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Regulatory



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Regulating the Generic Drug Process

Guidance for the design
and conduct of international
bioequivalence trials.

Generic alternatives to brand-name prescription medications are emerging as a dominant force in the global drug market as an increasing number of prescription drugs lose patent protection. In the United States, approximately 110 drugs will go off-patent between 2007 and 2010, creating opportunities for generic drug manufacturers to bring less expensive pharmaceutical equivalents to market.¹

The availability of generic drugs provides advantages to consumers because of the cost savings over brand-name equivalents, resulting in increased accessibility to prescription drugs and increased compliance with drug regimens.^{2,3}

Likewise, the importance of generics to the pharmaceutical industry continues to grow: In the U.S., generics comprised 63% of all prescriptions dispensed in the 12 months ending June 2007, representing an increase of approximately 16% since 2001.¹

Understanding generics

Generic, non-systemically absorbed products (e.g., dermal, otic, ophthalmic, intranasal, and inhalation products) are typically approved for marketing after their therapeutic equivalence is demonstrated in clinical trials, where the efficacy of the generic and marketed product is compared. In contrast, pharma companies planning to market systemically absorbed, generic, solid, oral, immediate-release products (e.g., tablets and capsules)

are not required to perform efficacy trials to support regulatory approval of their product because the safety and effectiveness of the active ingredient have been previously established.

Rather, the generic product must



demonstrate bioequivalence to the brand-name original. Equivalence trials are designed to compare the release, absorption, and elimination of the active ingredient from two formulations of a product (i.e., the unmarketed generic and corresponding brand-name product) and, if successful, demonstrate similarity between both within pre-established, statistically defined, pharmacokinetic parameters.

Although there are core principles that guide the planning and implementation of bioequivalence trials, there are notable variations in region-specific regulatory requirements for the design, conduct, and analysis of these studies. Understanding differences in region-specific requirements is essential as the pharmaceutical industry trends toward globalization.

This becomes apparent when a bioequivalence trial intended to support registration of a generic drug in one region is managed through a contract research organization (CRO) based in a second region and is conducted in a third region, requiring that regulatory requirements issued by countries where the trial is conducted and where the test product is intended to be registered both be satisfied.

Global undertaking

Geographical regions with considerable activity in the area of generic drug development include the United States, Canada, the European Union, and India. Therefore, this article will discuss study design features reviewed in guidance documents issued by the United States' FDA,^{4,5} Canada's Health Canada (HC),^{6,7} the EU's European Medicines Evaluation Agency (EMA),⁸ and India's Central Drugs Standard Control Organization (CDSCO).⁹

We will provide an overview of bioequivalence trials designed to support approval of solid, oral, immediate-release drug products. The guidance documents reviewed here primarily apply to studies of systemically absorbed drug products with uncomplicated characteristics, excluding drug products with characteristics, such as nonlinear pharmacokinetics, long half-lives, high toxicity or narrow therapeutic ranges.

Before a meaningful review of these guidance documents can be undertaken, it is important to understand the role they serve in the design and implementation of bioequivalence trials. Guidance documents are intended to provide recommendations and explanations on how to comply with the regulatory obligations put forward by the agencies. Guidance documents are not intended to provide binding regulations;

therefore, alternate study designs may be considered if supported by sound scientific rationale.

