Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA
Guidance for Industry

DRAFT GUIDANCE

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

August 2021
Generics

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Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance provides recommendations to applicants planning to include bioequivalence (BE) information in abbreviated new drug applications (ANDAs) and ANDA supplements. In addition, this guidance describes how to meet the BE requirements set forth in the Federal Food, Drug, and Cosmetic Act (FD&C Act) and FDA regulations. This guidance is generally applicable to dosage forms intended for oral administration and to non-orally administered drug products in which reliance on systemic exposure measures is suitable for establishing BE (e.g., transdermal delivery systems and certain rectal and nasal drug products). This guidance will also be useful to applicants planning BE studies intended to be conducted during the post-approval period for changes to a drug product approved under an ANDA.

This guidance revises the draft guidance for industry *Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA* that was issued in December 2013.[2]

The contents of this document do not have the force and effect of law and are not meant to bind the public in any way, unless specifically incorporated into a contract. This document is intended only to provide clarity to the public regarding existing requirements under the law.

[1] This guidance has been prepared by the Office of Generic Drugs in the Center for Drug Evaluation and Research (CDER) in cooperation with CDER's Office of Translational Sciences and the Office of Pharmaceutical Quality at the Food and Drug Administration.

[2] FDA recommends that applicants for investigational new drug applications, new drug applications, and new drug application supplements consult the draft guidance for industry *Bioavailability Studies Submitted in NDAs or INDs — General Considerations* (February 2019), which addresses bioavailability studies for these submission types. When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm. FDA also recommends that ANDA applicants consult routinely published product-specific guidances (PSGs) when considering the appropriate BE study and/or other studies for a proposed drug product. For more information about FDA's PSG publications and to search for the most recent version of a PSG, see the Product-Specific Guidances for Generic Drug Development web page at https://www.fda.gov/drugs/guidances-drugs/product-specific-guidances-generic-drug-development.

FDA guidance documents, including this guidance, show be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidance means that something is suggested or recommended, but not required.

II. BACKGROUND

To receive approval for an ANDA, an applicant generally must demonstrate among other things, that its proposed drug product is bioequivalent to the reference listed drug (RLD).[3] The FD&C Act provides that a generic drug is bioequivalent to the listed drug if:

> The rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses.[4]

For most products, the focus of BE studies is on the release of the drug substance from the drug product into the systemic circulation. During such BE studies, an applicant compares the systemic exposure profile of a test drug product to that of the RLD designated in FDA's *Approved Drug Products with Therapeutic Evaluations* (the Orange Book).[5, 6]

III. ESTABLISHING BIOEQUIVALENCE

Under FDA regulations, an applicant must use "the most accurate, sensitive, and reproducible approach available among those set forth" in 21 CFR 320.24(b) to demonstrate BE.[7] As noted in 21 CFR 320.24, in vivo and/or in vitro methods can be used to establish BE. These methods include comparative pharmacokinetic (PK), in vitro tests predictive of human in vivo bioavailability (BA) (in vitro-in vivo correlation (IVIVC)), pharmacodynamic (PD), clinical endpoint, and in vitro studies.[8]

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[3] See section 505(j)(2)(A)(iv) of the FD&C Act (21 U.S.C. 355(j)(2)(A)(iv)) and 21 CFR 314.94(a)(7). In general, to obtain approval of an ANDA for a generic drug, an ANDA applicant first must identify the previously approved drug product it seeks to duplicate, i.e., the RLD, and must show, among other things, that the generic drug is bioequivalent to the RLD. A reference standard (RS) selected by FDA is the specific drug product that the ANDA applicant must use in conducting any in vivo BE testing required to support approval of its ANDA. The RS, selected by FDA, is ordinarily the RLD. For ease of the reader, this guidance document will only use the terms RLD or reference product when describing regulatory requirements and recommendations relating to BE. For more information regarding the distinction between an RLD and RS, refer to FDA's guidance for industry *Referencing Approved Drug Products in ANDA Submissions* (October 2020).

[4] Section 505(j)(8)(B)(i) of the FD&C Act. See also section 505(j)(8)(B)(ii) and (C) of the FD&C Act; 21 CFR 320.1(e); and 21 CFR 320.23(b).

