 60 subjects to meet current FDA bioequivalence criteria. The intrasubject variability may be due to the drug itself or to the drug formulation or to both. The FDA has held public forums to determine whether the current bioequivalence guidelines need to be changed for these highly variable drugs ().

Table 15.12 Problems in Bioavailability and Bioequivalence

Drugs with high intrasubject variability	Inhalation
Drugs with long elimination half-life	Ophthalmic
Biotransformation of drugs	Intranasal
Stereoselective drug metabolism	Bioavailable drugs that should not produce peak drug levels
Drugs with active metabolites	Potassium supplements
Drugs with polymorphic metabolism	Endogeneous drug levels
Nonbioavailable drugs (drugs intended for local effect)	Hormone replacement therapy
Antacids	Biotechnology-derived drugs
Local anesthetics	Erythropoietin interferon
Anti-infectives	Protease inhibitors
Anti-inflammatory steroids	Complex drug substances
Dosage forms for nonoral administration	Conjugated estrogens
Transdermal	

For drugs with very long elimination half-lives or a complex elimination phase, a complete plasma drug

concentration–time curve (ie, three elimination half-lives or an AUC representing 90% of the total AUC) may be difficult to obtain for a bioequivalence study using a crossover design. For these drugs, a truncated (shortened) plasma drug concentration–time curve (0–72 hr) may be more practical. The use of a truncated plasma drug concentration–time curve allows for the measurement of peak absorption and decreases the time and cost for performing the bioequivalence study.

Many drugs are stereoisomers, and each isomer may give a different pharmacodynamic response and may have a different rate of biotransformation. The bioavailability of the individual isomers may be difficult to measure because of problems in analysis. Some drugs have active metabolites, which should be quantitated as well as the parent drug. Drugs such as thioridazine and selegilene have two active metabolites. The question for such drugs is whether bioequivalence should be proven by matching the bioavailability of both metabolites and the parent drug. Assuming both biotransformation pathways follow first-order reaction kinetics, then the metabolites should be in constant ratio to the parent drug. Genetic variation in metabolism may present a bioequivalence problem. For example, the acetylation of procainamide to N-acetylprocainamide demonstrates genetic polymorphism, with two groups of subjects consisting of rapid acetylators and slow acetylators. To decrease intersubject variability, a bioequivalence study may be performed on only one phenotype, such as the rapid acetylators.

Some drugs (eg, benzocaine, hydrocortisone, anti-infectives, antacids) are intended for local effect and formulated as topical ointments, oral suspensions, or rectal suppositories. These drugs should not have significant systemic bioavailability from the site of administration. The bioequivalence determination for drugs that are not absorbed systemically from the site of application can be difficult to assess. For these nonsystemic-absorbable drugs, a "surrogate" marker is needed for bioequivalence determination (). For example, the acid-neutralizing capacity of an oral antacid and the binding of bile acids to cholestyramine resin have been used as surrogate markers in lieu of *in-vivo* bioequivalence studies.

Table 15.13 Possible Surrogate Markers for Bioequivalence Studies

Drug Product	**Drug**	**Possible Surrogate Marker for Bioequivalence**
Metered-dose inhaler	Albuterol	Forced expiratory volume (FEV_1)
Topical steroid	Hydrocortisone	Skin blanching
Anion-exchange resin	Cholestyramine	Binding to bile acids
Antacid	Magnesium and aluminum hydroxide gel	Neutralization of acid
Topical antifungal	Ketoconazole	Drug uptake into stratum corneum

Various drug delivery systems and newer dosage forms are designed to deliver the drug by a nonoral route, which may produce only partial systemic bioavailability. For the treatment of asthma, inhalation of the drug (eg, albuterol, beclomethasone dipropionate) has been used to maximize drug in the respiratory passages and to decrease systemic side effects. Drugs such as nitroglycerin given transdermally may differ in release rates, in the amount of drug in the transdermal delivery system, and in the surface area of the skin to which the transdermal delivery system is applied. Thus, the determination of bioequivalence among different manufacturers of transdermal delivery systems for the same active drug is difficult. Dermatokinetics are pharmacokinetic studies that investigate drug uptake into skin layers after topical drug administration. The drug is applied topically, the skin is peeled at various time periods after the dose, using transparent tape, and the drug concentrations are measured in the skin.