Study design

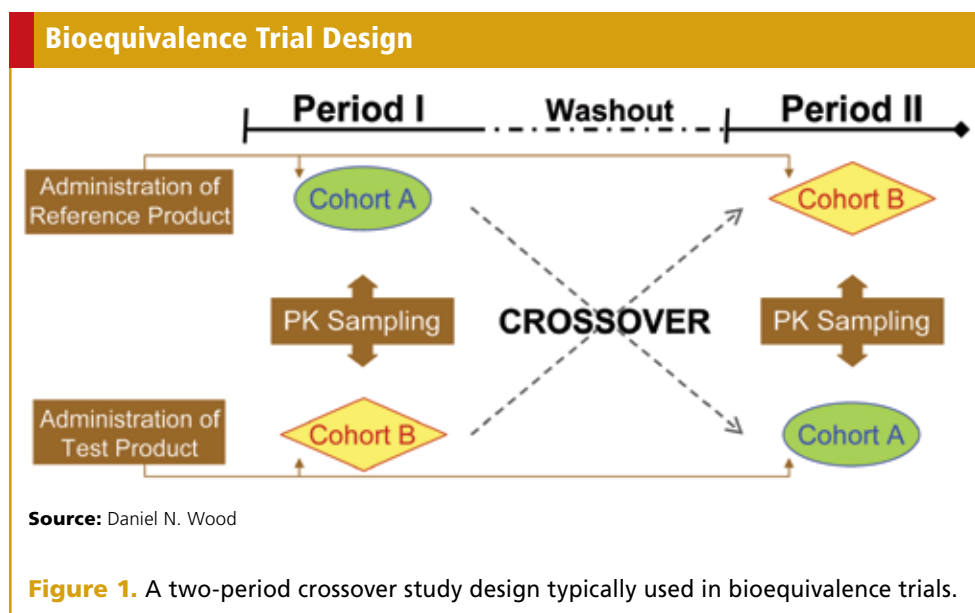
In all regions, bioequivalence trials comparing solid, oral, immediate-release formulations are typically designed as two-period, two-sequence, crossover studies (See Figure

Bioequivalence trials comparing solid, oral, immediate-release formulations are typically designed as two-period crossover studies.

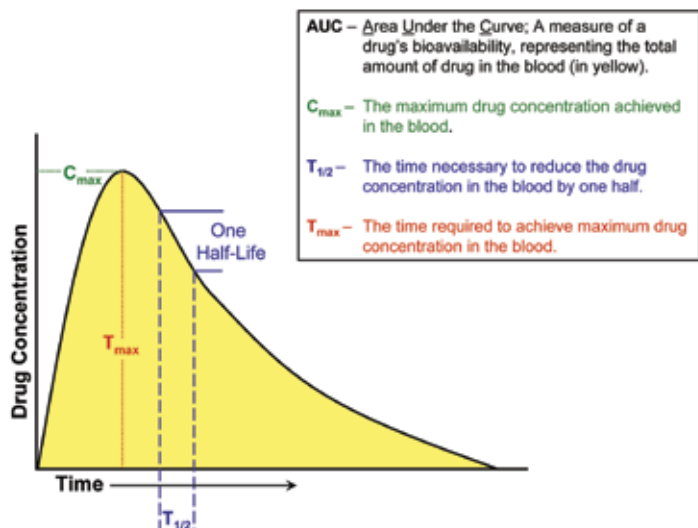
1). In this design, trial subjects are randomized to receive either the generic product (the test product) or corresponding brand-name product (the reference product) in the first study period (period I). In the second study period (period II), subjects are then "crossed-over" so that they receive the formulation opposite of the one they were given in the first period. In this way, each subject receives both the test and reference products.

A washout period separates the first and second periods to allow clearance of the test or reference product from the subject's system. After administration of either the test or reference product in periods I and II, a series of samples are taken from each subject to determine concentrations of the active ingredient from each formulation.

Sampling is typically performed by collection of blood, although urine may be collected in certain cases. HC guidance specifies that urine be used when blood concentrations of the study drug are too dilute to be detected accurately and when more than 40% of the study drug is eliminated in the urine unchanged. For the purposes of this article, we will assume that blood is the biological fluid used to determine



Pharmacokinetic Variables



Source: Daniel N. Wood

Figure 2. Appropriate timing of sample collection ensures accurate assessment of pharmacokinetic variables.

bioequivalence.

Trial intricacies

The duration of study periods is largely dictated by the number of samples that are required to characterize the absorption, distribution, and elimination phases of the study drug. Sampling should be identical for each period and should begin with a pre-dose sample, generally taken within an hour prior to study drug administration, to obtain baseline values. Sampling time should correspond to 80% of the Area Under the Curve (AUC), a measure of the total amount of drug in circulation over time. This period typically covers at least three half-lives of the study drug after it has reached maximum concentration.

Exact timing of a sample collection should be timed such that specific pharmacokinetic variables can be accurately gauged.

