Guidance for Industry

Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
October 2000
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Table of Contents

GUIDANCE FOR INDUSTRY[1]

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This guidance represents the Food and Drug Administration=s current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations.

I. INTRODUCTION

This guidance is intended to provide recommendations to sponsors and/or applicants planning to include bioavailability (BA) and bioequivalence (BE) information for orally administered drug products in investigational new drug applications (INDs), new drug applications (NDAs), abbreviated new drug applications (ANDAs), and their supplements. This guidance addresses how to meet the BA and BE requirements set forth in 21 CFR part 320 as they apply to dosage forms intended for oral administration.[2] The guidance is also generally applicable to non-orally administered drug products where reliance on systemic exposure measures is suitable to document BA and BE (e.g., transdermal delivery systems and certain rectal and nasal drug products). The guidance should be useful for applicants planning to conduct BA and BE studies during the IND period for an NDA, BE studies intended for submission in an ANDA, and BE studies conducted in the postapproval period for certain changes in both NDAs and ANDAs.[3]

This guidance is designed to reduce the need for FDA drug-specific BA/BE guidances. As a result, this guidance replaces a number of previously issued FDA drug-specific BE guidances (see the list in Appendix 1). On rare occasions, FDA may decide to provide additional BA/BE guidances for specific drug products.

II. BACKGROUND

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[1] This guidance has been prepared by the Biopharmaceutics Coordinating Committee in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration (FDA).

[2] These dosage forms include tablets, capsules, solutions, suspensions, conventional/immediate release, and modified (extended, delayed) release drug products.

[3] Other Agency guidances are available that consider specific scale-up and postapproval changes (SUPAC) for different types of drug products to help satisfy regulatory requirements in both 21 CFR part 320 and 21 CFR 314.70.

A. General

Studies to measure BA and/or establish BE of a product are important elements in support of INDs, NDAs, ANDAs, and their supplements. As part of INDs and NDAs for orally administered drug products, BA studies focus on determining the process by which a drug is released from the oral dosage form and moves to the site of action. BA data provide an estimate of the fraction of the drug absorbed, as well as its subsequent distribution and elimination. BA can be generally documented by a systemic exposure profile obtained by measuring drug and/or metabolite concentration in the systemic circulation over time. The systemic exposure profile determined during clinical trials in the IND period can serve as a benchmark for subsequent BE studies.

Studies to establish BE between two products are important for certain changes prior to approval for a pioneer product in NDA and ANDA submissions, and in the presence of certain postapproval changes in NDAs and ANDAs. In BE studies, an applicant compares the systemic exposure profile of a test drug product to that of a reference drug product. For two orally administered drug products to be bioequivalent, the active drug ingredient or active moiety in the test product should exhibit the same rate and extent of absorption as the reference drug product.

Both BA and BE studies are required by regulations, depending on the type of application being submitted. Under 21 CFR 314.94, BE information is required to ensure therapeutic equivalence between a pharmaceutically equivalent test drug product and a reference listed drug. Regulatory requirements for documentation of BA and BE are provided in 21 CFR part 320, which contains two subparts. Subpart A covers general provisions, while Subpart B contains 18 sections delineating the following general BA/BE requirements:

- Requirements for submission of BA and BE data (320.21)
- Criteria for waiver of an in vivo BA or BE study (320.22)
- Basis for demonstrating in vivo BA or BE (320.23)
- Types of evidence to establish BA or BE (320.24)
- Guidelines for conduct of in vivo BA studies (320.25)
- Guidelines on design of single-dose BA studies (320.26)
- Guidelines on design of multiple-dose in vivo BA studies (320.27)
- Correlations of BA with an acute pharmacological effect or clinical evidence (320.28)
- Analytical methods for an in vivo BA study (320.29)
- Inquiries regarding BA and BE requirements and review of protocols by FDA (320.30)
- Applicability of requirements regarding an IND application (320.31)
- Procedures for establishing and amending a BE requirement (320.32)
- Criteria and evidence to assess actual or potential BE problems (320.33)
- Requirements for batch testing and certification by FDA (320.34)

- Requirements for in vitro batch testing of each batch (320.35)
- Requirements for maintenance of records of BE testing (320.36)
- Retention of BA samples (320.38)
- Retention of BE samples (320.63)

B. Bioavailability

Bioavailability is defined in 21 CFR 320.1 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, bioavailability may be assessed by measurements intended to reflect the rate and extent to which the active ingredient or active moiety becomes available at the site of action." This definition focuses on the processes by which the active ingredients or moieties are released from an oral dosage form and move to the site of action.

From a pharmacokinetic perspective, BA data for a given formulation provide an estimate of the relative fraction of the orally administered dose that is absorbed into the systemic circulation when compared to the BA data for a solution, suspension, or intravenous dosage form (21 CFR 320.25 (d) (2) and (3)). In addition, BA studies provide other useful pharmacokinetic information related to distribution, elimination, the effects of nutrients on absorption of the drug, dose proportionality, linearity in pharmacokinetics of the active moieties and, where appropriate, inactive moieties. BA data may also provide information indirectly about the properties of a drug substance prior to entry into the systemic circulation, such as permeability and the influence of presystemic enzymes and/or transporters (e.g., p-glycoprotein).

BA for orally administered drug products may be documented by developing a systemic exposure profile obtained from measuring the concentration of active ingredients and/or active moieties and, when appropriate, its active metabolites over time in samples collected from the systemic circulation. Systemic exposure patterns reflect both release of the drug substance from the drug product and a series of possible presystemic/systemic actions on the drug substance after its release from the drug product. Additional comparative studies should be performed to understand the relative contribution of these processes to the systemic exposure pattern.