Drugs such as potassium supplements are given orally and may not produce the usual bioavailability parameters of AUC, C_{max}, and t_{max}. For these drugs, more indirect methods must be used to ascertain bioequivalence. For example, urinary potassium excretion parameters are more appropriate for the measurement of bioavailability of potassium supplements. However, for certain hormonal replacement drugs (eg, levothyroxine), the steady-state hormone concentration in hypothyroid individuals, the thyroidal-stimulating hormone level, and pharmacodynamic endpoints may also be appropriate to measure.

Generic Substitution

To contain drug costs, most states have adopted generic substitution laws to allow pharmacists to dispense a generic drug product for a brand-name drug product that has been prescribed. Some states have adopted a *positive formulary*, which lists therapeutically equivalent or interchangeable drug products that pharmacists may dispense. Other states use a *negative formulary*, which lists drug products that are not therapeutically equivalent, and/or the interchange of which is prohibited. If the drug is not in the negative formulary, the unlisted generic drug products are assumed to be therapeutically equivalent and may be interchanged.

Approved Drug Products with Therapeutic Equivalence Evaluations (*Orange Book*)

Due to public demand, the FDA Center for Drug Evaluation and Research publishes annually a listing of approved drug products, *Approved Drug Products with Therapeutic Equivalence Evaluations* (commonly known as the *Orange Book*). The Orange Book is available on the Internet at www.fda.gov/cder/orange/default.htm.

The Orange Book contains therapeutic equivalence evaluations for approved drug products made by various manufacturers. These marketed drug products are evaluated according to specific criteria. The evaluation codes used for these drugs are listed in . The drug products are divided into two major categories: "A" codes apply to drug products considered to be therapeutically equivalent to other pharmaceutically equivalent products, and "B" codes apply to drug products that the FDA does not at this time consider to be therapeutically equivalent to other pharmaceutically equivalent products. A list of therapeutic-equivalence-related terms and their definitions is also given in the monograph. According to the FDA, evaluations do not mandate that drugs be purchased, prescribed, or dispensed, but provide public information and advice. The FDA evaluation of the drug products should be used as a guide only, with the practitioner exercising professional care and judgment.

Table 15.14 Therapeutic Equivalence Evaluation Codes
A Codes
Drug products considered to be therapeutically equivalent to other pharmaceutically equivalent products
AA Products in conventional dosage forms not presenting bioequivalence problems
AB Products meeting bioequivalence requirements
AN Solutions and powders for aerosolization
AO Injectable oil solutions
AP Injectable aqueous solutions
AT Topical products
B Codes
Drug products that the FDA does not consider to be therapeutically equivalent to other pharmaceutically equivalent products
B* Drug products requiring further FDA investigation and review to determine therapeutic equivalence
BC Extended-release tablets, extended-release capsules, and extended-release injectables
BD Active ingredients and dosage forms with documented bioequivalence problems
BE Delayed-release oral dosage forms
BN Products in aerosol–nebulizer drug delivery systems
BP Active ingredients and dosage forms with potential bioequivalence problems
BR Suppositories or enemas for systemic use
BS Products having drug standard deficiencies
BT Topical products with bioequivalence issues
BX Insufficient data

Adopted from: *Approved Drug Products with Therapeutic Equivalence Evaluations* (Orange Book) (www.fda.gov/cder/orange/default.htm) 2003.