The exact timing of sample collection during each period depends on the nature of the drug under investigation (e.g., the drug's half-life or absorption time), but should be timed such that specific pharmacokinetic variables can be accurately gauged, including the AUC, the maximum concentration of the drug in the blood (C_{max}), and the drug's half-life in the blood ($T_{1/2}$) (see Figure 2). FDA, HC, and CDSCO guidances suggest that collection of at least 11 post-administration samples per subject per dose is an adequate quantity to achieve this objective, while EMEA guidance does not

outline a minimum number of samples.

The duration of the intervening washout period is also outlined in the region-specific guidance documents and is largely driven by the half-life of the moiety that is being measured to demonstrate bioequivalence. This moiety is often the active ingredient in the reference product, so we will refer to it here as the study drug. Both CDSCO and FDA guidances stipulate that the washout period falling between each study period lasts at least five half-lives of the study drug.

EMA guidance requires that study periods “be separated by adequate washout periods,” but does not specify a minimum quantity of time between treatments for single dose studies. However, for studies conducted with more than a single administration of study drug (i.e., steady-state studies), it is recommended that a minimum of three times the half-life of the study drug be observed.

HC uses a more stringent guideline, which recommends that the washout period be at least 10 times the half-life of the study drug. Further, HC has placed an upper limit for the entire duration of the washout period, not to exceed four weeks, and also suggests that the study drug be given at the same time and same day of the week in each period.

Although FDA, CDSCO, and EMA guidances do not specify that bioequivalence trials be blinded, HC guidance requires that bioequivalence trials be conducted under double-blind conditions. HC suggests that not only the study subjects but also individuals who administer the study drug and analyze study samples and study data all be blinded to the identity of the formulation being administered.

Moreover, HC guidance stipulates that study personnel responsible for adverse event monitoring also be blinded and that each subject should be questioned about adverse events on each study day. These blinding requirements should be considered carefully during study design.

Standardization

Bioequivalence studies should be designed to standardize both intra-subject and inter-subject variation to the extent that it is possible. Intra-subject variation, or differences arising from intrinsic characteristics of members of a study population, can be minimized by identifying the parameters that define eligible study subjects (e.g., health status and other physical characteristics).

Inter-subject variation, or the difference between the extrinsic factors that subjects encounter during the conduct of the study, is controlled by regulating the study environment and test conditions. These variables consist of the type, quantity, and timing of food and beverage intake, as well as the use of other products by subjects, such as tobacco. Formulation differences between the test and reference products can be more easily identified when intra-subject

and inter-subject variation has been minimized by standardization of a study's parameters. Typically, subjects recruited to participate in bioequivalence trials consist of healthy volunteers, representative of the general population. Appropriate medical procedures should be performed at screening to confirm that potential subjects are in good health. At minimum, screening evaluations should include medical history, physical exam, evaluation of concomitant medications, and laboratory tests.

Canadian guidance specifies that screening procedures for prospective subjects also include a psychological component to identify potentially noncompliant subjects. Importantly, drugs with significant side-effects (e.g., cytotoxic compounds) may necessitate that bioequivalence studies be conducted in the intended treatment population. This practice prevents healthy subjects from being placed at undue risk, in the absence of a treatment benefit. Other important considerations for study participants include age, height, weight, and race. Although FDA, HC, and EMEA guidances

suggest that subjects should be at least 18, CDSCO guidance does not specifically mention a lower age limit for subjects. While HC and EMEA guidances suggest that volunteers be no older than 55, FDA and CDSCO guidances do not specify an upper age limit for inclusion. Canadian, Indian, and U.S. guidances specify that drugs intended to be used in the elderly should be tested in studies enrolling, at least in part, subjects of the appropriate older age.

Height and weight are of specific concern to HC, whose guidance requires subjects be within 15% of normal ranges, and to the EMEA, whose guidance stipulates that subjects be of weight within normal range. Only FDA specifies that race should be representative of the general population, highlighting the diversity of available subjects within the United States when compared to other regions.

Women

Female subjects should be included in studies when the product is intended to be used to treat women. As with all subjects, safety is a guiding principle for the recruitment of female participants, particularly those of child-bearing potential. Female subjects of child-bearing potential should undergo pregnancy testing to confirm they are not pregnant.

