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Commentary

Bioavailability and Bioequivalence: An FDA Regulatory Overview

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Bioavailability and/or bioequivalence studies play a key role in the drug development period for both new drug products and their generic equivalents. For both, these studies are also important in the postapproval period in the presence of certain manufacturing changes. Like many regulatory studies, the assessment of bioavailability and bioequivalence can generally be achieved by considering the following three questions. What is the primary question of the study? What are the tests that can be used to address the question? What degree of confidence is needed for the test outcome? This article reviews the regulatory science of bioavailability and bioequivalence and provides FDA's recommendations for drug sponsors who intend to establish bioavailability and/or demonstrate bioequivalence for their pharmaceutical products during the developmental process or after approval.

KEY WORDS: bioavailability, bioequivalence, guidances, New Drug Applications, Abbreviated New Drug Applications, generic drugs.

INTRODUCTION

Bioavailability (BA) and bioequivalence (BE) studies provide important information in the overall set of data that ensure the availability of safe and effective medicines to patients and practitioners. BA and BE measures are frequently expressed in systemic exposure measures, such as area under the plasma concentration-time curve (AUC) and maximum concentration (Cmax). These measures of systemic exposure are assumed to relate in some way to safety and efficacy outcomes that may be expressed in biomarkers, surrogate endpoints, or clinical benefit endpoints (1). Based on this assumption, BA and BE information has been determined to have practical and public health value for pharmaceutical sponsors, for regulatory agencies, and for patients and practitioners. The purpose of this article is to review the current approaches to measure BA and establish BE based on recent draft and final guidances issued by the Food and Drug Administration (FDA). This review will cover (i) background, (ii) general concepts, (iii) test procedures, (iv) criteria for comparisons, (v) additional topics, and (vi) future directions. Science and technical issues may be expressed via the following questions to allow a basis for mutual understanding: What is the primary question in a BA or BE study? What are the tests that can be used to address the question? What degree of confidence is needed for the test outcomes? (2).

BACKGROUND

With the growth in bioanalytical capacity in the mid-1950s, available data indicated that compromised product performance, as expressed in BA measures, might be more readily detected. These data led to national and international efforts to define BA and BE and to determine appropriate procedures for their assessment. In the United States, the Congressional Office of Technology Assessment issued a key report that recommended the importance of BA and BE studies and indicated further steps to ensure that this information became part of the drug development and regulatory processes (3). Many recommendations of this report were subsequently adopted by FDA and were published in 1977 as regulations entitled *Part 320—Bioavailability and Bioequivalence Requirements,* which contain subparts A (*General Provisions*) and B (*Procedures for Determining the Bioavailability or Bioequivalence of Drug Products*) (4). The focus of these regulations was on BA and pharmacokinetic information needed for submission in a New Drug Application (NDA) and to some extent on evidence of BE (relative BA).

With passage of the 1984 Drug Price Competition and Patent Term Restoration amendments to the Food, Drug and Cosmetic Act, BE took on added importance for generic drugs. As defined in implementing regulations, an applicant submitting an Abbreviated New Drug Application (ANDA) under Section 505(j) of the Act (excepting Suitability Petitions submitted under 505(j)(2)(c) of the Act) must demon-

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strate both pharmaceutical equivalence (PE) and BE between the generic product and listed innovator reference drug product. With acceptance of this documentation by FDA, along with other information, the generic product is deemed bioequivalent, therapeutically equivalent, and interchangeable with the listed reference drug product.

More recently, information to document PE and BE has become important in the presence of certain postapproval changes. Depending on the magnitude of the change(s) in components and composition and/or method of manufacture, FDA may recommend that a pharmaceutical manufacturer holding either an approved NDA or ANDA redocument BE (and perhaps PE as well) between the pre- and postchange product (NDA) or postchange generic product and reference listed drug (ANDA). The general approach was established in FDA guidances on scale-up and postapproval changes (SUPAC) and subsequently codified in Section 115 of FDAMA (5). The need to ensure continuing BE (and PE) in the presence of certain postapproval changes is critical to a society in which both innovator and generic products are in the marketplace. If either the innovator or generic equivalent changes substantially after approval, assurance of interchangeability is possible only with some documentation.

Relative BA studies are useful in comparing the systemic exposure profiles of different dosage forms and routes of administration. In this context, BA information, sometimes together with pharmacokinetic or pharmacodynamic and other data, can be used to demonstrate the similarity of two dosage forms and ensure comparable clinical outcomes (6).