One regulatory objective is to assess, through appropriately designed BA studies, the performance of the formulations used in the clinical trials that provide evidence of safety and efficacy (21 CFR 320.25(d)(1)). The performance of the clinical trial dosage form may be optimized, in the context of demonstrating safety and efficacy, before marketing a drug product. The systemic exposure profiles of clinical trial material can be used as a benchmark for subsequent formulation changes and may thus be useful as a reference for future BE studies.

Although BA studies have many pharmacokinetic objectives beyond formulation performance as described above, it should be noted that subsequent sections of this guidance focus on using

relative BA (referred to as product quality BA) and, in particular, BE studies as a means to document product quality. In vivo performance, in terms of BA/BE, may be considered to be one aspect of product quality that provides a link to the performance of the drug product used in clinical trials and thus to the database containing evidence of safety and efficacy.

C. Bioequivalence

Bioequivalence is defined at 21 CFR 320.1 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." As noted in the statutory definitions, both BE and product quality BA focus on the release of a drug substance from a drug product and subsequent absorption into the systemic circulation. For this reason, similar approaches to measuring BA in an NDA should generally be followed in demonstrating BE for an NDA or an ANDA. Establishing product quality BA is a benchmarking effort with comparisons to an oral solution, oral suspension, or an intravenous formulation. In contrast, demonstrating BE is usually a more formal comparative test that uses specified criteria for comparisons and predetermined BE limits for the criteria.

1. IND/NDAs

BE documentation may be useful during the IND/NDA period to establish links between (1) early and late clinical trial formulations; (2) formulations used in clinical trial and stability studies, if different; (3) clinical trial formulations and to-be-marketed drug product; and (4) other comparisons, as appropriate. 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. The need to redocument BE during the IND period is generally left to the judgment of the sponsor, who may wish to use the principles of relevant guidances (in this guidance, see sections II.C.3, Postapproval Changes, and III.D, In Vitro Studies) to determine when changes in components, composition, and/or method of manufacture suggest a need to perform further in vitro and/or in vivo studies.

A test product may fail to meet BE limits because the test product has higher or lower measures of rate and extent of absorption compared to the reference product or because the performance of the test or reference is more variable. In some cases, nondocumentation of BE may arise because of inadequate numbers of subjects in the study relative to the magnitude of intrasubject variability, and not because of either high or low relative BA of the test product. Adequate design and execution of a BE study will facilitate understanding of the causes of nondocumentation of BE.

Where the test product generates plasma levels that are substantially above those of the reference product, the regulatory concern is not therapeutic failure, but the adequacy of

the safety database from the test product. Where the test product has levels that are substantially below those of the reference product, the regulatory concern becomes therapeutic efficacy. When the variability of the test product rises, the regulatory concern relates to both safety and efficacy, because it may suggest that the test product does not perform as well as the reference product, and the test product may be too variable to be clinically useful.

Proper mapping of individual dose-response or concentration-response curves is useful in situations where the drug product has plasma levels that are either higher or lower than the reference product and are outside usual BE limits. In the absence of individual data, population dose-response or concentration-response data acquired over a range of doses, including doses above the recommended therapeutic doses, may be sufficient to demonstrate that the increase in plasma levels would not be accompanied by additional risk. Similarly, population dose- or concentration-response relationships observed over a lower range of doses, including doses below the recommended therapeutic doses, may be able to demonstrate that reduced levels of the test product compared to the reference product are associated with adequate efficacy. In either event, the burden is on the sponsor to demonstrate the adequacy of the clinical trial dose-response or concentration-response data to provide evidence of therapeutic equivalence. In the absence of this evidence, a failure to document BE may suggest a need for a reformulation, a change in the method of manufacture for the test product, and/or a repeat of the BE study.

2. ANDAs

BE studies are a critical component of ANDA submissions. The purpose of these studies is to demonstrate BE between a pharmaceutically equivalent generic drug product and the corresponding reference listed drug (21 CFR 314.94 (a)(7)). Together with the determination of pharmaceutical equivalence, establishing BE allows a regulatory conclusion of therapeutic equivalence.

3. Postapproval Changes

Information on the types of in vitro dissolution and in vivo BE studies that should be conducted for immediate-release and modified-release drug products approved as either NDAs or ANDAs in the presence of specified postapproval changes is provided in the FDA guidances for industry entitled *SUPAC-IR: Immediate Release Solid Oral Dosage Forms: Scale-Up and Post-Approval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation* (November 1995)*;* and *SUPAC-MR: Modified Release Solid Oral Dosage Forms: Scale-Up and Post-Approval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation* (September 1997). In the presence of certain

major changes in components, composition, and/or method of manufacture after approval, in vivo BE should be redemonstrated. For approved NDAs, the drug product after the change should be compared to the drug product before the change. For approved ANDAs, the drug product after the change should be compared to the reference listed drug. Under section 506A(c)(2)(B) of the Federal Food, Drug, and Cosmetic Act, postapproval change requiring completion of studies in accordance with 21 CFR part 320 must be submitted in a supplement and approved by FDA before distributing a drug product made with the change.

III. METHODS TO DOCUMENT BA AND BE

As noted at 21 CFR 320.24, several in vivo and in vitro methods can be used to measure product quality BA and establish BE. In descending order of preference, these include pharmacokinetic, pharmacodynamic, clinical, and in vitro studies. These general approaches are discussed in the following sections of this guidance. Product quality BA and BE frequently rely on pharmacokinetic measures such as AUC and Cmax that are reflective of systemic exposure.