[5] The Orange Book is available at https://www.accessdata.fda.gov/scripts/cder/ob/.

[6] 21 CFR 314.3(b) and FDA's guidance for industry *Referencing Approved Drug Products in ANDA Submissions* (October 2020).

[7] See 21 CFR 320.24(a).

[8] See 21 CFR 320.24(b).

A. Pharmacokinetic Studies

1. General Considerations

As provided above, the statutory definition of BE, expressed in terms of rate and extent of absorption of the active ingredient or moiety, emphasizes the use of PK endpoints in an accessible biological matrix (such as whole blood, plasma, and/or serum) to indicate release of the drug substance from the drug product into the systemic circulation.[9] BE frequently relies on PK endpoints such as **C_{max}**[10] and **AUC** that are reflective of the rate and extent of absorption, respectively.

If serial measurements of the drug and/or its metabolites in plasma, serum, or whole blood cannot be accomplished, measurement of urinary excretion can be used to demonstrate BE.

2. Pilot Studies

If the applicant chooses, a pilot study in a small number of subjects can be carried out before proceeding with a pivotal BE study. This pilot study can be used to validate analytical methodology, assess PK variability, estimate sample size to achieve adequate power, optimize sample collection time intervals, and provide other information. ANDA applicants are required to submit information from all BE studies conducted with the same formulation of the proposed drug product.[11]

3. Pivotal Bioequivalence Studies

General recommendations for a standard BE study based on PK endpoints are provided in Appendix A.

4. Study Designs

FDA recommends that applicants use (1) a two-period, two-sequence, two-treatment, single-dose crossover study design, (2) a single-dose parallel study design, or (3) a single-dose replicate study design for BE studies. The BE studies generally should be conducted on the highest strength of the drug product, unless safety considerations preclude the use of that dose in study subjects. The general recommendations for study designs provided in Appendix A should be considered in designing studies. FDA recommends that applicants use the average BE method of analysis with these study designs.

For most dosage forms that release a drug intended to be systemically available, FDA recommends that applicants perform a two-period, two-sequence, two-treatment, single-dose,

[9] See section 505(j)(8)(B) of the FD&C Act.

[10] Terms that appear in bold type are defined in the glossary at the end of this guidance.

[11] See 21 CFR 314.94(a)(7) and FDA's guidance for industry *Submission of Summary Bioequivalence Data for ANDAs* (May 2011).

crossover study using either healthy subjects or other populations, as appropriate. In this design, each subject should receive each treatment (the test and the reference product) in a random order.

A replicate crossover study design (either partial or fully replicate) is appropriate for drugs whether the reference product is a highly variable drug or not. A replicate design can have the advantage of using fewer subjects compared to a non-replicate design, although each subject in a replicate design study would receive more treatments.

Further, a replicate design is recommended to be used under the following scenarios:

- A replicate design is advantageous over a non-replicate design for non-narrow therapeutic index (NTI) drugs with a high intrasubject variability.[12] Either a partial or fully replicate design may be used, but a reference-scaled BE analysis approach should only be applied to specific PK metrics that exhibit a high within-subject variability for the reference product in the pivotal BE study. Refer to Appendix B for the method of statistical analysis for the reference-scaled average BE analysis approach for highly variable drugs and to product-specific guidances (PSGs)[13] for detailed recommendations for particular highly variable drugs.

- A fully replicate design is recommended for NTI drugs,[14] where within-subject variability for both the reference and test products can be computed and a reference scaled-average BE analysis can be conducted to properly adjust the BE acceptance criteria. Refer to Appendix C for the method of statistical analysis for the reference-scaled average BE analysis approach for NTI drugs and to PSGs for detailed recommendations for particular NTI drugs.

FDA's recommendations for replicate study designs and the average BE approach method can also be found in the guidance for industry *Statistical Approaches to Establishing Bioequivalence* (February 2001).

Applicants wishing to use variations of these study designs or analysis methods (e.g., a sequential design) may submit a controlled correspondence[15] with specific questions about their approach before starting the study.

5. Study Population

In general, unless otherwise recommended in a PSG:

- Healthy subjects or other populations as appropriate are recruited.