The concept of therapeutic equivalence as used to develop the Orange Book applies only to drug products containing the same active ingredient(s) and does not encompass a comparison of different therapeutic agents used for the same condition (eg, propoxyphene hydrochloride versus pentazocine hydrochloride for the treatment of pain). Any drug product in the Orange Book that is repackaged and/or distributed by other than the application holder is considered to be therapeutically equivalent to the application holder's drug product even if the application holder's drug product is single source or coded as nonequivalent (eg, BN). Also, distributors or repackagers of an application holder's drug product are considered to have the same code as the application holder. Therapeutic equivalence determinations are not made for unapproved, off-label indications. With this limitation, however, the FDA believes that products classified as therapeutically equivalent can be substituted with the full expectation that the substituted product will produce the same clinical effect and safety profile as the prescribed product (www.fda.gov/cder/orange/default.htm). Professional care and judgment should be exercised in using the Orange Book. Evaluations of therapeutic equivalence for prescription drugs are based on scientific and medical evaluations by the FDA. Products evaluated as therapeutically equivalent can be expected, in the judgment of the FDA, to have equivalent clinical effect and no difference in their potential for adverse effects when used under the conditions of their labeling. However, these products may differ in other characteristics such as shape, scoring configuration, release mechanisms, packaging, excipients (including colors, flavors, preservatives), expiration date/time, and, in some instances, labeling. If

products with such differences are substituted for each other, there is a potential for patient confusion due to differences in color or shape of tablets, inability to provide a given dose using a partial tablet if the proper scoring configuration is not available, or decreased patient acceptance of certain products because of flavor. There may also be better stability of one product over another under adverse storage conditions, or allergic reactions in rare cases due to a coloring or a preservative ingredient, as well as differences in cost to the patient.

FDA evaluation of therapeutic equivalence in no way relieves practitioners of their professional responsibilities in prescribing and dispensing such products with due care and with appropriate information to individual patients. In those circumstances where the characteristics of a specific product, other than its active ingredient, are important in the therapy of a particular patient, the physician's specification of that product is appropriate. Pharmacists must also be familiar with the expiration dates/times and labeling directions for storage of the different products, particularly for reconstituted products, to assure that patients are properly advised when one product is substituted for another.

Frequently Asked Questions

1. Why are preclinical animal toxicology studies and clinical efficacy drug studies in human subjects not required by the FDA to approve a generic drug product as a therapeutic equivalent to the brand-name drug product?

2. What do sequence, washout period, and period mean in a crossover bioavailability study?

3. Why does the FDA require a food intervention (food effect) study for some generic drug products before granting approval? For which drug products are food effect studies required?

4. What type of bioequivalence studies are required for drugs that are not systemically absorbed or for those drugs in which the C_{max} and AUC cannot be measured in the plasma?

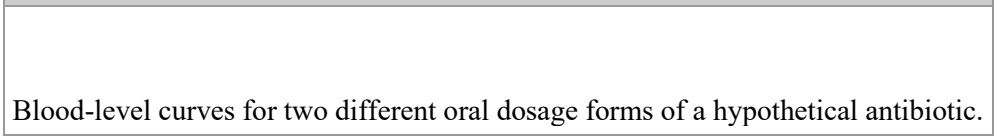
5. How does inter- and intrasubject variability affect the statistical demonstration of bioequivalence for a drug product?

6. Can chemically equivalent drug products that are not bioequivalent (ie, bioinequivalent) to each other have similar clinical efficacy?

Learning Questions

1. An antibiotic was formulated into two different oral dosage forms, A and B. Biopharmaceutic studies revealed different antibiotic blood level curves for each drug product (). Each drug product was given in the same dose as the other. Explain how the various possible formulation factors could have caused the differences in blood levels. Give examples where possible. How would the corresponding urinary drug excretion curves relate to the plasma level–time curves?

Figure 15-11.



Blood-level curves for two different oral dosage forms of a hypothetical antibiotic.

2. Assume that you have just made a new formulation of acetaminophen. Design a protocol to compare your drug product against the acetaminophen drug products on the market. What criteria would you use for proof of bioequivalence for your new formulation? How would you determine if the acetaminophen was completely (100%) systemically absorbed?

