United States Food and Drug Administration Requirements for Approval of Generic Drug Products

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As generic products become more available for the treatment of psychiatric disorders, clinicians must stay abreast of the U.S. Food and Drug Administration (FDA) requirements for the approval of generic drug products. The FDA declares that pharmaceutical equivalents only are therapeutically equivalent, and pharmacokinetic data are all that is usually required to determine therapeutic equivalence. The rationale behind the overall concept of bioequivalence is that if 2 pharmaceutical equivalents provide identical plasma concentration-time profiles in humans, there is no evidence to demonstrate that the 2 identical dosage forms will exhibit a difference in safety and efficacy. This article reviews current terminology used in abbreviated new drug applications for generic products, typical bioequivalence study designs, and FDA bioequivalence guidance for clozapine.

(J Clin Psychiatry 2001;62[suppl 5]:4–9)

As generic products become more available for the treatment of psychiatric disorders, clinicians must stay abreast of the U.S. Food and Drug Administration (FDA) requirements for the approval of generic drug products. This article reviews current terminology used in abbreviated new drug applications for test products, typical bioequivalence study designs, and FDA bioequivalence guidance for clozapine.

FDA REQUIREMENTS FOR THE APPROVAL OF TEST PRODUCTS

The FDA declares that pharmaceutical equivalents only are therapeutically equivalent. Bioavailability is the rate and extent that a drug reaches the systemic circulation after administration. Bioequivalence is a comparison of the bioavailability of a test product and a reference (Reference Listed Drug, brand, innovator) product.

Drug products are usually determined to be therapeutically equivalent by the FDA on the basis of pharmacokinetic measurements, rather than through the use of clinical trials in patients or pharmacodynamic studies. To gain FDA approval,[1] a test drug must (1) contain the same active ingredients as the reference drug, although inactive ingredients may vary; (2) be identical to the reference drug in strength, dosage form, and route of administration; (3) have the same use indications; (4) be bioequivalent to the reference drug; (5) meet the same batch requirements for identity, strength, purity, and quality; and (6) be manufactured under the same strict FDA standards of Current Good Manufacturing Practice regulations required for reference products.

Pharmaceutical alternatives are drug products that contain the same therapeutic moiety, but are different salts, esters, or complexes of that moiety (e.g., tetracycline hydrochloride and tetracycline phosphate complex), or are different dosage forms (e.g., tablets and capsules) or strengths.[2] Pharmaceutical alternatives may be interchangeable in clinical practice even though the FDA does not consider them to be pharmaceutically equivalent.

The rationale behind the overall concept of bioequivalence is that if 2 pharmaceutical equivalents provide identical plasma concentration-time profiles in humans, there is no evidence to demonstrate that the 2 identical dosage forms will exhibit a difference in safety and efficacy. The word *similar* is actually more appropriate than the word *identical* because no 2 profiles are ever exactly identical; however, in order to deter arguments about the degree of pharmacologic similarity, the word *identical* is used. Most researchers believe that if 2 pharmaceutical equivalents are similar—within constraints—there will be therapeutic equivalence as well.

Parameters Used to Measure Bioequivalence

The key parameters used to determine bioequivalence include the area under the concentration-time curve (AUC [t] and infinity [∞]), the time to peak plasma concentration (T_{max}), and the peak plasma concentration (C_{max}). AUC is a

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Presented at the symposium "Comparison of Bioequivalence of Generic vs. Branded Clozapine," which was held July 29, 2000, in New York, N.Y., and supported by an unrestricted educational grant from Novartis Pharmaceuticals Corporation.

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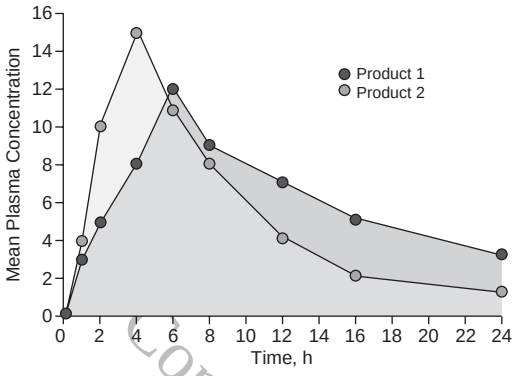
Figure 1. Bioequivalence Data



function of the amount of product absorbed; the more product absorbed, the greater the AUC. T_{max} is a function of the rate of absorption, and C_{max} is a function of both rate and extent of absorption. AUCt is the area up to the last sampling time, and AUC∞ is the total AUC extrapolated to the time when drug is no longer measurable. As shown in Figure 1, Product 2 is absorbed more rapidly than Product 1 because of the shorter T_{max} (4 vs. 6 h) and also has a higher C_{max} (15 vs. 12). The areas under the concentration-time curves are similar for the 2 products, with Product 2 having higher concentrations prior to 6 h but lower concentrations beyond 6 h.