Definitions in the Food, Drug, and Cosmetic Act

Bioavailability (BA) is defined in the Act as "the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action. For drug products that are not intended to be absorbed into the bloodstream, BA may be assessed by measurements intended to reflect the rate and extent to which the active ingredient or active moiety becomes available at the site of action." Bioequivalence (BE) is defined in the Act as "the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study."

Table I. FDA Core Guidances on Bioavailability and Bioequivalence

- Waiver of *in vivo* bioavailability and bioequivalence studies for immediate-release solid oral dosage forms based on a biopharmaceutics classification system (published August 2000)
- Bioavailability and bioequivalence studies for orally administered drug products—General considerations (published October 2000)
- Statistical approaches to establishing bioequivalence (published January 2001)
- Bioanalytical methods validation for human studies (published May 2001)
- Food-effect bioavailability and bioequivalence studies (draft published October 1997)
- Topical dermatological drug product NDAs and ANDAs—bioavailability, bioequivalence, *in vitro* release, and associated studies (draft published July 1998)
- Bioavailability and bioequivalence studies for nasal aerosols and nasal sprays for local actions (draft published June 1999)
- Bioavailability and bioequivalence studies for oral inhalation drug products for local action: MDIs and DPIs (in preparation)

Regulations

An NDA submission (7) includes the following six technical sections: chemistry, manufacturing, and controls; nonclinical pharmacology and toxicology; human pharmacokinetics and BA; microbiology; clinical data; and statistical data. An ANDA submission (8) contains several comparable sections, including a BE section, but does not report nonclinical, clinical safety and efficacy, and BA studies.

Guidances

A set of draft and final general BA and BE guidances has been developed by FDA over the last several years to provide recommendations to sponsors to meet statutory and regulatory requirements (Table I). They are intended to supplement, and in certain instances replace, drug-specific guidances previously issued by the agency.

THE FIRST QUESTION: GENERAL CONCEPTS

A primary question in BA and BE focuses on the performance of one or more drugs or drug products. This question is considered in the following two sections of the review.

Bioavailability

For most orally administered and other (*e.g.,* transdermal) drug products, BA may be described by a systemic exposure profile obtained from measuring the blood or plasma concentration of active ingredient(s) and/or active moiety(ies) over time after administration of the drug product. From a pharmacokinetic perspective, in addition to systemic exposure, BA studies may provide additional useful information about metabolism, transport, distribution, and elimination of the drug, dose proportionality, nutrients effects on drug absorption, *etc.* From a drug product performance perspective, BA studies also benchmark the performance of the formulation(s) used in the clinical trials that provide evidence of safety and efficacy. The performance of further reformulation of this product and subsequently its generic equivalents should be linked to the benchmark performance of the clinical trial dosage form and indirectly to the safety-efficacy database. Based on different study goals and designs, a distinction may be made between BA studies that are intended to provide pharmacokinetic information and those that are intended to focus on product quality. The former studies may be termed "pharmacokinetic BA" studies, whereas the latter studies have been termed "product quality BA" studies (9).

Bioequivalence

BE assesses the relative BA of two drug products, and thus, focuses on comparative drug product performance. Although establishing product quality BA is a benchmarking effort, sometimes conducted without comparisons, demonstration of BE is usually a formal comparative test between a test and reference product that uses specified criteria for comparisons and predetermined BE limits as target goalposts. BE

evaluation may be important in several circumstances, as discussed in the sections below.

INDs-NDAs

BE documentation may be useful during the IND-NDA period to establish links between: (i) early and late clinical trial formulations; (ii) formulations used in clinical studies and stability studies, if different; and (iii) clinical trial formulations and the to-be-marketed drug product. In each comparison, the new formulation or new method of manufacture is the test product, and the prior formulation or method of manufacture is the reference product. It may not be possible to conclude BE because the test product produces higher or lower measures of rate and extent of absorption or because the performance of the test or reference is more variable. In some cases, "bio*in*equivalence" is observed because of inadequate numbers of subjects entered into the BE study.

ANDAs

Sponsors of ANDAs are required to establish BE between a pharmaceutically equivalent generic drug product and the corresponding listed drug.

Postapproval Changes

Information on the types of *in vivo* BE studies and *in vitro* dissolution needed for postapproval changes to drug products approved as either NDAs or ANDAs are provided in FDA guidances. In the presence of certain major changes in components and composition, and/or method of manufacture after approval, *in vivo* BE between pre- and postchange product may need to be reestablished. Under such circumstances, for approved NDAs, the drug product after change should be compared with the drug product before change, whereas for approved ANDAs, the drug product after change should be compared with the reference listed drug.