3. The data in represent the average findings in antibiotic plasma samples taken from 10 humans (average weight 70 kg), tabulated in a four-way crossover design.

Table 15.15 Comparison of Plasma Concentrations of Antibiotic, as Related to Dosage Form and Time

	Plasma Concentration (g/ml)			
Time after Dose (hr)	**IV Solution (2 mg/kg)**	**Oral Solution (10 mg/kg)**	**Oral Tablet (10 mg/kg)**	**Oral Capsule (10 mg/kg)**
0.5	5.94	23.4	13.2	18.7
1.0	5.30	26.6	18.0	21.3
1.5	4.72	25.2	19.0	20.1
2.0	4.21	22.8	18.3	18.2
3.0	3.34	18.2	15.4	14.6
4.0	2.66	14.5	12.5	11.6
6.0	1.68	9.14	7.92	7.31
8.0	1.06	5.77	5.00	4.61

10.0	0.67	3.64	3.16	2.91
12.0	0.42	2.30	1.99	1.83
	29.0	145.0	116.0	116.0

a. Which of the four drug products in would be preferred as a reference standard for the determination of relative bioavailability? Why?
b. From which oral drug product is the drug absorbed more rapidly?
c. What is the absolute bioavailability of the drug from the oral solution?
d. What is the relative bioavailability of the drug from the oral tablet compared to the reference standard?
e. From the data in , determine:
(1) Apparent V_D
(2) Elimination $t_{1/2}$
(3) First-order elimination rate constant k
(4) Total body clearance
f. From the data above, graph the cumulative urinary excretion curves that would correspond to the plasma concentration time curves.
4. Aphrodisia is a new drug manufactured by the Venus Drug Company. When tested in humans, the pharmacokinetics of the drug assume a one-compartment open model with first-order absorption and first-order elimination:

The drug was given in a single oral dose of 250 mg to a group of college students 21–29 years of age. Mean body weight was 60 kg. Samples of blood were obtained at various time intervals after the administration of the drug, and the plasma fractions were analyzed for active drug. The data are summarized in .

Table 15.16 Data Summary of Active Drug Concentration in Plasma Fractions

Time (hr)	**C_p (g/mL)**	**Time (hr)**	**C_p (g/mL)**
0	0	12	3.02
1	1.88	18	1.86
2	3.05	24	1.12
3	3.74	36	0.40
5	4.21	48	0.14
7	4.08	60	0.05
9	3.70	72	0.02

a. The minimum effective concentration of Aphrodisia in plasma is 2.3 g/mL. What is the onset time of this drug?

b. The minimum effective concentration of Aphrodisia in plasma is 2.3 g/mL. What is the duration of activity of this drug?
c. What is the elimination half-life of Aphrodisia in college students?
d. What is the time for peak drug concentration (t_{max}) of Aphrodisia?
e. What is the peak drug concentration (C_{max})?
f. Assuming that the drug is 100% systemically available (ie, fraction of drug absorbed equals unity), what is the AUC for Aphrodisia?
5. You wish to do a bioequivalence study on three different formulations of the same active drug. Lay out a Latin-square design for the proper sequencing of these drug products in six normal, healthy volunteers. What is the main reason for using a crossover design in a bioequivalence study? What is meant by a "random" population?
6. Four different drug products containing the same antibiotic were given to 12 volunteer adult males (age 19–28 years, average weight 73 kg) in a four-way crossover design. The volunteers were fasted for 12 hours prior to taking the drug product. Urine samples were collected up to 72 hours after the administration of the drug to obtain the maximum urinary drug excretion, D_u^{∞}. The data are presented in .