New Drug Applications and Abbreviated New Drug Applications

New drug applications (NDAs) are submitted to the FDA for the manufacture and marketing of new chemical entities. An NDA must contain data that include chemistry, pharmacology, and biopharmaceutics.[3] An abbreviated new drug application (ANDA) must be submitted to the FDA for review and approval to market a generic product. An ANDA includes all the information on chemistry and manufacturing controls found in an NDA. However, ANDAs are generally not required to include preclinical (animal) and clinical (human) data to establish safety and effectiveness because those parameters were established when the reference drug was approved (Table 1). Exceptions to this rule occur when pharmacokinetics cannot be measured because the drug is not intended to be absorbed into the systemic circulation. For example, a pharmacodynamic "skin blanching" study can be done for topical corticosteroids, or a clinical trial in patients may be necessary to compare a reference and generic product used in the treatment of diarrhea.

Bioequivalence studies do not only apply to generic drug products. Brand name (innovator) companies also conduct such studies to demonstrate that the dosage form used in the early clinical trials performs identically to the final dosage form to be marketed. Additionally, product

Table 1. Comparison of FDA Requirements for New Drug Applications (NDAs) and Abbreviated New Drug Applications (ANDAs)[a]

Required Studies	NDA	ANDA
Animal studies, toxicity, carcinogenicity, teratogenicity	Yes	No
Phase 1 in humans	Yes	No
Clinical trials in patients	Yes	In special cases
Bioequivalence in volunteers	Yes	Yes

[a]Abbreviation: FDA = U.S. Food and Drug Administration.

manufacturers may want to change a formulation, site of manufacture, or manufacturing process after a drug is in the marketplace.[4] These types of changes can be put in place only after the drug manufacturer provides sufficient evidence to the FDA that the proposed change will not affect the bioavailability of the product.

The Orange Book

The publication *Approved Drug Products with Therapeutic Equivalence Evaluations*,[2] commonly called the Orange Book (which is available online), identifies reference and test drug products approved by the FDA. Drugs manufactured prior to 1938, such as phenobarbital and digitalis, are not included in the Orange Book. However, companies that manufacture some of these so-called "grandfathered" drugs may be obliged to conduct bioavailability studies in the future because of controversy about interchangeability of products, e.g., levothyroxine.

A therapeutic equivalence code is designated for each product in the Orange Book; this therapeutic equivalence code allows readers to quickly determine whether the FDA has approved a product that is therapeutically equivalent to a reference drug. Drug products that have no known or suspected bioequivalence problems are given an AA designation; drugs with actual or potential bioequivalence problems that have been resolved by adequate in vivo and/or in vitro evidence supporting bioequivalence are given an AB designation. Drug products for which actual or potential bioequivalence problems have not been resolved by adequate evidence of bioequivalence are designated as B-rated drugs; the problem in B-rated products may relate to specific dosage forms or active ingredients. Therapeutic equivalence in A-rated drug products is usually based on bioequivalence testing. B-rated products are never considered to be interchangeable with A-rated products or other B-rated products. In addition to the therapeutic equivalence code, the Orange Book lists active ingredients, dosage forms, route, strength, proprietary name, and the older of the NDA or ANDA for each drug product.

BIOEQUIVALENCE STUDY DESIGNS

The standard fasting bioequivalence study is a 2-way crossover trial conducted in 18 to 60 healthy volunteers.

Single-dose test and reference drug products are administered to fasting subjects, and blood or plasma levels of the drug and metabolites are measured over time. Characteristics of the concentration-time curves (AUC and C_{max}) are examined by statistical methods; the T_{max} is evaluated if a test product demonstrates delayed absorption or if rate of absorption has clinical significance, e.g., an analgesic. Statistical analysis of fasting studies is based on log-transformed C_{max} and AUC confidence limits within 80% and 125%.

The FDA mandates that a food study, termed a high-fat meal, be conducted for most controlled-release (and for many immediate-release) dosage forms. Although under review by the FDA, the food trial presently is a 3-way crossover design: test-fed, reference-fed, and test-fast. In order for FDA approval, the ratio of the test and reference means must be within ± 20%, but confidence limits are not applied. A 2-way crossover design has been proposed for the food study, in which the test-fast would be omitted and confidence limits would be applied to the test- and reference-fed phases; if the new proposal is accepted, the confidence limits will be 80% and 125% for AUC and 70% and 143% for C_{max}. The high-fat meal used for the food study is indeed high in fat content; it consists of a buttered English muffin, a slice of American cheese, a slice of Canadian bacon, a fried egg, a serving of hash brown potatoes, 8 oz whole milk, and 6 oz orange juice. This meal provides a hearty and appropriate challenge for the absorption of a dosage form, especially for controlled-release products.