THE SECOND QUESTION: TEST PROCEDURES

The second question focuses on the test procedures that are considered adequate to address the primary BA and BE question. Several *in vivo* and *in vitro* methods are appropriate to document BA and BE. In descending order of preference, the US regulations include pharmacokinetic, pharmacodynamic, clinical, and *in vitro* studies (4). Willingness to rely on test procedures other than clinical studies is based on the assumption that pharmacokinetic and pharmacodynamic approaches and/or *in vitro* approaches, along with appropriate goalposts, adequately reflect clinical safety and efficacy outcomes.

Pharmacokinetic Studies

The statutory definition of BA and BE, expressed in rate and extent of absorption of the active moiety or ingredient to the site of action, emphasizes the use of pharmacokinetic measures to indicate release of the drug substance from the drug product with absorption into the systemic circulation. This approach rests on an understanding that measurement of the active moiety or ingredient at the site(s) of action is generally not possible and that some predetermined relationship exists between the drug concentration at the site of action relative to that in the systemic circulation. A typical BE study is conducted as a crossover study, in which clearance and physiologic variables (*e.g.,* gastric emptying, motility, and pH) are assumed to have less interoccasion variability within an individual compared with variability between individuals. Where needed, a pilot study may be useful to validate analytic methodology, to assess intra- and intersubject variability in systemic exposure measures, and to optimize sample collection times. Although some authors have stated that multiple-dose studies are useful in establishing BA and BE (10), single-dose studies to document BE may be preferred because they are generally more sensitive in assessing *in vivo* release of the drug substance from the drug product (11–13).

A goal in BA and BE studies is to assess rate and extent of drug absorption. Extent of absorption is readily measured by AUC either to the last sampled time point ($AUC_{0\text{-}t}$) or following extrapolation to time infinity ($AUC_{0\text{-}\infty}$). Measurement of the true rate of absorption is difficult, given that rate varies continuously over time (14,15). A recent FDA guidance, therefore, has recommended that measures of systemic exposure be used to reflect clinically important differences between test and reference products in BA and BE studies (16). These measures include (i) total exposure ($AUC_{0\text{-}t}$ or $AUC_{0\text{-}\infty}$ for single-dose studies and $AUC_{0\text{-}t}$ for steady-state studies), (ii) peak exposure (Cmax), and (iii) early exposure (partial AUC to peak time of the reference product for an immediate-release drug product). Reliance on systemic exposure measures will reflect comparable rate and extent of absorption, which in turn, will achieve the underlying goal of assuring comparable therapeutic effects.

Pharmacologic Effect (Pharmacodynamic) Studies

Locally acting drug products include oral inhalation drug products, such as metered dose inhalers and dry powder inhalers, and topically applied dermatologic drug products such as creams and ointments. These drug products deliver an active moiety or active ingredient to local sites of action where they exert their primary clinical effects. Pharmacokinetic studies measure systemic exposure but are generally inappropriate to document local delivery BA and BE. In such cases, BA may be measured, and BE may be established, based on a pharmacodynamic (PD) study, providing an appropriate PD endpoint is available, which can be studied with sufficient accuracy, sensitivity, and reproducibility. Bronchodilator drug products, such as albuterol metered dose inhalers, produce relaxation of airway smooth muscle. For these drug products, a PD endpoint, based either on increase in forced expiratory volume in 1 s (FEV_1) or on measurement of PD_{20} or PC_{20} (the dose or concentration, respectively, of a challenge agent) (17,18), is clinically relevant and may be used for BA and BE studies.

An essential component of a BA or BE study based on a PD response is documentation of a dose-response relationship. The dose-response curve should be characterized as part of the study. In the absence of other evidence, the commonly used Emax model is assumed as the default model. To establish BE, the study is conducted in the sensitive region of the dose-response curve (19). A BE study conducted near the plateau of response will be insensitive to differences in drug delivery between the test and reference products and will, thus, require increased numbers of subjects to detect product

differences. PD response measurements of the test and reference products determined in the BE study may be converted to estimates of delivered dose of the test and reference products by using a dose-scale approach (20). The benefits of the dose-scale approach to BE assessment arise from the translation of nonlinear PD measurements to linear dose measurements.