A. Pharmacokinetic Studies

1. General Considerations

The statutory definitions of BA and BE, expressed in terms of rate and extent of absorption of the active ingredient or moiety to the site of action, emphasize the use of pharmacokinetic measures in an accessible biological matrix such as blood, plasma, and/or serum to indicate release of the drug substance from the drug product into the systemic circulation.[4] This approach rests on an understanding that measuring the active moiety or ingredient at the site of action is generally not possible and, furthermore, that some relationship exists between the efficacy/safety and concentration of active moiety and/or its important metabolite or metabolites in the systemic circulation. To measure product quality BA and establish BE, reliance on pharmacokinetic measurements may be viewed as a bioassay that assesses release of the drug substance from the drug product into the systemic circulation. A typical study is conducted as a crossover study. In this type of study, clearance, volume of distribution, and absorption, as determined by physiological variables (e.g. gastric emptying, motility, pH), are assumed to have less interoccasion variability compared to the variability arising from formulation performance. Therefore, differences between two products due to formulation factors can be determined.

[4] If serial measurements of the drug or its metabolites in plasma, serum, or blood cannot be accomplished, measurement of urinary excretion may be used to document BE.

2. Pilot Study

If the sponsor chooses, a pilot study in a small number of subjects can be carried out before proceeding with a full BE study. The study can be used to validate analytical methodology, assess variability, optimize sample collection time intervals, and provide other information. For example, for conventional immediate-release products, careful timing of initial samples may avoid a subsequent finding in a full-scale study that the first sample collection occurs after the plasma concentration peak. For modified-release products, a pilot study can help determine the sampling schedule to assess lag time and dose dumping. A pilot study that documents BE may be acceptable, provided that its design and execution are suitable and a sufficient number of subjects (e.g., 12) have completed the study.

3. Pivotal Bioequivalence Studies

General recommendations for a standard BE study based on pharmacokinetic measurements are provided in Appendix 2.

4. Nonreplicate Study Designs

Nonreplicate study designs are recommended for BE studies of most orally administered, immediate-release dosage forms. However, sponsors and/or applicants have the option of using replicate designs for BE studies of these drug products. These studies are described in section III.A.5 below. The recommended method of analysis of nonreplicate or replicate studies to establish BE is discussed in section IV. General recommendations for nonreplicate study designs are provided in Appendix 2.

5. Replicate Study Designs

Replicate study designs are recommended for BE studies of modified-release dosage forms and highly variable drug products (within-subject coefficient of variation ≥ 30%), including those that are immediate release, modified-release, and other orally administered drug products. The recommended method of analysis of replicate studies to establish BE is discussed in section IV.

Replicate study designs offer several scientific advantages compared to nonreplicate designs. The advantages of replicate study designs are that they (1) allow comparisons of within-subject variances for the test and reference products; (2) indicate whether a test product exhibits higher or lower within-subject variability in the bioavailability measures when compared to the reference product; (3) suggest whether a subject-by-formulation (S*F) interaction may be present; (4) provide more information about factors underlying formulation performance; and (5) reduce the number of subjects needed in the BE study.

6. Study Population

Unless otherwise indicated by a specific guidance, subjects recruited for in vivo BE studies should be 18 years of age or older and capable of giving informed consent. This guidance recommends that in vivo BE studies be conducted in individuals representative of the general population, taking into account age, sex, and race factors. If the drug product is intended for use in both sexes, the sponsor should attempt to include similar proportions of males and females in the study. If the drug product is to be used predominantly in the elderly, the sponsor should attempt to include as many subjects of 60 years of age or older as possible. The total number of subjects in the study should provide adequate power for BE demonstration, but it is not expected that there will be sufficient power to draw conclusions for each subgroup. Statistical analysis of subgroups is not recommended. Restrictions on admission into the study should generally be based solely on safety considerations. In some instances, it may be useful to admit patients into BE studies for whom a drug product is intended. In this situation, sponsors and/or applicants should attempt to enter patients whose disease process is stable for the duration of the BE study. In accordance with 21 CFR 320.31, for some products that will be submitted in ANDAs, an IND may be required for BE studies to ensure patient safety.

7. Single-Dose/Multiple-Dose Studies

Instances where multiple-dose studies may be useful are defined at 21 CFR 320.27(a)(3). However, this guidance generally recommends single-dose pharmacokinetic studies for both immediate- and modified-release drug products to demonstrate BE because they are *generally* more sensitive in assessing release of the drug substance from the drug product into the systemic circulation (see section V). If a multiple-dose study design is necessary, appropriate dosage administration and sampling should be carried out to document attainment of steady state.

8. Bioanalytical Methodology

Bioanalytical methods for BA and BE studies should be accurate, precise, selective, sensitive, and reproducible. A separate FDA guidance entitled *Bioanalytical Methods Validation for Human Studies* (published in draft in December 1998) will be available, when finalized, to assist sponsors in validating bioanalytical methods.

9. Pharmacokinetic Measures of Systemic Exposure

Both direct (e.g., rate constant, rate profile) and indirect (e.g., Cmax, Tmax, mean absorption time, mean residence time, Cmax normalized to AUC) pharmacokinetic measures are limited in their ability to assess rate of absorption. This guidance,

therefore, recommends a change in focus from these direct or indirect measures of absorption rate to measures of systemic exposure. Cmax and AUC can continue to be used as measures for product quality BA and BE, but more in terms of their capacity to assess exposure than their capacity to reflect rate and extent of absorption. Reliance on systemic exposure measures should reflect comparable rate and extent of absorption, which in turn should achieve the underlying statutory and regulatory objective of ensuring comparable therapeutic effects. Exposure measures are defined relative to early, peak, and total portions of the plasma, serum, or blood concentration-time profile, as follows:

a. Early Exposure

For orally administered immediate-release drug products, BE may generally be demonstrated by measurements of peak and total exposure. An early exposure measure may be indicated on the basis of appropriate clinical efficacy/safety trials and/or pharmacokinetic/pharmacodynamic studies that call for better control of drug absorption into the systemic circulation (e.g., to ensure rapid onset of an analgesic effect or to avoid an excessive hypotensive action of an antihypertensive). In this setting, the guidance recommends use of partial AUC as an early exposure measure. The partial area should be truncated at the population median of Tmax values for the reference formulation. At least two quantifiable samples should be collected before the expected peak time to allow adequate estimation of the partial area.

b. Peak Exposure

Peak exposure should be assessed by measuring the peak drug concentration (Cmax) obtained directly from the data without interpolation.

c. Total Exposure

For single-dose studies, the measurement of total exposure should be:

- Area under the plasma/serum/blood concentration-time curve from time zero to time t (AUC_{0-t}), where t is the last time point with measurable concentration for individual formulation.