Multiple-dose, steady-state studies are largely reserved for controlled-release dosage forms or when plasma drug concentrations are too low to be quantitated after a single dose. Multiple-dose studies may be conducted in patients when it has been determined that single doses of drug are dangerous when given to healthy volunteers. The need for multiple-dose studies is also under review by FDA. Statistical analysis is also based on log-transformed C_{max}, C_{min}, and AUC 0–τ with confidence limits between 80% and 125%.

AVERAGE AND INDIVIDUAL CONCEPTS OF BIOEQUIVALENCE

An August 1999 FDA Guidance to Industry recommended that the criteria for average bioequivalence be supplemented by a new approach termed individual bioequivalence. At present, however, average bioequivalence is the accepted procedure for submitting bioequivalence data to the FDA.

Average Bioequivalence

The current criteria for establishing average bioequivalence are based on the use of statistical confidence limits, which can be confusing. The objective of the FDA's approval criteria is to be 90% confident that the ratios of the test/reference log-transformed mean values for AUC and C_{max} are within 80% to 125%. This criterion does not mean that there can be a 20% to 25% difference between the mean of the 2 products. The confusion may lie in thinking that one test product can be 80% of the reference and another test product can be 125% of the reference; but if one generic product is substituted for another generic product the range can become quite large. In fact, if the ratio of the test and reference means is close to 80% or 125%, it is unlikely that the lower or upper confidence limit will be within the range of 80% to 125%.

Table 2. Examples of Bioequivalence Confidence Intervals[a]

	Test/Reference AUC Ratio (%)		
Subject	Example 1	Example 2	Example 3
A	110	110	140
B	120	170	120
C	110	50	100
D	100	130	120
Mean	110	110	120
Variability	Low	High	Low
CI	105 to 115	80 to 140	110 to 130
Outcome	Pass	Fail	Fail

[a]Abbreviations: AUC = area under the concentration-time curve, CI = confidence interval.

An illustration of the FDA approval criteria for confidence limits is demonstrated in Table 2. In example 1, the AUC ratios of test/reference products are similar in all 4 subjects, and the mean AUC response is 110%. Since there is low variability and the confidence interval is 105% to 115%—which is within the acceptable confidence limits of 80% and 125%—the test product will pass the comparison with the reference product. There is greater variability in the AUC ratios among subjects in example 2, even though the mean AUC response is also 110%. Because of the degree of variability, the confidence interval is 80% to 140%; this test product will fail because it exceeded the upper-end of the acceptable confidence limit of 125%. Example 3 demonstrates little variability, but the AUC ratios of the test/reference products are high in 3 of 4 subjects; the mean AUC response is 120%, and the confidence interval is 110% to 130%. This test product will fail because the mean responses were high and the upper end of the acceptable confidence limit was exceeded.

Individual Bioequivalence

Individual bioequivalence is based on a replicate design, which considers variances in addition to the differences of averages.[5] In individual bioequivalence, each subject is administered every product twice. Moreover, the confidence limits may be scaled if the reference product is more variable than the test product. For example, if a reference product has extremely erratic absorption, the test/reference bioequivalence data may be so variable that a test product will not fit within the recommended confi-

Table 3. Subject-by-Formulation Interaction[a]

	Test/Reference AUC Ratio (%)	
Subject	Replicate 1	Replicate 2
1	105	110
2	120	115
3	85	95
4	40	35
5	100	100
Mean	90	92

[a]Abbreviation: AUC = area under the concentration-time curve.

dence limits of 80% and 125%. The idea is to avoid penalizing a potentially acceptable test product when the reference product shows erratic absorption.

One of the variances in the individual bioequivalence criterion measures subject-by-formulation interaction, i.e., the extent to which the test/reference difference varies from person to person. Table 3 shows an example of subject-by-formulation interaction. Of 5 subjects, all the subjects except subject 4 have similar test/reference AUC ratios. However, the ratio in subject 4 is much lower than that of the other subjects. Did subject 4 vomit or spit the testing tablet out? Is the ratio low because the test product was low or because the reference product was high? Is subject 4 an outlier or is the low AUC ratio true of 20% of the population? Perhaps the test product is an organic base that requires stomach acid in order to be effective, and suppose subject 4 is achlorhydric or is taking over-the-counter antacids. Whatever the reason, the test product in subject 4 demonstrates less absorption than the reference product and is an example of a confirmed subject-by-formulation interaction. Sophisticated statistics are involved in individual bioequivalence, and some of the replicate designs deal with highly variable drug products in which scaling of the confidence limits of the reference product may be allowed.