[12] See Appendix B.
[13] See footnote 2.
[14] See e.g., the draft PSG on Warfarin Sodium tablets (December 2012), which is available on the Product-Specific Guidances for Generic Drug Development web page at https://www.fda.gov/drugs/guidances-drugs/product-specific-guidances-generic-drug-development. When final, this guidance will represent the FDA's current thinking on this topic.
[15] See FDA's guidance for industry *Controlled Correspondence Related to Generic Drug Development* (December 2020).

- Subjects recruited for in vivo BE studies should be 18 years of age or older.

- If a drug product is intended for use in both sexes, the applicant should include similar proportions of males and females in the study or provide a justification supporting the use of a single-sex population. Likewise, if a drug product is intended for use in a single sex, then the applicant should only include subjects of that sex. Females should not be pregnant or lactating, and, if applicable, should practice abstention or contraception.

- If the drug product is predominantly intended for use in the elderly, the applicant should include as many subjects as possible at or above age 60 or provide a justification if no subject at or above age 60 is included in the study.

- In general, a BE assessment in adults between two products can be used to support a BE assessment in pediatric patients. If the drug product is predominantly intended for use in pediatric patients younger than 6 years, the applicant should justify that the BE study results obtained from adult subjects are relevant to the pediatric population. FDA recommends that this justification include information supporting that the inactive ingredients in the proposed products are appropriate for use in the pediatric population.

- The total number of subjects in a study should be sufficient to provide adequate statistical power for a BE demonstration in the proposed study design.

We also recommend that any restrictions on admission into a study be primarily based on safety considerations. Sometimes, safety considerations preclude the use of either healthy subjects or the general population.[16] In such situations, applicants should attempt to enroll patients for whom the drug is intended to treat and whose disease process and treatments are stable for the duration of the BE study. An investigational new drug application may be required for certain products (such as cytotoxic products).[17]

6. Single-Dose Studies

We usually recommend single-dose PK studies for both immediate- and modified-release drug products to demonstrate BE because these studies are generally more sensitive than steady-state studies in assessing differences in the release of the drug substance from the drug product into the systemic circulation.

[16] *Healthy subjects* are in general non-smoking adults 18 years of age or older without existing medical conditions or required medications that exert physiological effects. However, *general population* is a broad collection of adults 18 years of age or older with or without stable, chronic medical conditions, who may or may not be treated with therapeutic drugs that will not interfere with the test medication or bioassay. Individuals in the general population may be enrolled in BE studies if they are in relatively stable condition and their medications are not considered to interfere with the test medication or bioassay. The inclusion criteria for *healthy subjects* are more restrictive than the criteria for the *general population*, and *healthy subjects* is a subset of *general population*. These two terms are not used interchangeably.

[17] See 21 CFR 312.2(c) and 320.31.

7. Steady-State Studies

When safety considerations suggest using patients who are already receiving a medication, often the only approach to establish BE without disrupting a patient's ongoing treatment is in a steady-state study. If a steady-state study is used, we recommend that applicants carry out appropriate dosage administration and sampling to demonstrate the attainment of steady state.

8. Bioanalytical Methodology

We recommend applicants ensure that their bioanalytical methods for BE studies are accurate, precise, selective, sensitive, and reproducible. The guidance for industry *Bioanalytical Method Validation* (May 2018) is available to assist applicants in validating bioanalytical methods.

9. Pharmacokinetic Measures of Rate and Extent of Absorption

a. Rate of absorption (peak exposure)

For both single-dose and steady-state studies, FDA recommends that applicants assess the rate of absorption by measuring the C_{max} obtained directly from the data (i.e., without interpolation). $\mathbf{T_{max}}$ can also provide important information regarding the rate of absorption. Applicants should evaluate T_{max} differences between their product and the reference product for any clinical implications.

b. Extent of absorption (total exposure)

For single-dose studies, FDA recommends that the indicators for the extent of absorption be both of the following:

- Area under the plasma, serum, or blood concentration-time curve from time zero to time t ($\mathbf{AUC_{0\text{-}t}}$), where t is the last time point with a measurable concentration

- Area under the plasma, serum, or blood concentration-time curve from time zero to time infinity ($\mathbf{AUC_{0\text{-}inf}}$), where:

  $AUC_{0\text{-}inf} = AUC_{0\text{-}t} + C_t/\lambda_z$

  - C_t is the last measurable drug concentration

  - λ_z is the terminal or elimination rate constant calculated according to an appropriate method

For steady-state studies, FDA recommends that the indicator for the extent of absorption be the area under the plasma, serum, or blood concentration-time curve over a dosing interval at steady-state ($\mathbf{AUC_{0\text{-}tau}}$, where *tau* is the length of the dosing interval).

c. Partial exposure

Although BE generally can be demonstrated by measurements of C_{max} and AUC, FDA recommends applicants use a partial AUC **(pAUC**) as an exposure measure if specified in the applicable PSG. For instance, pAUC may be used for certain modified-release products in which the different phases of release correspond to a clinical effect. The beginning and ending times for the pAUC should relate to a clinically relevant measure. FDA recommends that sufficient quantifiable samples be collected to allow adequate estimation of the pAUC. As mentioned in section I of this guidance, for further information on specific products, applicants should consult the FDA's website to determine whether a PSG for the proposed product is available.[18]

For drugs with a long elimination half-life, a truncated AUC can be used,[19] provided that the truncated AUC covers the complete absorption phase.

10. Fed Bioequivalence Studies

Co-administration of food with oral drug products can impact BA. Therefore, fed BE studies can determine whether test and RLD products are bioequivalent when co-administered with meals. The design of the fed BE study should generally be one of the designs described in section III.A.4 of this guidance. The fed BE study for products where variability is different (i.e., when compared to fasting conditions) may use a different design from the fasting BE study based on the considerations in section III.A.4 of this guidance. Refer to Appendix A for details on study design.

For an orally administered immediate-release product, FDA recommends that applicants conduct a fed BE study, in addition to a fasting BE study, except when the RLD labeling states that the product should be taken on an empty stomach or when serious adverse events are anticipated with administration of the drug product under fed conditions. Similarly, both fasting and fed BE studies are recommended for products even when the RLD labeling states that the product should be taken with food, except when serious adverse events are anticipated with fasting administration, we recommend that applicants conduct only a fed study; a fasting study is not recommended.

For all orally administered modified-release drug products, FDA recommends that applicants conduct a fed BE study, in addition to a fasting BE study, irrespective of dosing instructions in the RLD labeling. However, a fed study is not recommended when serious adverse events are anticipated with administration of the drug product under fed conditions. Similarly, when serious adverse events are anticipated with fasting administration, we recommend that applicants conduct only a fed study; a fasting study is not recommended.

If neither a fasting nor fed BE study can be safely conducted in healthy subjects or the general population, then a BE study in patients is recommended.

[18] See footnote 2.

[19] See section V.B of this guidance.

11. Sprinkle Bioequivalence Studies

If the labeling of a modified-release RLD product states that the product can be administered sprinkled in soft foods, FDA recommends that applicants conduct a sprinkle BE study. For each treatment arm of a sprinkle BE study, the product should be sprinkled on one of the soft foods mentioned in the labeling of the RLD, normally applesauce. Aside from administration in the soft food, a sprinkle BE study should follow the recommendations for the fasting BE study described in Appendix A. When serious adverse events are anticipated with fasting administration, a sprinkle BE study should follow the recommendations for the fed BE study described in Appendix A.

12. Bioequivalence Studies of Products Administered in Specific Beverages

If the labeling specifies that the product must be administered in a specific beverage or beverages, applicants should administer the product mixed with one of the beverages mentioned in the labeling for BE studies. If additional beverages are listed in the labeling, applicants should provide evidence that the use of these additional beverages would not result in BE differences.

If applicants have questions not addressed in the applicable PSG about the use of other vehicles or about the design or analysis of such BE studies, they should contact the Office of Generic Drugs via a controlled correspondence.