- Area under the plasma/serum/blood concentration-time curve from time zero to time infinity ($AUC_{0-\infty}$), where $AUC_{0-\infty} = AUC_{0-t} + C_t/\lambda_z$, C_t is the last measurable drug concentration and λ_z is the terminal or elimination rate constant calculated according to an appropriate method. The terminal half-life ($t_{1/2}$) of the drug should also be reported.

For steady-state studies, the measurement of total exposure should be the area under the plasma, serum or blood concentration-time curve from time zero to time τ over a dosing interval at steady state ($AUC_{0-\tau}$), where τ is the length of the dosing interval.

B. Pharmacodynamic Studies

Pharmacodynamic studies are not recommended for orally administered drug products when the drug is absorbed into the systemic circulation and a pharmacokinetic approach can be used to assess systemic exposure and establish BE. However, in those instances where a pharmacokinetic approach is not possible, suitably validated pharmacodynamic methods can be used to demonstrate BE.

C. Comparative Clinical Studies

Where there are no other means, well-controlled clinical trials in humans may be useful to provide supportive evidence of BA or BE. However, the use of comparative clinical trials as an approach to demonstrate BE is generally considered insensitive and should be avoided where possible (21 CFR 320.24). The use of BE studies with clinical trial endpoints may be appropriate to demonstrate BE for orally administered drug products when measurement of the active ingredients or active moieties in an accessible biological fluid (pharmacokinetic approach) or pharmacodynamic approach is infeasible.

D. In Vitro Studies

Under certain circumstances, product quality BA and BE can be documented using in vitro approaches (21 CFR 320.24). For highly soluble, highly permeable, rapidly dissolving, orally administered drug products, documentation of BE using an in vitro approach (dissolution studies) is appropriate based on the biopharmaceutics classification system.[5] This approach may also be suitable under some circumstances in assessing BE during the IND period, for NDA and ANDA submissions, and in the presence of certain postapproval changes to approved NDAs and ANDAs. In addition, in vitro approaches to document BE for *nonbioproblem* drugs approved prior to 1962 remain acceptable (21 CFR 320.33).

Dissolution testing is also used to assess batch-to-batch quality, where the approach may become one of the tests, with defined procedures, in a drug product specification to allow batch release. Dissolution testing is also used to (1) provide process control and quality assurance, and (2) assess the need for further BE studies relative to minor postapproval changes, where dissolution can function as a signal of bioinequivalence. In vitro dissolution characterization is encouraged for all product formulations investigated (including prototype formulations),

[5] See the FDA guidance for industry on *Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System* (August 2000). This document provides complementary information on the Biopharmaceutics Classification System (BCS).

particularly if in vivo absorption characteristics are being defined for the different product formulations. Such efforts may enable the establishment of an in vitro-in vivo correlation. When an in vitro-in vivo correlation or association is available (21 CFR 320.22), the in vitro test can serve not only as a quality control specification for the manufacturing process, but also as an indicator of how the product will perform in vivo. The following guidances provide recommendations on the development of dissolution methodology, setting specifications, and the regulatory applications of dissolution testing: (1) *Dissolution Testing of Immediate Release Solid Oral Dosage Forms* (August 1997); and (2) *Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations* (September 1997).

This guidance recommends that dissolution data from three batches for both NDAs and ANDAs be used to set dissolution specifications for modified-release dosage forms, including extended-release dosage forms.

IV. COMPARISON OF BA MEASURES IN BE STUDIES

An equivalence approach has been and continues to be recommended for BE comparisons. The recommended approach relies on (1) a criterion to allow the comparison, (2) a confidence interval for the criterion, and (3) a BE limit. Log-transformation of exposure measures prior to statistical analysis is recommended. BE studies are performed as single-dose, crossover studies. To compare measures in these studies, data have been analyzed using an average BE criterion. This guidance recommends continued use of an average BE criterion to compare BA measures for replicate and nonreplicate BE studies of both immediate- and modified-release products. However, sponsors have the option to explain why they would use another criterion (e.g., an individual BE criterion for replicate design studies of highly variable drug products). Sponsors should document selection of the criterion in the study protocol. Sponsors and/or applicants wishing further information on this approach should contact the appropriate CDER review division. The criteria to allow comparison of BE measures will be provided in a separate FDA guidance for industry.[6] When the individual or population BE criterion is used, in addition to meeting the BE limit based on confidence bounds, the point estimate of the geometric test/reference mean ratio should fall within 80-125%.

V. DOCUMENTATION OF BA AND BE

An in vivo study is generally recommended for all solid oral dosage forms approved after 1962 and for *bioproblem* drug products approved prior to 1962. Waiver of in vivo studies for different strengths of a drug product may be granted under 21 CFR 320.22 (d)(2) when (1) the drug product is in the same

[6] *Average, Population, and Individual Approaches to Establishing Bioequivalence* (draft guidance published August 1999). When finalized, this guidance will provide recommendations on criteria for comparison of BE measures.

dosage form, but in a different strength; (2) this different strength is *proportionally similar* in its active and inactive ingredients to the strength of the product for which the same manufacturer has conducted an acceptable in vivo study; and (3) the new strength meets an appropriate in vitro dissolution test. This guidance defines *proportionally similar* in two ways:

Definition 1: All active and inactive ingredients are in exactly the same proportion between different strengths (e.g., a tablet of 50-mg strength has all the inactive ingredients, exactly half that of a tablet of 100-mg strength, and twice that of a tablet of 25-mg strength).