Table 15.17 Urinary Drug Excretion Data Summary		
Drug Product	**Dose (mg/kg)**	**Cumulative Urinary Drug Excretion (D_u^∞), 0–72 hr (mg)**
IV solution	0.2	20
Oral solution	4	380
Oral tablet	4	340
Oral capsule	4	360

a. What is the absolute bioavailability of the drug from the tablet?
b. What is the relative bioavailability of the capsule compared to the oral solution?
7. According to the prescribing information for cimetidine (Tagamet), following IV or IM administration, 75% of the drug is recovered from the urine after 24 hours as the parent compound. Following a single oral dose, 48% of the drug is recovered from the urine after 24 hours as the parent compound. From this information, determine what fraction of the drug is absorbed systemically from an oral dose after 24 hours.
8. Define *bioequivalence requirement*. Why does the FDA require a bioequivalence requirement for the manufacture of a generic drug product?
9. Why can we use the time for peak drug concentration (t_{max}) in a bioequivalence study for an estimate of the rate of drug absorption, rather than calculating the k_a?
10. Ten male volunteers (18–26 years of age) weighing an average of 73 kg were given either 4 tablets each containing 250 mg of drug (drug product A) or 1 tablet containing 1000 mg of drug (drug product B). Blood levels of the drug were obtained and the data are summarized in .

Table 15.18 Blood Level Data Summary for Two Drug Products				
		Drug Product		
		A	**B**	
Kinetic Variable	**Unit**	**4 x 250-mg Tablet**	**1000-mg Tablet**	**Statistic**
Time for peak drug concentration (range)	hr	1.3 (0.7–1.5)	1.8 (1.5–2.2)	$p < 0.05$
Peak concentration (range)	g/mL	53 (46–58)	47 (42–51)	$p < 0.05$
AUC (range)	g hr/mL	118 (98–125)	103 (90–120)	NS
$t_{1/2}$	hr	3.2 (2.5–3.8)	3.8 (2.9–4.3)	NS

a. State a possible reason for the difference in the time for peak drug concentration ($t_{max,A}$) after drug product A compared to the $t_{max,B}$ after drug product B. (Assume that all the tablets were made from the same formulation—that is, the drug is in the same particle size, same salt form, same excipients, and same ratio of excipients to active drug.)
b. Draw a graph relating the cumulative amount of drug excreted in urine of patients given drug product A compared to the cumulative drug excreted in urine after drug product B. Label axes!
c. In a second study using the same 10 male volunteers, a 125-mg dose of the drug was given by IV bolus and the

AUC was computed as 20 g hr/mL. Calculate the fraction of drug systemically absorbed from drug product B (1 x 1000 mg) tablet using the data in .

Table 15.19 Disintegration Times and Dissolution Rates of Tolazamide Tablets[a]		
Tablet	**Mean Disintegration Time[b] Min (Range)**	**Percent Dissolved in 30 Min[c] (Range)**
A	3.8 (3.0–4.0)	103.9 (100.5–106.3)
B	2.2 (1.8–2.5)	10.9 (9.3–13.5)
C	2.3 (2.0–2.5)	31.6 (26.4–37.2)
D	26.5 (22.5–30.5)	29.7 (20.8–38.4)

[a] $N = 6$.
[b] By the method of USP-23.

[c] Dissolution rates in pH 7.6 buffer.
From , with permission.

11. After performing a bioequivalence test comparing a generic drug product to a brand-name drug product, it was observed that the generic drug product had greater bioavailability than the brand-name drug product.
a. Would you approve marketing the generic drug product, claiming it was superior to the brand-name drug product?
b. Would you expect identical pharmacodynamic responses to both drug products?
c. What therapeutic problem might arise in using the generic drug product that might not occur when using the brand-name drug product?