In theory and probably in practice, there are valid reasons why one subject reacts differently to a drug product on a consistent basis than other subjects. From a regulatory perspective, however, questions arise about the best way to proceed with the information obtained from replicate testing. The problems with individual bioequivalence designs include an ongoing debate about statistical analysis and the lack of prospective studies to determine the value of the design. Moreover, scaled confidence limits for highly variable drug products may result in (1) limits outside the accepted 80% and 125% if the reference product is more variable than the test product, and (2) limits that vary for different test products.

FDA Guidance for Clozapine

Healthy volunteers may have significant adverse reactions to clozapine that apparently do not occur often in patients with schizophrenia. In August 1994, Pokorny et al.[6] conducted a study of 17 healthy volunteers in whom a single 25-mg dose of clozapine was administered. Ten of the subjects had orthostatic hypotension, 8 developed severe bradycardia of less than 40 beats/minute, and 2 experienced cardiac arrest with pauses of 10 and 60 seconds, respectively. In October 1994, a citizen's petition was filed by Sandoz Pharmaceuticals that requested the prohibition of clozapine studies in healthy volunteers. The FDA responded in May 1997; it denied the 1994 petition and cited the November 1996 Guidance for Clozapine Tablets as the recommended approach for bioequivalency studies of clozapine. The Guidance noted that the Office of Generic Drugs had received reports of cardiovascular adverse reactions in subjects participating in clozapine bioequivalence studies and offered information from a medical consultant to the Office who would be available to provide information about ways to prevent and, if they occur, manage these adverse reactions. The Guidance further stipulated (1) that the half-life of clozapine tablets is 8 hours; (2) that 27% to 50% of the drug reaches the systemic circulation because of first-pass metabolism; (3) that clozapine, when taken in proper dosage form, is 90% to 95% absorbed within 3.5 hours (T_{max} = 1.5 h); and (4) that absorption is not affected by food intake. Moreover, according to the Guidance, an oral tablet dose of clozapine is bioequivalent to a solution dose.

The 1996 FDA Guidance for Clozapine Tablets permitted the approval of 25-mg and 100-mg clozapine tablets to be based on a bioequivalence study of one half of a 25-mg tablet. It is not unusual for the FDA to permit the approval of a lower strength of product if a higher strength has been shown to be bioequivalent to the reference product. However, for clozapine, the requirement for a human bioequivalence study was waived for the highest strength and not the lowest strength. In addition, for a waiver of an in vivo study, the in vitro dissolution of the test product must be similar to that of the reference product, and the various strengths of the product must be "proportionally similar." The dissolution testing indicated that the test and reference products were similar, except at the first (10 min) sampling time. However, the 25-mg and 100-mg formulations of the test product were not strictly proportional in composition, since the 2 strengths contained the same total quantity of excipients, even though the clozapine dose differed 4-fold.

The 1996 FDA guidance offered 2 designs for determining bioequivalence of clozapine. The first design is a fasting, single-dose trial conducted in healthy subjects, which was used by Mylan Pharmaceuticals and Zenith Goldline Pharmaceuticals. The design is a 2-way crossover in 24 to 35 subjects, aged between 18 and 50 years, with a 5-day washout, continuous cardiac monitoring, and blood sampling for 72 hours. In the Zenith Goldline study (data on file, FDA Center for Drug Evaluation and Research, Office of Generic Drugs, Rockville, Md.), the dose of clozapine was one half of a 25-mg tablet

Table 4. Clozapine Bioequivalence Data[a]

Parameter	Test/Reference Ratios,%	
	Zenith Goldline	Mylan
AUC∞	103	98
Confidence interval	96 to 110	94 to 102
C_{max}	100	99
Confidence interval	81 to 118	91 to 111

[a]Data on file, FDA Center for Drug Evaluations and Research, Office of Generic Drugs, Rockville, Md. Abbreviations: AUC∞ = area under the concentration-time curve, C_{max} = peak plasma concentration.