Definition 2: The total weight of the dosage form remains nearly the same for all strengths (within $\pm$ 5 percent of the total weight of the strength on which a bio-study was performed), the same inactive ingredients are used for all strengths, and the change in any strength is obtained by altering the amount of the active ingredient and one or more of the inactive ingredients.[7] For example, with respect to an approved 5-mg tablet, the total weight of new 1- and 2.5-mg tablets remains nearly the same, and the changes in the amount of active ingredient are offset by a change in one or more inactive ingredients. This definition is generally applicable to high-potency drug substances where the amount of active drug substance in the dosage form is relatively low (e.g., $\leq$ 5 mg).

A. Solutions

For oral solutions, elixirs, syrups, tinctures, or other solubilized forms, BA and/or BE can be demonstrated using nonclinical studies (21 CFR 320.22(b)(3)(i)). Generally, in vivo BE studies are waived for solutions on the assumption that release of the drug substance from the drug product is self-evident and that the solutions do not contain any excipient that significantly affects drug absorption (21 CFR 320.22 (b) (3) (iii)). However, there are certain excipients, such as sorbitol or mannitol, that can reduce the bioavailability of drugs with low intestinal permeability in amounts sometimes used in oral liquid dosage forms.

B. Suspensions

BA and BE for a suspension should generally be established as for immediate-release solid oral dosage forms, and both in vivo and in vitro studies are recommended.

C. Immediate-Release Products: Capsules and Tablets

1. General Recommendations

For product quality BA and BE studies, where the focus is on release of the drug substance from the drug product into the systemic circulation, a single-dose, fasting

[7] The changes in the inactive ingredients should be within the limits defined by the SUPAC –IR and SUPAC-MR guidances.

study should be performed. In vivo BE studies should be accompanied by in vitro dissolution profiles on all strengths of each product. For ANDAs, the BE study should be conducted between the test product and reference listed drug using the strength specified in *Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book).*

2. Waivers of In Vivo BE Studies (Biowaivers)

a. INDs, NDAs, and ANDAs: Preapproval

When the drug product is in the same dosage form, but in a different strength, and is proportionally similar in its active and inactive ingredients, an in vivo BE demonstration of one or more lower strengths can be waived based on dissolution tests and an in vivo study on the highest strength.[8]

For an NDA, biowaivers of a higher strength will be determined to be appropriate based on (1) clinical safety and/or efficacy studies including data on the dose and the desirability of the higher strength; (2) linear elimination kinetics over the therapeutic dose range; (3) the higher strength being proportionally similar to the lower strength; and (4) the same dissolution procedures being used for both strengths and similar dissolution results obtained. A dissolution profile should be generated for all strengths.

The f_2 test should be used to compare profiles from the different strengths of the product. An f_2 value $\geq$ 50 indicates a sufficiently similar dissolution profile such that further in vivo studies are not necessary. For an f_2 value < 50, further discussions with CDER review staff may help to determine whether an in vivo study is important (21 CFR 320.22 (d)(2)(ii)). The f_2 approach is not suitable for rapidly dissolving drug products (e.g., $\geq$ 85% dissolved in 15 minutes or less).

For an ANDA, conducting an in vivo study on a strength that is not the highest may be appropriate for reasons of safety, subject to approval by review staff. In addition, as with an NDA, the Agency will consider a waiver request for a recently approved higher strength when an in vivo BE study was performed on a lower strength of the same drug product submitted in an ANDA under the following circumstances:

- Linear elimination kinetics has been shown over the therapeutic dose range.

- The higher strength is proportionally similar to the lower strength.

[8] This recommendation modifies a prior policy of allowing biowaivers for only three lower strengths on ANDAs.

- Comparative dissolution testing on the higher strength of the test and reference drug product is submitted and found acceptable.

- The sponsor initiated the BE study on the lower strength within five working days of the approval date of a higher strength of the reference listed drug. A study is considered initiated when the first subject is dosed.

Sponsors of ANDAs wishing to submit a biowaiver request under these circumstances should first contact the Regulatory Support Branch, Office of Generic Drugs, for advice on the proper filing procedure.

b. NDAs and ANDAs: Postapproval

Information on the types of in vitro dissolution and in vivo BE studies for immediate-release drug products approved as either NDAs or ANDAs in the presence of specified postapproval changes are provided in an FDA guidance for industry entitled *SUPAC-IR: Immediate Release Solid Oral Dosage Forms: Scale-Up and Post-Approval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation* (November 1995). For postapproval changes, the in vitro comparison should be made between the prechange and postchange products. In instances where dissolution profile comparisons are recommended, an f_2 test should be used. An f_2 value of $\geq$ 50 suggests a sufficiently similar dissolution profile and no further in vivo studies are needed. When in vivo BE studies are recommended, the comparison should be made for NDAs between the prechange and postchange products, and for ANDAs between the postchange and reference listed drug products.

D. Modified-Release Products

Modified-release products include delayed-release products and extended (controlled)-release products.

As defined in the *U.S. Pharmacopeia* (USP), delayed-release drug products are dosage forms that release the drugs at a time later than immediately after administration (i.e., these drug products exhibit a lag time in quantifiable plasma concentrations). Typically, coatings (e.g., enteric coatings) are intended to delay the release of medication until the dosage form has passed through the acidic medium of the stomach. In vivo tests for delayed-release drug products are similar those for to extended-release drug products. In vitro dissolution tests for these products should document that they are stable under acidic conditions and that they release the drug only in a neutral medium (e.g., pH 6.8).

Extended-release drug products are dosage forms that allow a reduction in dosing frequency as compared to when the drug is present in an immediate-release dosage form. These drug products can also be developed to reduce fluctuations in plasma concentrations. Extended-release products can be capsules, tablets, granules, pellets, and suspensions. If any part of a drug product includes an extended-release component, the following recommendations apply.