12. The following study is from :
Tolazamide Formulations. Four tolazamide tablet formulations were selected for this study. The tablet formulations were labeled A, B, C, and D. Disintegration and dissolution tests were performed by standard USP-23 procedures.
Subjects. Twenty healthy adult male volunteers between the ages of 18 and 38 (mean, 26 years) and weighing between 61.4 and 95.5 kg (mean, 74.5 kg) were selected for the study. The subjects were randomly assigned to 4 groups of 5 each. The four treatments were administered according to 4 x 4 Latin-square design. Each treatment was separated by 1-week intervals. All subjects fasted overnight before receiving the tolazamide tablet the following morning. The tablet was given with 180 mL of water. Food intake was allowed at 5 hours postdose. Blood samples (10 mL) were taken just before the dose and periodically after dosing. The serum fraction was separated from the blood and analyzed for tolazamide by high-pressure liquid chromatography.
Data Analysis. Serum data were analyzed by a digital computer program using a regression analysis and by the percent of drug unabsorbed by the method of (see). AUC was determined by the trapezoidal rule and an analysis of variance was determined by Tukey's method.
a. Why was a Latin-square crossover design used in this study?
b. Why were the subjects fasted before being given the tolazamide tablets?
c. Why did the authors use the Wagner–Nelson method rather than the Loo–Riegelman method for measuring the amount of drug absorbed?
d. From the data in only, from which tablet formulation would you expect the highest bioavailability? Why?
e. From the data in , did the disintegration times correlate with the dissolution times? Why?
f. Do the data in appear to correlate with the data in ? Why?
g. Draw the expected cumulative urinary excretion–time curve for formulations A and B. Label axes and identify each curve.
h. Assuming formulation A is the reference formulation, what is the relative bioavailability of formulation D?
i. Using the data in for formulation A, calculate the elimination half-life ($t_{1/2}$) for tolazamide.

Table 15.20 Mean Tolazamide Concentrations[a] in Serum

		Treatment (g/mL)				
	Time (hr)	**A**	**B**	**C**	**D**	**Statistic[b]**
	0	10.8 ± 7.4	1.3 ± 1.4	1.8 ± 1.9	3.5 ± 2.6	
	1	20.5 ± 7.3	2.8 ± 2.8	5.4 ± 4.8	13.5 ± 6.6	
	3	23.9 ± 5.3	4.4 ± 4.3	9.8 ± 5.6	20.0 ± 6.4	
	4	25.4 ± 5.2	5.7 ± 4.1	13.6 ± 5.3	22.0 ± 5.4	
	5	24.1 ± 6.3	6.6 ± 4.0	15.1 ± 4.7	22.6 ± 5.0	
	6	19.9 ± 5.9	6.8 ± 3.4	14.3 ± 3.9	19.7 ± 4.7	
	8	15.2 ± 5.5	6.6 ± 3.2	12.8 ± 4.1	14.6 ± 4.2	
	12	8.8 ± 4.8	5.5 ± 3.2	9.1 ± 4.0	8.5 ± 4.1	
	16	5.6 ± 3.8	4.6 ± 3.3	6.4 ± 3.9	5.4 ± 3.1	

	24	2.7 ± 2.4	3.1 ± 2.6	3.1 ± 3.3	2.4 ± 1.8	
C_{max}, g/mL[c]		27.8 ± 5.3	7.7 ± 4.1	16.4 ± 4.4	24.0 ± 4.5	
t_{max}, hr[d]		3.3 ± 0.9	7.0 ± 2.2	5.4 ± 2.0	4.0 ± 0.9	
$AUC_{0–24}$, g hr/mL[e]		260 ± 81	112 ± 63	193 ± 70	231 ± 67	

[a]Concentrations ± 1 SD, $n = 20$.
[b]For explanation see text.
[c]Maximum concentration of tolazamide in serum.
[d]Time of maximum concentration.
[e]Area under the 0–24-hr serum tolazamide concentration curve calculated by trapezoidal rule.
From , with permission.

13. If *in-vitro* drug dissolution and/or release studies for an oral solid dosage form (eg, tablet) does not correlate with the bioavailability of the drug *in-vivo*, why should the pharmaceutical manufacturer continue to perform *in-vitro* release studies for each production batch of the solid dosage form?