Comparative Clinical Trials

In the absence of pharmacokinetic and pharmacodynamic approaches, adequate and well-controlled clinical trials may be used to establish BA or, when comparative, BE. A number of draft or final FDA guidances provide general information about the conduct of clinical studies (6,21).

In Vitro Dissolution Studies

In 1974, the Congressional Office of Technology Assessment's Drug Bioequivalence Study Panel made eleven recommendations (3), one of which stated:

> It is neither feasible nor desirable that studies of bioavailability be conducted for all drugs or drug products. Certain classes of drugs for which evidence of bioequivalence is critical should be identified. Selection of these classes of drugs should be based on clinical importance, ratios of therapeutic to toxic concentrations in blood, and certain pharmaceutical characteristics.

Based on this and other recommendations of the Panel, the 1977 BA and BE regulations defined criteria to determine whether certain drug products approved before 1962 were or were not drug products with BA and BE problems. Manufacturers of drug products in the category with BA and BE problems were required to demonstrate BE using *in vivo* studies. In contrast, *in vitro* studies for pre-1962 drugs could be used to demonstrate BE for drug products without BA and BE problems. This approach was not used for drug products approved after 1962, where *in vivo* BE studies have generally been required by FDA. More recently, a biopharmaceutics classification system (BCS) categorizes drug substances as having either high or low solubility and permeability and drug products as exhibiting rapid dissolution (22). According to this approach, drug substances may be classified into four primary groups (highly soluble/highly permeable, highly permeable/poorly soluble, highly soluble/poorly permeable, poorly soluble/poorly permeable). Similarly, drug products may be classified as rapidly dissolving. Using the BCS approach, a highly permeable, highly soluble drug substance formulated into a rapidly dissolving drug product may need only *in vitro* dissolution studies to establish BE (23). Dissolution tests can also be used to reduce the number of *in vivo* studies in other circumstances, and to (i) assess batch-to-batch quality and support batch release; (ii) provide process control and quality assurance; and (iii) assess the need for further BE studies relative to minor postapproval changes, where they function as a signal of bio*in*equivalence.

THE THIRD QUESTION: CRITERIA FOR COMPARISONS

The third question in the series of three questions focuses on the degree of certainty needed in the analysis of relative BA or BE studies. An equivalence approach is generally recommended. The approach usually relies on (i) a criterion to allow the comparison, (ii) a confidence interval for the criterion, and (iii) a BE limit (also called the goalpost). Log-transformation of exposure measures is generally recommended. To compare measures in these studies, data are analyzed by using an average BE criterion with other criteria allowed more recently (16,24–25).

ADDITIONAL TOPICS

Approaches Depending on Dosage Form

Generally, *in vivo* BE studies are waived for solubilized oral dosage forms on the assumption that release of the drug substance from the drug product is self-evident, providing they do not contain any excipient that significantly affects drug absorption. For oral suspensions and immediate release capsules and tablets, a single-dose *in vivo* fasting study is usually sufficient. Food-effect studies for NDAs are always encouraged and fed BE studies for ANDAs may be needed in specified circumstances. Fed BE studies for ANDAs focus on demonstrating equivalence between test and reference products when coadministered with high fat/high calorie meals. For both extended and delayed release drug products, FDA previously recommended the following BA and BE studies (26,27): (i) a single-dose fasting study, (ii) a single-dose fed study, and (iii) a steady-state study. However, a new guidance from the Agency has indicated that steady-state study is not necessary. Instead, replicate design is recommended for the single-dose fasting study (16). For miscellaneous dosage forms, such as buccal, sublingual, and chewable tablets, FDA has recommended single-dose *in vivo* BE studies. Chewable tablets should be studied by using an *in vitro* dissolution test under the same conditions as a nonchewable tablet because they might be swallowed without proper chewing.

Moieties to Be Measured

Parent Drug vs. Metabolites

Moieties to be measured in BA and BE studies are the active drug ingredient or active moiety in the administered dosage form (parent drug) and, when appropriate systemically, its active metabolites. According to this approach, both active ingredient or active moiety and active metabolites should be measured in BA studies, if analytically feasible. For BE studies, only the parent drug should be measured, although there are situations in which active metabolites are to be measured (16). The rationale for this approach is that the concentration-time profile of the parent drug is more sensitive to changes in formulation performance than the metabolite, which includes the processes of metabolite formation, distribution, and elimination.