1. NDAs: BA and BE Studies

An NDA can be submitted for a previously unapproved new molecular entity, or for a new salt, new ester, prodrug, or other noncovalent derivative of a previously approved new molecular entity, formulated as a modified-release drug product. The first modified-release drug product for a previously approved immediate-release drug product should be submitted as an NDA. Subsequent modified-release products that are pharmaceutically equivalent and bioequivalent to the listed drug product should be submitted as ANDAs. BA recommendations for the NDA of an extended-release product are considered at 21 CFR 320.25(f). The purpose for an in vivo BA study for which a controlled-release claim is made is to determine if all of the following conditions are met:

- The drug product meets the controlled release claims made for it.
- The BA profile established for the drug product rules out the occurrence of any dose dumping.
- The drug product's steady-state performance is equivalent to a currently marketed noncontrolled release or controlled-release drug product that contains the same active drug ingredient or therapeutic moiety and that is subject to an approved full new drug application.
- The drug product's formulation provides consistent pharmacokinetic performance between individual dosage units.

As noted at 21 CFR 320.25 (f) (2), *the reference material(s) for such a BA study shall be chosen to permit an appropriate scientific evaluation of the controlled release claims made for the drug product*, such as:

- A solution or suspension of the active drug ingredient or therapeutic moiety
- A currently marketed noncontrolled-release drug product containing the same active drug ingredient or therapeutic moiety and administered according to the dosage recommendations in the labeling

- A currently marketed controlled-release drug product subject to an approved full new drug application containing the same active drug ingredient or therapeutic moiety and administered according to the dosage recommendations in the labeling

To satisfy the CFR recommendations for BA studies for an extended-release drug product submitted as an NDA, this guidance recommends the following studies:

- A single-dose, fasting study on all strengths of tablets/capsules and highest strength of beaded capsules

- A single-dose, food-effect study on the highest strength

- A steady-state study on the highest strength

When substantial changes in the components/composition and/or method of manufacture for an extended-release drug product occur between the to-be-marketed NDA dosage form and the clinical trial material, BE studies are recommended.

2. ANDAs: BE Studies

For extended-release products submitted as ANDAs, the following studies are recommended: (1) a single-dose, replicate, fasting study comparing the highest strength of the test and reference listed drug product; and (2) a food-effect, nonreplicate study comparing the highest strength of the test and reference product (section VI.A). Because single-dose studies are considered more sensitive in addressing the primary question of BE (i.e., release of the drug substance from the drug product into the systemic circulation), multiple-dose studies are generally not recommended, even in instances where nonlinear kinetics are present.

3. Waivers of In Vivo BE Studies (Biowaivers): NDAs and ANDAs

a. Beaded Capsules — Lower Strength

For extended-release beaded capsules where the strength differs only in the number of beads containing the active moiety, a single-dose, fasting BE study should be carried out only on the highest strength, with waiver of in vivo studies for lower strengths based on dissolution profiles. A dissolution profile should be generated for each strength using the recommended dissolution method. The f_2 test should be used to compare profiles from the different strengths of the product. An f_2 value of $\geq$ 50 can be used to confirm that further in vivo studies are not needed.

b. Tablets — Lower Strength

For extended-release tablets, when the drug product is in the same dosage form but in a different strength, is proportionally similar in its active and inactive ingredients, and has the same drug release mechanism, an in vivo BE determination of one or more lower strengths can be waived based on dissolution profile comparisons, with an in vivo study only on the highest strength. The drug products should exhibit similar dissolution profiles between the highest strength and the lower strengths based on the f_2 test in at least three dissolution media (e.g., pH 1.2, 4.5 and 6.8). The dissolution profile should be generated on the test and reference products of all strengths.

4. Postapproval Changes

Information on the types of in vitro dissolution and in vivo BE studies for extended-release drug products approved as either NDAs or ANDAs in the presence of specified postapproval changes are provided in an FDA guidance for industry entitled *SUPAC-MR: Modified Release Solid Oral Dosage Forms: Scale-Up and Post-Approval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation (September* 1997). For postapproval changes, the in vitro comparison should be made between the prechange and postchange products. In instances where dissolution profile comparisons are recommended, an f_2 test should be used. An f_2 value of $\geq$ 50 suggests a similar dissolution profile. A failure to demonstrate similar dissolution profiles may result in the need to perform an in vivo BE study. When in vivo BE studies are conducted, the comparison should be made for NDAs between the prechange and postchange products, and for ANDAs between the postchange product and reference listed drug.

E. Miscellaneous Dosage Forms

Rapidly dissolving drug products, such as buccal and sublingual dosage forms, should be tested for in vitro dissolution and in vivo BA and/or BE. Chewable tablets should also be evaluated for in vivo BA and/or BE. Chewable tablets (as a whole) should be subject to in vitro dissolution because they might be swallowed by a patient without proper chewing. In general, in vitro dissolution test conditions for chewable tablets should be the same as for nonchewable tablets of the same active ingredient/moiety. Infrequently, different test conditions or acceptance criteria may be indicated for chewable and nonchewable tablets, but these differences, if they exist, should be resolved with the appropriate review division.

VI. SPECIAL TOPICS

A. Food-Effect Studies

Coadministration of food with oral drug products may influence drug BA and/or BE. Food-effect BA studies focus on the effects of food on the release of the drug substance from the drug product as well as the absorption of the drug substance. BE studies with food focus on demonstrating comparable BA between test and reference products when coadministered with meals. Usually, a single-dose, two-period, two-treatment, two-sequence crossover study is recommended for both food-effect BA and BE studies.