The timing of pregnancy testing is sometimes study specific, but Canadian and Indian guidances suggest that testing should be conducted before the first and last doses of the study drug. Although Canadian guidance states that urine pregnancy testing should be employed, serum pregnancy testing is more sensitive and may be used instead.

Female subjects should confirm that they do not intend to or are unlikely to become pregnant. Operationally, women must confirm that they practice abstinence or that they are using a medically acceptable form of birth control; however, Indian guidance precludes women who are taking contraceptive drugs from participating in bioequivalence studies.

External influences

Smoking, alcohol use, consumption of certain types of fruit and fruit juices (e.g., grapefruit), and intake of xanthine-containing food and beverages (e.g., chocolate, coffee, and tea) should be standardized for all subjects for a period of time prior to the administration of each dose of study drug through collection of the last pharmacokinetic sample in the last period. Indian guid-

Retention Samples

Compliance with retention sample regulations is an important consideration for the conduct of bioequivalence studies. Retention (or reserve) samples are quantities of the study drug (test and reference products) that are held 'in reserve' for any future testing or analysis which may be required after the marketing application has been submitted. Typically, retention samples are randomly selected from batches of the test and reference products so that they are representative of the study drug administered to study subjects during the conduct of the bioequivalence trial. Retention samples may be analyzed by regulatory agencies to ensure that the results of bioequivalence studies are reliable. Health Canada guidance does not outline requirements for retention samples. Both the European and Indian regulatory agencies describe requirements for retention samples in their general bioequivalence guidances, while FDA has issued a specific guidance document to address the issue of retention samples which outlines requirements for bioequivalence studies conducted to support registration of a product in the United States.¹¹

- For solid, oral products, **FDA** requires a quantity of study drug which will allow conduct of five times the release tests, not to exceed 300 units (e.g., tablets or capsules) of each the test and reference product. Although FDA guidance does not specify the retention period for these samples, the Code of Federal Regulations (21CFR320.38) requires that retention samples should be held for a period of at least five years after the date on which the application was approved.
- **EMEA** guidance states that a sufficient quantity of study drugs to permit re-testing should be held for one year after the products' expiry or two years after completion of the study or until the test product has received approval, whichever is longest.
- **CDSCO** guidance specifies that a sufficient quantity of test and reference product should be held to allow performance (in duplicate) of all *in vitro* and *in vivo* tests required for the bioequivalence trial. Retention samples should be held for three years after the completion of the bioequivalence study or one year after the products' expiry, whichever is shorter.

ance suggests implementation of these restrictions for a minimum of 48 hours prior to study initiation through the end of the study, while FDA specifically requires subjects to abstain from alcohol use for 24 hours before each period begins through collection of the last sample.

Though CDSCO, EU, and HC guidance does not address tobacco use other than smoking, greatest standardization can be achieved by restricting other types of tobacco use (e.g., oral tobacco). Canadian and European guidances suggest that nonsmokers should be enrolled in bioequivalence studies, but stipulates that subjects who smoke may be included if they are identified.

Fed vs fasting

For most solid, oral formulations, bioequivalence should be demonstrated under fasting conditions, and recommendations are similar across all regions.

FDA suggests administration of the test or reference product with 240 mL of water, after an overnight fast of at least 10 hours and with a meal served no sooner than four hours after dose administration. Subjects are permitted to consume water as desired except for a period of one hour before and after administration of the study drug. In each period, subjects should receive their meals at approximately the same time (e.g., at four hours post-dose).

Canadian and Indian guidance also suggest a minimum fasting period of 10 hours followed by a meal at four hours post-dose. HC's guidelines for fluid intake differ slightly from FDA guidance in that subjects are permitted 250 mL of water

The presence of food in the digestive system can influence the pharmacokinetics of certain drug products, resulting in clinically significant physiological effects.

up to two hours before drug administration and another 250 mL of xanthine-free fluids (e.g., certain juices or water) two hours after drug administration. European guidance is less specific, but suggests that each of the components discussed here be standardized for each period and for all subjects.

The presence of food in the digestive system can influence the pharmacokinetics of certain drug products, resulting in clinically significant physiological effects. Therefore, consideration should be given to the suitability of conducting a bioequivalence study in subjects in the fed state. When appropriate, fed bioequivalence studies are conducted in addition to fasting bioequivalence studies, and in some cases they may be conducted instead of fasting bioequivalence studies.

