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)
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Revision 1

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BA and BE Studies for Orally Administered Drug Products — General Considerations

This guidance represents the Food and Drug Administration's (FDA'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 contains advice on how to meet the BA and BE requirements set forth in part 320 (21 CFR part 320) as they apply to dosage forms intended for oral administration.[2] The guidance is also generally applicable to nonorally 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). We believe that the guidance will 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 revises the October 2000 guidance. We have revised our recommendations regarding (1) study design and dissolution methods development, (2) comparisons of BA measures, (3) the definition of proportionality, and (4) waivers for bioequivalence studies. The guidance also makes other revisions for clarification. We believe that these revisions provide clear guidance to sponsors conducting BA and BE studies for orally administered drug products.

[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 part 320 and § 314.70 (21 CFR 314.70).

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

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 before 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 (RLD). For two orally administered drug products to be bioequivalent, the active drug ingredient or active moiety in the test product must exhibit the same rate and extent of absorption as the reference drug product (see 21 CFR 320.1(e) and 320.23(b)).

Both BA and BE studies are required by regulations, depending on the type of application being submitted. Under § 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 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 § 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 can also provide information indirectly about the properties of a drug substance before 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 can be documented by developing a systemic exposure profile. A profile can be obtained by 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. We recommend that additional comparative studies 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)). Before marketing a drug product, the performance of the clinical trial dosage form can be optimized, in the context of demonstrating safety and efficacy. The systemic exposure profiles of clinical trial material can be used as a benchmark for subsequent formulation changes and can be useful as a reference for future BE studies.

Although BA studies have many pharmacokinetic objectives beyond formulation performance as described above, we note 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, can 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 to the database containing evidence of safety and efficacy.

C. Bioequivalence

Bioequivalence is defined in § 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. As a result, we recommend that similar approaches to measuring BA in an NDA 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 such criteria.

1. IND/NDAs

BE documentation can be useful during the IND or 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. We recommend that the determination to redocument BE during the IND period be generally left to the judgment of the sponsor, who can 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 further in vitro and/or in vivo studies be performed.

A test product can 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 product is more variable. In some cases, nondocumentation of BE can 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, failure to document BE may suggest the product should be reformulated, the method of manufacture for the test product be changed, and/or the BE study be repeated.

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 we recommend 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; 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*. In the presence of certain major changes in components, composition, and/or method of manufacture after approval, we recommend that in vivo BE be redemonstrated. For approved NDAs, we also recommend that the drug product after the change be compared to the drug product before the change. For approved ANDAs, we also recommend that the drug product after the change be compared to the reference listed drug. Under section 506A(c)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 356a(c)(2)(B)), postapproval changes requiring completion of studies in accordance with 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 in § 320.24, several in vivo and in vitro methods can be used to measure product quality BA and to 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 because of 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 can 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 can be appropriate, provided 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 Attachment A.

4. Study Designs

Nonreplicate crossover study designs are recommended for BE studies of immediate-release and modified-release dosage forms. However, sponsors and/or applicants have the option of using replicate designs for BE studies for these drug products. Replicate study designs may offer several scientific advantages compared to nonreplicate designs. The advantages of replicate study designs may be that they (1) allow comparisons of within-subject variances for the test and reference products, (2) provide more information about the intrinsic factors underlying formulation performance, and (3) reduce the number of subjects participating in the BE study. The recommended method of analysis of nonreplicate or replicate studies to establish BE is average bioequivalence, as discussed in section IV. General recommendations for nonreplicate study designs are provided in Attachment A. Recommendations for replicate study designs can be found in the guidance for industry *Statistical Approaches to Establishing Bioequivalence.*

5. Study Population

We recommend that, unless otherwise indicated by a specific guidance, subjects recruited for in vivo BE studies 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. We recommend that if the drug product is intended for use in both sexes, the sponsor attempt to include similar proportions of males and females in the study. If the drug product is to be used predominantly in the elderly, we also recommend that the sponsor attempt to include as many subjects of 60 years of age or older as possible. We recommend that the total number of subjects in the study 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. We recommend that restrictions on admission into the study 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, we recommend that sponsors and/or applicants attempt to enter patients whose disease process is stable for the duration of the BE study. In accordance with § 320.31, for some products that will be submitted in ANDAs, an IND may be required for BE studies to ensure patient safety.