Table 5. Reasons for Lack of Data on Therapeutic Failures of Generic Drug Products

Compliance
Wrong drug, incorrect dose
Change in disease process, physiology
Liability concerns
Lack of incentive to report
Drug-drug interaction
Difficult documentation unless rechallenge
No failures

(12.5 mg), given to 24 men aged between 18 and 49 years. A total of 19 subjects completed the study; there were 2 dropouts because of severe adverse events. The AUC data were variable, although symmetrical, and had borderline acceptability (Table 4). The mean test/reference AUC∞ ratio was 103% with a confidence interval of 96% to 110%. The mean test/reference C_{max} ratio was 100% with a confidence interval of 81% to 118%. The Mylan study (data on file, FDA Center for Drug Evaluation and Research, Office of Generic Drugs, Rockville, Md.) also used one half of a 25-mg tablet (12.5 mg) dose of clozapine in 41 men aged between 18 and 50 years. A total of 34 subjects completed the study; there were 5 dropouts because of adverse events. The bioavailability data were also quite favorable (see Table 4). The mean test/reference AUC∞ ratio was 98% with a confidence of 94% to 102%. The mean test/reference C_{max} ratio was 99% with a confidence interval of 91% to 111%.

The second design is a multiple-dose trial conducted in schizophrenic patients. The design is a 2-way crossover in which patients receive a stable, equally divided dose of clozapine every 12 hours. Blood samples are drawn to determine at least 3 successive trough values, and AUC is calculated between zero and 12 hours on the last day of the trial. Creighton (Geneva Pharmaceuticals) used this design and although this formulation of clozapine was approved, it is not currently being marketed.

The Orange Book currently lists clozapine products manufactured by 4 different companies approved for marketing. Clozaril (Novartis Pharmaceuticals) is the reference listed drug. The other manufacturers are Geneva Pharmaceuticals, Mylan Pharmaceuticals, and Zenith Goldline Pharmaceuticals. Each company manufactures 2 dosage forms, 25 mg and 100 mg, and all products have an AB rating.

AREAS OF POTENTIAL WEAKNESS IN THE FDA APPROVAL SYSTEM

There are several areas of potential weakness in the current FDA approval system: (1) When the present system of average bioequivalence is used, subject-by-formulation interactions—such as those demonstrated by achlorhydric subjects or elderly subjects—cannot be tested. (2) Companies that manufacture test products may engage in lot shopping for bioequivalent comparison. Lot shopping by a company involves dissolution testing of numerous lots of a reference drug to find the product closest to one's own test product. Interestingly, Japanese generic companies are required to obtain 3 different lots of a reference product; after dissolution testing on the 3 lots, the product that has the middle value is used as the test product. (3) There is no requirement to submit all data for an ANDA. In fact, if a firm wishes to repeat a bioequivalence study several times because a study or studies did not confirm bioequivalence, there is nothing illegal about only submitting the study that passed. In contrast, when a firm submits an NDA, they cannot exclude any data from the FDA submission. (4) Products are not restudied in vivo once they have been approved. (5) No one knows the effect of product aging on bioequivalence. The test product is usually a fresh product that has been recently manufactured, whereas the reference product may or may not be fresh. (6) In a bioequivalence study, both test and reference products are taken with 8 ounces of water, and most patients do not drink that much water when taking a product orally.

Despite drawbacks, millions of doses of generic drugs have been dispensed with no well-documented instances of therapeutic failure for products manufactured in accordance with FDA-approved requirements for an ANDA. There are cases in which erring companies have chosen to go outside of FDA-approved manufacturing policies, but the results have been grossly inferior products that are ultimately brought to the attention of the FDA. Why are there so few examples of therapeutic failures of generic drug products (Table 5)? Compliance is always an issue. Either the wrong drug or an incorrect dose of drug may have been administered. A change in the patient's disease or physiology can also occur. Perhaps failure of the product is due to a drug-drug interaction. There may be reluctance to record instances of therapeutic failure because of liability concerns. Furthermore, most busy practitioners have few incentives to write or publish a report of 1 or 2 therapeutic failures. Additionally, therapeutic failures are difficult to document unless the patient is rechallenged. Finally, perhaps there have been no therapeutic failures or, if failures have occurred, the number is so minuscule as to be inconsequential.

CONCLUSION

The FDA only rates pharmaceutically equivalent generic drug products as therapeutically equivalent. The FDA's decision is usually based on bioequivalence data that are obtained in healthy human studies. Pharmacodynamic or clinical trials in patients are not usually required. Currently, the statistical analysis is based on average data and the application of confidence limits. Although several areas of potential weakness exist in the current FDA approval system for generic drug products, millions of doses of generic drugs have been dispensed with no well-documented instances of therapeutic failure when products are manufactured according to FDA requirements for ANDAs.

Drug names: clozapine (Clozaril and others), levothyroxine (Synthroid and others).

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