Enantiomers vs. Racemates

For BA studies, measurement of both enantiomers may be important. For BE studies, measurement of the racemate using an achiral assay has been recommended, without measurement of individual enantiomers except when (i) the enantiomers exhibit different pharmacodynamic characteristics; (ii) the enantiomers exhibit different pharmacokinetics; (iii) the primary activity resides with the minor enantiomer; and

(iv) nonlinear absorption is present (as expressed by a change in the enantiomer concentration ratio with change in the input rate of the drug) for at least one of the enantiomers (16).

Drug Products with Complex Mixtures

Certain drug products may contain complex drug substances, *i.e.,* active moiety(ies) or active ingredient(s), which are mixtures of multiple synthetic and/or natural source components. Some or all of the components of these complex drug substances may not be characterized with regard to chemical structure and/or biological activity. In this circumstance, BA and BE studies may be based on selected markers of peak and total exposure.

Drugs with Long Half-Lives

In a BA study involving a drug product with a long half-life, adequate characterization of the half-life necessitates blood sampling over a long period of time. For BE determination of drug products with long half-lives (*e.g.,* >24 h), a nonreplicate single-dose crossover study may be conducted provided an adequate washout period is used. If the crossover study is problematic, a parallel BE study design may be appropriate. For a crossover or parallel study design, sample collection time should be adequate to ensure completion of gastrointestinal transit (approximately 2–3 days) for drug products and absorption of drug substances.

Orally Administered Drugs Intended for Local Action

Documentation of BA where the drug substance produces its effects via local action in the gastrointestinal tract has been achieved via clinical safety and efficacy studies and/or suitably designed and validated *in vitro* studies. Similarly, documentation of BE for certain postapproval changes may be achieved via clinical efficacy and safety studies and/or suitably designed and validated *in vitro* studies. To ensure comparable safety, additional studies with and without food may be necessary to understand the degree of systemic exposure that occurs after administration of a drug product intended for local action in the gastrointestinal tract.

Drugs with Narrow Therapeutic Ranges

Drugs with narrow therapeutic ranges (NTR) can be defined as those that require therapeutic drug concentration or pharmacodynamic monitoring and/or where product labeling indicates a narrow therapeutic range designation. Additional testing and controls may be needed to ensure the quality of drug products containing NTR drugs. Although this approach is designed to provide increased assurance of interchangeability for NTR drug products, it is not designed to influence the practice of medicine and pharmacy.

FUTURE DIRECTIONS

Many scientists have worked over the years to develop regulations and guidances that indicate when and how product quality BA and BE studies should be conducted. In the last decade, the topic has also been taken up by the World Health Organization (WHO), with publication of two documents that delineate general BA and BE approaches (28) and establish the concept of an International Comparator Pharmaceutical Product (29). During this time period, the International Conference on Harmonization (ICH) has worked to develop a series of guidelines in the areas of efficacy, safety, and quality. As a further step, ICH has developed a Common Technical Document (CTD) to provide a format (table of contents) for a core set of information that can be submitted to the regulatory agencies of Japan, the United States, and Europe (30). Although BA and BE guidelines have not been harmonized in ICH, Module 2 of the CTD, which focuses on report summaries, contains a section (G/1) that covers information on biopharmaceutics and associated analytical methods. In this section, the ICH document recommends that an overview should be provided for BA, comparative BA, BE, and *in vitro* dissolution profile database. The progress in ICH and WHO is complementary and creates an opportunity for convergence globally on harmonization of BA and BE approaches. This harmonization could focus on standardization of nomenclature, agreement on general concepts (first question), choice of test procedures (second question), and consideration of criteria and goalposts, which reflect regulatory decision-making standards (third question). As a further objective, certain test procedures may be elaborated in harmonized pharmacopeial general chapters.

Although global harmonization is a general goal, differing regulatory approaches and differing levels of commitment and resources continue to create formidable barriers. Harmonization may be promoted by a better understanding of factors underlying product performance through replicate designs of BA and BE studies and increased reliance on dissolution through application of BCS. Extension of the BCS based on applied regulatory research may further reduce the need for *in vivo* BA and BE studies and, thus, reduce regulatory burden without sacrificing important public health objectives related to product quality and performance. Alternative *in vitro* and *in vivo* approaches may be useful to document BA and BE for locally acting drug products and, thus, avoid costly, time-consuming and insensitive clinical trials. In sum, many scientific, technical, and regulatory opportunities are available to improve and harmonize BA and BE approaches and to ensure product quality over time for both innovator and generic products. The end results of this continuing effort would be to develop optimally performing products for use by patients and practitioners in the global community.

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