6. Single-Dose/Multiple-Dose Studies

Instances where multiple-dose studies can be useful are defined under § 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). We recommend that if a multiple-dose study design is important, appropriate dosage administration and sampling be carried out to document attainment of steady state.

7. Bioanalytical Methodology

We recommend sponsors ensure that bioanalytical methods for BA and BE studies are accurate, precise, selective, sensitive, and reproducible. A separate FDA guidance entitled *Bioanalytical Method Validation* is available to assist sponsors in validating bioanalytical methods.

8. 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. We recommend that reliance on systemic exposure measures reflect comparable rate and extent of absorption, which in turn would 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 can generally be demonstrated by measurements of peak and total exposure. An early exposure measure may be informative 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. We recommend that the partial area be truncated at the population median of Tmax values for the reference formulation. We also recommend that at least two quantifiable samples be collected before the expected peak time to allow adequate estimation of the partial area.

b. Peak Exposure

We recommend that peak exposure be assessed by measuring the peak drug concentration (Cmax) obtained directly from the data without interpolation.

c. Total Exposure

For single-dose studies, we recommend that the measurement of total exposure 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. We recommend that the terminal half-life ($t_{1/2}$) of the drug also be reported.

For steady-state studies, we recommend that the measurement of total exposure be the area under the plasma, serum, or blood concentration-time curve from time zero to time tau over a dosing interval at steady state (AUC_{0-tau}), where tau 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 can be useful to provide supportive evidence of BA or BE. However, we recommend that the use of comparative clinical trials as an approach to demonstrate BE generally be considered insensitive and be avoided where possible (21 CFR 320.24). The use of BE studies with clinical trial endpoints can

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(b)(5) and 21 CFR 320.22(d)(3)). For highly soluble, highly permeable, rapidly dissolving, and 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 documenting BE for *nonbioproblem* drugs approved before 1962 remain appropriate (21 CFR 320.33).

Dissolution testing is also used to assess batch-to-batch quality, where the dissolution tests, with defined procedures and acceptance criteria, are used to allow batch release. We recommend that dissolution testing is also used to (1) provide process control and quality assurance, and (2) assess whether further BE studies relative to minor postapproval changes be conducted, where dissolution can function as a signal of bioinequivalence. In vitro dissolution characterization is encouraged for all product formulations investigated (including prototype formulations), 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 320.24(b)(1)(ii)), 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*; and (2) *Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations.*

We recommend that the following information generally be included in the dissolution method development report for solid oral dosage forms:

For an NDA:

- The pH solubility profile of the drug substance
- Dissolution profiles generated at different agitation speeds (e.g., 100 to 150 revolutions per minute (rpm) for U.S. Pharmacopeia (USP) Apparatus I (basket), or 50 to 100 rpm for USP Apparatus II (paddle))

[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*. This document provides complementary information on the Biopharmaceutics Classification System (BCS).

- Dissolution profiles generated on all strengths in at least three dissolution media (e.g., pH 1.2, 4.5, and 6.8 buffer). Water can be used as an additional medium. If the drug being considered is poorly soluble, appropriate concentrations of surfactants are recommended.

It is recommended that the sponsor select the agitation speed and medium that provide adequate discriminating ability, taking into account all the available in vitro and in vivo data.

For ANDAs:

- For immediate-release drug products, we recommend that the appropriate USP method be submitted. If there is no USP method available, we recommend that the FDA method for the reference listed drug be used. If the USP and/or FDA methods are not available, we recommend that the dissolution method development report described above be submitted.
- For modified-release products, dissolution profiles using the appropriate USP method (if available) can be submitted. If there is no USP method available, we recommend that the FDA method for the reference listed drug be used. In addition, we recommend that profiles using at least three other dissolution media (e.g., pH 1.2, 4.5, and 6.8 buffer) and water be submitted.