B. Moieties to Be Measured

1. Parent Drug Versus Metabolites

The moieties to be measured in biological fluids collected in BA and BE studies are either the active drug ingredient or its active moiety in the administered dosage form (parent drug) and, when appropriate, its active metabolites (21 CFR 320.24(b)(1)(i)).[9] This guidance recommends the following approaches for BA and BE studies.

For BA studies (see section II.B), determination of moieties to be measured in biological fluids should take into account both concentration and activity. *Concentration* refers to the relative quantity of the parent drug or one or more metabolites in a given volume of an accessible biological fluid such as blood or plasma. *Activity* refers to the relative contribution of the parent drug and its metabolite(s) in the biological fluids to the clinical safety and/or efficacy of the drug. For BA studies, both the parent drug and its major active metabolites should be measured, if analytically feasible.

For BE studies, measurement of only the parent drug released from the dosage form, rather than the metabolite, is generally recommended. The rationale for this recommendation is that the concentration-time profile of the parent drug is more sensitive to changes in formulation performance than a metabolite, which is more reflective of metabolite formation, distribution, and elimination. The following are exceptions to this general approach.

- Measurement of a metabolite may be preferred when parent drug levels are too low to allow reliable analytical measurement in blood, plasma, or serum for an adequate length of time. The metabolite data obtained from these studies should be subject to a confidence interval approach for BE demonstration. If there is a clinical concern related to efficacy or safety for the parent drug, sponsors and/or applicants should

[9] A dosage form contains active and, usually, inactive ingredients. The active ingredient may be a prodrug that requires further transformation in vivo to become active. An active moiety is the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt, or other noncovalent derivative of the molecule, responsible for the physiological or pharmacological action of the drug substance.

contact the appropriate review division to determine whether the parent drug should be measured and analyzed statistically.

- A metabolite may be formed as a result of gut wall or other presystemic metabolism. If the metabolite contributes meaningfully to safety and/or efficacy, the metabolite and the parent drug should be measured. When the relative activity of the metabolite is low and does not contribute meaningfully to safety and/or efficacy, it does not need to be measured. The parent drug measured in these BE studies should be analyzed using a confidence interval approach. The metabolite data can be used to provide supportive evidence of comparable therapeutic outcome.

2. Enantiomers Versus Racemates

For BA studies, measurement of individual enantiomers may be important. For BE studies, this guidance recommends measurement of the racemate using an achiral assay. Measurement of individual enantiomers in BE studies is recommended only when all of the following conditions are met: (1) the enantiomers exhibit different pharmacodynamic characteristics; (2) the enantiomers exhibit different pharmacokinetic characteristics; (3) primary efficacy/safety activity resides with the minor enantiomer; and (4) 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. In such cases, BE criteria should be applied to the enantiomers separately.

3. Drug Products with Complex Mixtures as the Active Ingredients

Certain drug products may contain complex drug substances (i.e., active moieties or active ingredients that 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. Quantification of all active or potentially active components in pharmacokinetic studies to document BA/BE is neither necessary nor desirable. Rather, BA and BE studies should be based on a small number of markers of rate and extent of absorption. Although necessarily a case-by-case determination, criteria for marker selection include amount of the moiety in the dosage form, plasma or blood levels of the moiety, and biological activity of the moiety relative to other moieties in the complex mixture. Where pharmacokinetic approaches are not feasible to assess rate and extent of absorption of a drug substance from a drug product, in vitro approaches may be preferred. Pharmacodynamic or clinical approaches may be called for if no quantifiable moieties are available for in vivo pharmacokinetic or in vitro studies.

C. Long Half-Life Drugs

In a BA/pharmacokinetic study involving an oral product with a long half-life drug, adequate characterization of the half-life calls for blood sampling over a long period of time. For a BE determination of an oral product with a long half-life drug, a nonreplicate, single-dose, crossover study can be conducted, provided an adequate washout period is used. If the crossover study is problematic, a BE study with a parallel design can be used. For either a crossover or parallel study, sample collection time should be adequate to ensure completion of gastrointestinal transit (approximately 2 to 3 days) of the drug product and absorption of the drug substance. Cmax, and a suitably truncated AUC can be used to characterize peak and total drug exposure, respectively. For drugs that demonstrate low intra-subject variability in distribution and clearance, an AUC truncated at 72 hours ($AUC_{0\text{-}72\ hr}$) may be used in place of $AUC_{0\text{-}t}$ or $AUC_{0\text{-}\infty}$. For drugs demonstrating high intra-subject variability in distribution and clearance, AUC truncation warrants caution. In such cases, sponsors and/or applicants should consult the appropriate review staff.

D. First Point Cmax

The first point of a concentration-time curve in a BE study based on blood and/or plasma measurements is sometimes the highest point, which raises a question about the measurement of true Cmax because of insufficient early sampling times. A carefully conducted pilot study may avoid this problem. Collection of an early time point between 5 and 15 minutes after dosing followed by additional sample collections (e.g., two to five) in the first hour after dosing may be sufficient to assess early peak concentrations. If this sampling approach is followed, data sets should be considered adequate, even when the highest observed concentration occurs at the first time point.

E. Orally Administered Drugs Intended for Local Action

Documentation of product quality BA for NDAs where the drug substance produces its effects by local action in the gastrointestinal tract can be achieved using clinical efficacy and safety studies and/or suitably designed and validated in vitro studies. Similarly, documentation of BE for ANDAs, and for both NDAs and ANDAs in the presence of certain postapproval changes, can be achieved using BE studies with clinical efficacy and safety endpoints and/or suitably designed and validated in vitro studies if the latter studies are either reflective of important clinical effects or are more sensitive to changes in product performance compared to a clinical study. To ensure comparable safety, additional studies with and without food may help to understand the degree of systemic exposure that occurs following administration of a drug product intended for local action in the gastrointestinal tract.