14. Is it possible for two pharmaceutically equivalent solid dosage forms containing different inactive ingredients (ie, excipients) to demonstrate bioequivalence *in-vivo* even though these drug products demonstrate differences in drug dissolution tests *in-vitro*?

15. For bioequivalence studies, t_{max}, C_{max}, and AUC, along with an appropriate statistical analyses, are the parameters generally used to demonstrate the bioequivalence of two similar drug products containing the same active drug.

a. Why are the parameters t_{max}, C_{max}, and AUC acceptable for proving that two drug products are bioequivalent?

b. Are pharmacokinetic models needed in the evaluation of bioequivalence?

c. Is it necessary to use a pharmacokinetic model to completely describe the plasma drug concentration–time curve for the determination of t_{max}, C_{max}, and AUC?

d. Why are log-transformed data used for the statistical evaluation of bioequivalence?

e. What is an add-on study?

References

Amidon, GL, Lennernas H, Shah VP, Crison JR: A theoretical basis for a biopharmaceutic drug classification: The correlation of *in-vitro* drug product dissolution and *in vivo* bioavailability. *Pharm Res***12:**413–420, 1995

Dighe SV, Adams WP: Bioequivalence: A United States regulatory perspective. In Welling PG, Tse FLS, Dighe SV (eds), *Pharmaceutical Bioequivalence*. New York, Marcel Dekker, 1991, chap 12

FDA Guidance Concerning Demonstration of Comparability of Human Biological Products, Including Therapeutic Biotechnology-Derived Products, April 1996

FDA Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products—General Considerations, March 2003

FDA Guidance for Industry: Dissolution Testing of Immediate Release Solid Oral Dosage Forms, August 1997

FDA Guidance for Industry: Statistical Approaches to Establishing Bioequivalence, January 2001

FDA Guidance for Industry: Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate Release Solid Oral Dosage Forms Containing Certain Active Moieties/Active Ingredients Based on a Biopharmaceutics Classification System, August 2000

Feldman CH, Hutchinson VE, Sher TH, et al: Interaction between nutrition and theophylline metabolism in children. *Ther Drug Monit* **4:**69–76, 1982 [PMID: 7071906]

Gardner S: Bioequivalence requirements and *in vivo* bioavailability procedures. *Fed Reg* **42:**1651, 1977

Hendles L, Iafrate RP, Weinberger M: A clinical and pharmacokinetic basis for the selection and use of slow release theophylline products. *Clin Pharmacokinet* **9:**95–135, 1984

Midha KA, Ormsby ED, Hubbard JW, McKay G, Hawes EM, Gavalas, McGilvery IJ: Logarithmic transformation in bioequivalence: Application with two formulations of perphenazine. *J Pharm Sci* **82:**138–144, 1993 [PMID: 8445525]

Moore JW, Flanner HH: Mathematical comparison of curves with an emphasis on *in vitro* dissolution profiles. *Pharm Tech* **20**(6):64–74, 1996

Mordenti J, Cavagnaro JA, Green JD: Design of biological equivalence programs for therapeutic biotechnology