B. General Considerations on Other Bioequivalence Studies

In certain circumstances, other types of approaches are recommended to support BE. Some general considerations regarding these approaches are described in the following sections. Applicants should consult FDA's guidances for industry for additional information on these methods as well.[20]

1. In Vitro Studies

In general, FDA does not recommend in vitro approaches for drug products that are intended to be systemically absorbed. However, under certain circumstances, BE can be evaluated using in vitro approaches (e.g., dissolution/drug-release testing).[21]

For highly soluble and rapidly dissolving, orally administered immediate-release drug products, in vitro data may be acceptable to demonstrate BE based on the biopharmaceutics classification system as described in the guidance for industry *M9 Biopharmaceutics Classification System-Based Biowaivers* (May 2021).

The following FDA guidances for industry provide recommendations on developing dissolution methodology, setting specifications, and the regulatory applications of dissolution testing for immediate-release drug products:

[20] See footnote 2.
[21] See 21 CFR 320.24(b)(5) and (6).

- *Dissolution Testing of Immediate Release Solid Oral Dosage Forms* (August 1997)

- *Dissolution Testing and Acceptance Criteria for Immediate-Release Solid Oral Dosage Form Drug Products Containing High Solubility Drug Substances* (August 2018)

2. In Vitro Tests Predictive of Human In Vivo Bioavailability (In Vitro-In Vivo Correlation Studies or "IVIVC")

IVIVC is a scientific approach to describe the relationship between an in vitro attribute of a dosage form (e.g., the rate or extent of drug release) and a relevant in vivo response (e.g., plasma drug concentration or amount of drug absorbed). This model relationship facilitates the rational development and evaluation of modified-release dosage forms and, less commonly, other dosage forms. Once an IVIVC is validated, the in vitro test serves as a surrogate for in vivo BA and/or BE testing, as well as a tool for formulation screening and for setting the dissolution/drug release acceptance criteria.

Additional information on the development and validation of an IVIVC can be found in the guidance for industry *Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations* (September 1997).

3. Pharmacodynamic Studies

A validated PD method can be used to demonstrate BE. However, FDA does not recommend PD studies for drug products that are intended to be absorbed into the systemic circulation and for which a PK approach can be used to establish BE.

4. Comparative Clinical Endpoint Studies

When it is not possible to use the previously described methods, well-controlled BE studies with comparative clinical endpoints in patients can be used to establish BE.

IV. ESTABLISHING BIOEQUIVALENCE FOR DIFFERENT DOSAGE FORMS

The following subsections provide recommendations for establishing BE for specific dosage forms. As explained below, in certain cases, a requirement for in vivo BE testing may be waived[22] or an alternative approach may be more accurate, sensitive, and reproducible.[23]

[22] See 21 CFR 320.22.

[23] In addition to waiver of an in vivo BE requirement under 21 CFR 320.22, there are certain circumstances in which BE can be evaluated using in vitro approaches under 21 CFR 320.24(b)(6). In such circumstances, an in vivo data requirement is not waived, but rather, FDA has determined that in vitro data are the most accurate, sensitive, and reproducible for a product, as required under 21 CFR 320.24(a).

A. Oral Solutions

For oral solutions, elixirs, syrups, tinctures, or other solubilized forms, the in vivo BE testing requirement may be waived if in vivo BE is self-evident.[24] In such instances, the applicant would be deemed to have complied with and fulfilled any requirement for in vivo BE data.[25] For example, an in vivo BE data requirement can be waived for an oral solution if the formulation has the same active ingredient in the same concentration and dosage form as the RLD and does not contain any excipient that significantly affects drug absorption or availability.[26]

B. Immediate-Release Products: Capsules and Tablets

1. Bioequivalence Study Designs and Dose

For immediate-release capsule and tablet products, FDA generally recommends that applicants conduct the following studies: (1) a single-dose, fasting BE study comparing the highest strength of the test and reference products and (2) a single-dose, fed BE study comparing the highest strength of the test and reference products.[27] If an applicant does not intend to submit an ANDA for the highest strength of the reference product, then FDA generally recommends using the highest strength included in the ANDA for BE studies.

Conducting an in vivo BE study on a strength other than the highest may be appropriate for reasons of safety. Use of a lower strength for reasons of safety is generally acceptable if the following conditions are met:

- Linear elimination has been documented over the therapeutic dose range.
- The recommendations in section IV.B.2 in this guidance are followed.