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 before 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.

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 before 1962. Waiver of in vivo studies for different strengths of a drug product can be granted under § 320.22(d)(2) when (1) the drug product is in the same 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 appropriate in vivo study; and (3) the new strength meets an

appropriate in vitro dissolution test. This guidance defines *proportionally similar* in the following ways:

- 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).

- Active and inactive ingredients are not in exactly the same proportion between different strengths as stated above, but the ratios of inactive ingredients to total weight of the dosage form are within the limits defined by the SUPAC-IR and SUPAC-MR guidances up to and including Level II.

- For high potency drug substances, where the amount of the active drug substance in the dosage form is relatively low, the total weight of the dosage form remains nearly the same for all strengths (within $\pm$ 10 % of the total weight of the strength on which a biostudy 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 ingredients and one or more of the inactive ingredients. The changes in the inactive ingredients are within the limits defined by the SUPAC-IR and SUPAC-MR guidances up to and including Level II.

Exceptions to the above definitions may be possible, if adequate justification is provided.

A. Solutions

For oral solutions, elixirs, syrups, tinctures, or other solubilized forms, in vivo BA and/or BE can be waived (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

We recommend that BA and BE for a suspension generally be established 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, we recommend that where the focus is on release of the drug substance from the drug product into the systemic circulation, a single-dose, fasting study be performed. We also recommend that in vivo BE studies be accompanied

by in vitro dissolution profiles on all strengths of each product. For ANDAs, we also recommend that the BE study be conducted between the test product and reference listed drug using the strength(s) 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 to the strength on which BA or BE testing has been conducted, 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. We recommend that a dissolution profile be generated for all strengths.

If an appropriate dissolution method has been established (see section III.D.), and the dissolution results indicate that the dissolution characteristics of the product are not dependent on the product strength, then dissolution profiles in one medium are usually sufficient to support waivers of in vivo testing. Otherwise, dissolution data in three media (pH 1.2, 4.5, and 6.8) are recommended. We recommend that the f_2 test be used to compare profiles from the different strengths of the product. An f_2 value ≥ 50 indicates a sufficiently similar dissolution profile such that further in vivo studies are not needed. For an f_2 value < 50, further discussions with CDER review staff may help to determine whether an in vivo study is appropriate (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 the Division of Bioequivalence, Office of Generic Drugs, and provided that the following conditions are met:

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

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

- The higher strengths of the test and reference products are proportionally similar to their corresponding lower strength.

- Comparative dissolution testing on the higher strength of the test and reference products is submitted and found to be appropriate.

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*. For postapproval changes, we recommend that the in vitro comparison be made between the prechange and postchange products. In instances where dissolution profile comparisons are suggested, we also recommend an f_2 test 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 called for, we recommend that the comparison 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 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 to those for extended-release drug products. We recommend that in vitro dissolution tests for these products 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 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, new salt, new ester, prodrug, or other noncovalent derivative of a previously approved new molecular entity formulated as a modified-release drug product. We recommend that the first modified-release drug product for a previously approved immediate-release drug product be submitted as an NDA. We also recommend that subsequent modified-release products that are pharmaceutically equivalent and bioequivalent to the listed drug product be submitted as ANDAs. BA requirements for the NDA of an extended-release product are listed in § 320.25(f). The purpose of 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 NDA.
- The drug product's formulation provides consistent pharmacokinetic performance between individual dosage units.

As noted in § 320.25(f)(2), "the reference material(s) for such a bioavailability 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 NDA containing the same active drug ingredient or therapeutic moiety and administered according to the dosage recommendations in the labeling

This guidance recommends that the following BA studies be conducted for an extended-release drug product submitted as an NDA:

- A single-dose, fasting study on all strengths of tablets and 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

BE studies are recommended when substantial changes in the components or 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.