F. Narrow Therapeutic Range Drugs

This guidance defines narrow therapeutic range[10] drug products as those containing certain drug substances that are subject to therapeutic drug concentration or pharmacodynamic monitoring, and/or where product labeling indicates a narrow therapeutic range designation. Examples include digoxin, lithium, phenytoin, theophylline, and warfarin. Because not all drugs subject to therapeutic drug concentration or pharmacodynamic monitoring are narrow therapeutic range drugs, sponsors and/or applicants should contact the appropriate review division at CDER to determine whether a drug should or should not be considered to have a narrow therapeutic range.

This guidance recommends that sponsors consider additional testing and/or controls to ensure the quality of drug products containing narrow therapeutic range drugs. The approach is designed to provide increased assurance of interchangeability for drug products containing specified narrow therapeutic range drugs. It is not designed to influence the practice of medicine or pharmacy.

Unless otherwise indicated by a specific guidance, this guidance recommends that the traditional BE limit of 80-125% for non-narrow therapeutic range drugs remain unchanged for the bioavailability measures (AUC and Cmax) of narrow therapeutic range drugs.

[10] This guidance uses the term "narrow therapeutic range" instead of "narrow therapeutic index" drug, although the latter is more commonly used.

APPENDIX 1

List of Guidances That Will Be Replaced

1. *Guidelines for the Evaluation of Controlled Release Drug Products* (April 1984).

2. *Statistical Procedures for Bioequivalence Studies Using a Standard Two-Treatment Crossover Design* (July 1992).

3. *Oral Extended (Controlled) Release Dosage Form: In Vivo Bioequivalence and In Vitro Dissolution Testing* (September 1993).

4. Draft Guidance for Industry, *In Vivo Bioequivalence Studies Based on Population and Individual Bioequivalence Approaches* (October 1997).

5. Drug specific bioequivalence guidances from the Division of Bioequivalence, Office of Generic Drugs, Office of Pharmaceutical Science, Center for Drug Evaluation and Research, FDA.

APPENDIX 2

General Pharmacokinetic Study Design and Data Handling

For both replicate and nonreplicate, in vivo pharmacokinetic BE studies, the following general approaches are recommended, recognizing that the elements may be adjusted for certain drug substances and drug products.

Study conduct:

- The test or reference products should be administered with about 8 ounces (240 ml) of water to an appropriate number of subjects under fasting conditions, unless the study is a food-effect BA/BE study.

- Generally, the highest marketed strength should be administered as a single unit. If necessary for analytical reasons, multiple units of the highest strength can be administered, providing the total single-dose remains within the labeled dose range.

- An adequate washout period (e.g., more than 5 half lives of the moieties to be measured) should separate each treatment.

- The lot numbers of both test and reference listed products and the expiration date for the reference product should be stated. The drug content of the test product should not differ from that of the reference listed product by more than 5 percent. The sponsor should include a statement of the composition of the test product and, if possible, a side-by-side comparison of the compositions of test and reference listed products. In accordance with 21 CFR 320.38, samples of the test and reference listed product must be retained for 5 years.

- Prior to and during each study phase, subjects should (1) be allowed water as desired except for one hour before and after drug administration; (2) be provided standard meals no less than 4 hours after drug administration; (3) abstain from alcohol for 24 hours prior to each study period and until after the last sample from each period is collected.

Sample collection and sampling times:

- Under normal circumstances, blood, rather than urine or tissue, should be used. In most cases, drug, or metabolites are measured in serum or plasma. However, in certain cases whole blood may be more appropriate for analysis. Blood samples should be

drawn at appropriate times to describe the absorption, distribution, and elimination phases of the drug. For most drugs, 12 to 18 samples, including a predose sample, should be collected per subject per dose. This sampling should continue for at least three or more terminal half lives of the drug. The exact timing for sample collection depends on the nature of the drug and the input from the administered dosage form. The sample collection should be spaced in such a way that the maximum concentration of the drug in the blood (Cmax) and terminal elimination rate constant (λ_z) can be estimated accurately. At least three to four samples should be obtained during the terminal log-linear phase to obtain an accurate estimate of λ_z from linear regression. The actual clock time when samples are drawn as well as the elapsed time related to drug administration should be recorded.

Subjects with predose plasma concentrations:

- If the predose concentration is less than or equal to 5 percent of Cmax value in that subject, the subject's data without any adjustments can be included in all pharmacokinetic measurements and calculations. If the predose value is greater than 5 percent of Cmax, the subject should be dropped from all BE study evaluations.

Data deletion due to vomiting:

- Data from subjects who experience emesis during the course of a BE study for immediate-release products should be deleted from statistical analysis if vomiting occurs at or before 2 times median Tmax. In the case of modified-release products, the data from subjects who experience emesis any time during the labeled dosing interval should be deleted.

The following pharmacokinetic information is recommended for submission:

- Plasma concentrations and time points
- Subject, period, sequence, treatment
- AUC_{0-t}, $AUC_{0-\infty}$, Cmax, Tmax, λ_z , and $t_{1/2}$
- Intersubject, intrasubject, and/or total variability, if available
- Subject-by-formulation interaction variance component (σ_D^2), if individual BE criterion is used
- Cmin (concentration at the end of a dosing interval), Cav (average concentration during a dosing interval), degree of fluctuation [(Cmax-Cmin)/Cav], and swing [(Cmax-Cmin)/Cmin] if steady-state studies are employed
- Partial AUC, requested only as discussed in section III. A.9.a.

In addition, the following statistical information should be provided for AUC_{0-t}, $AUC_{0-\infty}$, and Cmax:

- Geometric mean
- Arithmetic mean
- Ratio of means
- Confidence intervals

Logarithmic transformation should be provided for measures used for BE demonstration.

Rounding off of confidence interval values:

- Confidence interval (CI) values should not be rounded off; therefore, to pass a CI limit of 80-125, the value should be at least 80.00 and not more than 125.00.