products in clinical development: A perspective. *Pharm Res* **13:**1427–1437, 1996 [PMID: 8899831]
Polli JE, Rekhi GS, Augsburger LL, Shah VP: Methods to compare dissolution profiles and a rationale for wide dissolution specifications for metoprolol tartrate tablets. *J Pharm Sci* **86**(6):690–700, 1997
Purich E: Bioavailability/bioequivalence regulations: An FDA perspective. In Albert KS (ed), *Drug Absorption and Disposition, Statistical Considerations*. Washington, DC, American Pharmaceutical Asso-ciation, 1980
Report by the Bioequivalence Task Force 1988 on Recommendations from the Bioequivalence Hearings Conducted by the Food and Drug Administration, Sept 29–Oct 1, 1986. Rockville, MD, FDA, 1988
Schuirmann DJ: A comparison of the two one-sided tests procedure and the power approach for assessing the equivalence of average bioavailability. *J Pharmacokinet Biopharmaceut* **15:**657–680, 1987 [PMID: 3450848]
Shah P, Yacobi A, Barr WH, Benet LZ, Breimer D, et al: Evaluation of orally administered highly variable drugs and drug formulations. *Pharm Res* **13:**1590–1595, 1996 [PMID: 8956322]
Wagner JG, Nelson E: Percent absorbed time plots from blood level and for urinary excretion data. *J Pharm Sci* **52:**610–61, 1963 [PMID: 13998253]
Welling PG, Patel RB, Patel UR, et al: Bioavailability of tolazamide from tablets: Comparison of *in vitro* and *in vivo* results. *J Pharm Sci* **71:**1259–1263, 1982 [PMID: 7175719]
Westlake WJ: Use of confidence intervals in analysis of comparative bioavailability trials. *J Pharm Sci* **61:**1340–1341, 1972 [PMID: 5050398]
Yu LX, Amidon GL, Polli JE, Zhao H, Mehta MU, Conner DP, Shah VP, Lesko LJ, Chen ML, Lee VH, Hussain AS: Biopharmaceutics classification system: The scientific basis for biowaiver extensions. *Pharm Res* **19**(7):921–925, 2002

Bibliography

Abdou HM: *Dissolution, Bioavailability and Bioequivalence*. Easton, PA, Mack, 1989
Bennett RW, Popovitch NG: Statistical inferences as applied to bioavailability data: A guide for the practicing pharmacist. *Am J Hosp Pharm* **34:**712–723, 1977 [PMID: 578074]
Chodes DJ, DiSanto AR: *Basics of Bioavailability*. Kalamazoo, MI, Upjohn, 1974
Dighe SV: Biopharmaceutics program. *Clin Res Pract Drug Res Aff* **1:**61–76, 1983
DiSanto AR, Desante KA: Bioavailability and pharmacokinetics of prednisone in humans. *J Pharm Sci* **64:**109–112, 1975 [PMID: 1133681]
Hendeles L, Wienberger M, Bighley L: Absolute bioavailability of oral theophylline. *Am J Hosp Pharm* **34:**525–527, 1977 [PMID: 868891]
Kennedy D: Therapeutically equivalent drugs. *Fed Reg* **44:**2932–2952, 1979
Martin A, Dolusio JT (eds): *Industrial Bioavailability and Pharmacokinetics: Guidelines, Regulations and Controls*. Austin, TX, Austin Drug Dynamics Institute, University of Texas, 1977
Metzler CM: Bioavailability: A problem in equivalence. *Biometrics* **30:**309–317, 1974 [PMID: 4833140]
Report of the Blue Ribbon Committee on Generic Medicines. Generic Medicines: Restoring Public Confidence. Rockville, MD, FDA, 1990
Schumacher GE: Use of bioavailability data by practitioners, I. Pitfalls in interpreting the data. *Am J Hosp Pharm* **32:**839–842, 1975
Schumacher GE: Interpretation of bioavailability data by practitioners. *J Clin Pharmacol* **16:**554–559, 1976 [PMID: 977795]
Wagner JG: An overview of the analysis and interpretation of bioavailability studies in man. *Pharmacology* **8:**102–117, 1972 [PMID: 4644642]
Welling PG, Tse FLS, Dighe SV (eds): *Pharmaceutical Bioequivalence*. New York, Marcel Dekker, 1991
Westlake WJ: The design and analysis of comparative blood level trials. In Swarbrick J (ed), *Current Concepts in Pharmaceutical Sciences: Dosage Form Design and Bioavailability*. Philadelphia, Lea & Febiger, 1973, chap 5
Westlake WJ: Use of statistical methods in evaluation of *in vivo* performance of dosage forms. *J Pharm Sci* **62:**1579–1589, 1973 [PMID: 4584652]