2. ANDAs: BE Studies

For modified-release products submitted as ANDAs, the following studies are recommended: (1) a single-dose, nonreplicate, 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 (see 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

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

b. Tablets — Lower Strength

For modified-release tablets, when the drug product is in the same dosage form but in a different strength, when it is proportionally similar in its active and inactive ingredients, and when it 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. We recommend that the drug products 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). We recommend that the dissolution profile 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*. We recommend that for postapproval changes, the in vitro comparison be made between the prechange and postchange products. In instances where dissolution profile comparisons are recommended, an f_2 test can be used. An f_2 value of ≥ 50 suggests a similar dissolution profile. A failure to demonstrate similar dissolution profiles may indicate an in vivo BE study be performed. When in vivo BE studies are conducted, we recommend that the comparison 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

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

VI. SPECIAL TOPICS

A. Food-Effect Studies

Co-administration 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), we recommend that determination of moieties to be measured in biological fluids 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, we also recommend that both the parent drug and its major active metabolites 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 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. We recommend that the metabolite data obtained from these studies 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, we also recommend that sponsors and/or applicants 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, we also recommend that the metabolite and the parent drug be measured. When the relative activity of the metabolite is low and does not contribute meaningfully to safety and/or efficacy, it does not have to be measured. We recommend that the parent drug measured in these BE studies 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

[9] A dosage form contains active and, usually, inactive ingredients. The active ingredient may be a prodrug that becomes active with further in vivo transformation. 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.

the following conditions are met: (1) the enantiomers exhibit different pharmacodynamic characteristics, (2) the enantiomers exhibit different pharmacokinetic characteristics, (3) primary efficacy and 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, we recommend that BE factors 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 cannot 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 and BE is neither encouraged nor desirable. Rather, we recommend that BA and BE studies be based on a small number of markers of rate and extent of absorption. Although 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 infeasible 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 or 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, we recommend that sample collection time 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 intrasubject variability in distribution and clearance, an AUC truncated at 72 hours ($AUC_{0\text{-}72\ hr}$) can be used in place of $AUC_{0\text{-}t}$ or $AUC_{0\text{-}\infty}$. For drugs demonstrating high intrasubject variability in distribution and clearance, AUC truncation warrants caution. In such cases, we also recommend that sponsors and/or applicants 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, we recommend that data sets 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 containing certain drug substances 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 can contact the appropriate review division at CDER to determine whether a drug can or cannot 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 to 125 percent 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.

ATTACHMENT: 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 can be adjusted for certain drug substances and drug products.

Study conduct:

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

- Generally, the highest marketed strength can be administered as a single unit. If warranted 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) would separate each treatment.

- The lot numbers of both test and reference listed products and the expiration date for the reference product would be stated. The drug content of the test product cannot differ from that of the reference listed product by more than 5 percent. The sponsor can 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 § 320.38, samples of the test and reference listed product must be retained for 5 years.

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

Sample collection and sampling times:

- We recommend that under normal circumstances, blood, rather than urine or tissue, 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. We recommend that blood samples be drawn at appropriate times to describe the absorption, distribution, and elimination phases of the drug. For most drugs, we recommend that 12 to 18 samples, including a predose sample, be collected per subject per dose. This sampling can 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 can 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 can be obtained during the terminal log-linear phase to obtain an accurate estimate of λ_Z from linear regression. We recommend that the actual clock time when samples are drawn as well as the elapsed time related to drug administration be recorded.

Subjects with predose plasma concentrations:

- If the predose concentration is ≤ 5 percent of Cmax value in that subject, the subject's data without any adjustments can be included in all pharmacokinetic measurements and calculations. We recommend that if the predose value is > than 5 percent of Cmax, the subject be dropped from all BE study evaluations.

Data deletion due to vomiting:

- We recommend that data from subjects who experience emesis during the course of a BE study for immediate-release products 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 can 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
- 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, we recommend that the following statistical information be provided for AUC_{0-t}, $AUC_{0-\infty}$, and Cmax:

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

We also recommend that logarithmic transformation be provided for measures used for BE demonstration.

Rounding off of confidence interval values:

- We recommend that confidence interval (CI) values not be rounded off; therefore, to pass a CI limit of 80 to125, the value would be at least 80.00 and not more than 125.00.