HC and FDA have outlined the circumstances under which it would be appropriate to conduct bioequivalence studies under fed conditions in guidance documents spe-

cifically written to address fed bioequivalence studies, while CDSCO and EMEA briefly address the topic in their primary guidance documents. For immediate-release, oral drug products with uncomplicated characteristics, HC suggests that fed bioequivalence studies should be conducted in place of fasting bioequivalence studies when safety risks have previously been documented in the absence of food. Drugs with complicated characteristics, however, should ordinarily be conducted under both fed and fasting conditions.

FDA guidance differs, making a blanket recommendation that fed bioequivalence studies be conducted in addition to fasting bioequivalence studies, with the following exceptions:

- When the reference product labeling states that the product should be taken on an empty stomach
- When the reference product labeling omits mention of the effect of food
- When both the test and reference product are rapidly dissolving and contain a drug with high solubility and high permeability

CDSCO guidance suggests that fed bioequivalence studies should be conducted when it is recommended that the reference product be administered with food, while EMEA guidance suggests that bioequivalence studies be conducted in accordance with the reference product's labeling.

Sample menu

To minimize variation between subjects, the content of the test meal should be standardized. Meals that are high in fat and calories are frequently used as the test meal in fed bioequivalence studies. Recommendations for the content of the test meal, which is often a breakfast meal, vary slightly from region to region, with emphasis placed on adherence to the caloric content rather than a specific menu.

FDA and HC provide the same sample menu for the high-fat, high-calorie meal: two eggs fried in butter, two strips of bacon, two slices of toast with butter, four ounces of hash brown potatoes, and eight ounces of whole milk (500-600 fat calories, 250 carbohydrate calories, and 150 protein calories, for a total of 900-1000 calories). Indian guidance recommends a 1000 calorie meal consisting of at least 50% of calories from fats, 15% to 20% of calories from proteins, and the remaining calories from carbohydrates. CDSCO guidance does not provide a sample menu for the test meal, citing large cultural differences within India as a restrictive factor. In practice, a menu free of pork and beef products is often used to accommodate the greatest number of Indian study subjects.

The same constraints that pertain to the design and conduct of bioequivalence studies carried out under fasting conditions are also applicable to fed bioequivalence studies. CDSCO and FDA guidance suggest a minimum 10 hour fast before subjects are given the test meal. The time of initiation and completion of the meal should be stipulated in relation to administration of the investigational product. The recom-

mended completion time for the test meal varies between regions, with FDA suggesting a 30-minute window, CDSCO suggesting a 15-minute window, and HC making no recommendation so long as the time is standardized. When designing fed bioequivalence studies, it may be helpful to identify what percentage of the meal may remain unconsumed without constituting a protocol violation since some subjects may have trouble completing a high-fat, high-calorie meal within a short window of time.

Looking forward

The guidance documents discussed here are helpful for planning and implementing bioequivalence trials to support approval of generic drug products, but the documents are not able to provide comprehensive direction, by virtue of their general nature. The FDA has recognized the need for more specific guidance and has taken steps to address this issue.

FDA has issued a draft guidance document titled, "Bioequivalence Recommendations for Specific Products," which provides the framework for their online database of individual product recommendations [<http://www.fda.gov/cder/guidance/bioequivalence/default.htm>].¹⁰

As of May 2009, there are draft and finalized guidances for 459 individual products provided by FDA. Each product entry supplies study design considerations, including types of studies (i.e., fed or fasting), dosage strength to be used, study population, analytes to be measured, and appropriate biological fluid to be collected for measurement of the analyte. Use of product specific guidances, in conjunction with the FDA's general guidance documents, will help to remove ambiguity from the generic development process.

The changing pharmaceutical landscape and growth of the generic industry necessitate familiarity with the key principles for the conduct of bioequivalence trials. The global nature of drug development is associated with challenges to the completion of well-designed studies that will bring affordable, effective, and safe medications to patients around the world. This article is intended to clarify and summarize the global requirements for bioequivalence trials, thereby encouraging further development of generic alternatives.

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