In other cases (such as non-linear elimination), applicants may contact the Office of Generic Drugs via a controlled correspondence if there is no applicable PSG or if the proposed strength differs from what is recommended in the applicable PSG.

2. Demonstration of Bioequivalence: Additional Strengths

An in vivo BE requirement for one or more strength(s) can be waived based on (1) acceptable BE study(ies) on the designated strength, (2) acceptable in vitro dissolution testing of all the strengths, and (3) proportional similarity of the formulations across all strengths.[28]

In this guidance, *proportionally similar* means any of the following:

- All active and inactive ingredients are in similar proportion between different strengths (e.g., a tablet of 50-milligram (mg) strength has all the inactive ingredients—almost

[24] See 21 CFR 320.22(b)(3).
[25] Ibid.
[26] Ibid.
[27] See section III.A.10 of this guidance for more information on fed BE studies.
[28] See 21 CFR 320.22(d)(2).

exactly half that of a tablet of 100-mg strength, and almost twice that of a tablet of 25-mg strength).

- For drug products that meet the following criteria: (1) the total weight of the dosage form remains nearly the same for all strengths (within +/- 10 percent of the total weight of the strength on which a biostudy was performed), (2) the same inactive ingredients are used for all strengths, and (3) the change in any strength is obtained by altering the amount of the active ingredients and one or more of the inactive ingredients.

- Active and inactive ingredients that are not in similar proportion between different strengths can be considered *proportionally similar* with adequate justification. FDA's determination of proportionality will be assessed during the ANDA assessment.

Under any of these scenarios, we recommend that in vivo BE studies be accompanied by in vitro dissolution profiles on all strengths of each product with the method set forth in the U. S. Pharmacopeia (USP) drug product monograph or FDA's dissolution database method.[29] We also recommend that applicants conduct a BE study using the strength(s) recommended in the applicable PSG.[30]

For additional information on the BE study design for a specific product, we recommend that applicants consult FDA's Product-Specific Guidances for Generic Drug Development web page[31] to determine whether a PSG for the proposed product is available.

3. Post-Approval Changes

Refer to the guidance for industry *Immediate Release Solid Oral Dosage Forms: Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation* (November 1995) for information regarding the BE testing recommended for specified types of post-approval changes.

For post-approval changes generally, we recommend that applicants make the in vitro comparison between the pre-change and post-change products. When in vivo BE studies are recommended to support a post-approval change for an ANDA product, FDA recommends that applicants compare the post-change ANDA product to the RLD and not to the pre-change ANDA product.

C. Suspensions

FDA generally recommends that applicants establish BE for a suspension in the same manner as for other solid oral dosage forms. In vivo studies and dissolution testing should be performed as described in section IV.B of this guidance on immediate-release products or in section IV.D of this guidance on modified-release products.

[29] See section V.F of this guidance for more information on this method.
[30] See footnote 2.
[31] Ibid.

D. Modified-Release Products

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

1. Delayed-Release Products

A *delayed-release drug product* is a dosage form that releases the active pharmaceutical ingredient or active moiety at a time later than immediately after administration (e.g., the drug product exhibits a lag time in quantifiable plasma concentrations). Typically, the coatings (e.g., enteric coatings) of delayed-release products have been designed to delay the release of the 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, described below. 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., a pH of 6.8). For certain delayed-release products, differences in the delayed-release coating polymer(s) between the test and reference product can impact the PK profiles at a pH between acidic and neutral which may be clinically undesirable, thus dissolution testing in additional pH/media may be warranted. FDA recommends that applicants consult this guidance in conjunction with any relevant PSGs that contain product specific recommendations for a need to conduct dissolution testing in additional pH/media.[32]

2. Extended-Release Products

An *extended-release drug product* is a dosage form that both allows a reduction in the dosing frequency and reduces fluctuations in plasma concentrations when compared to an immediate-release dosage form. Extended-release products can be formulated as capsules, tablets, granules, pellets, or suspensions. If any part of a drug product includes an extended-release component, the product should be treated as a modified-release dosage form to establish BE, as specified in sections IV.D.3 and IV.D.4 of this guidance.

3. Bioequivalence Study Designs and Dose

For modified-release products, we generally recommend the following studies: (1) a single-dose, fasting BE study comparing the highest strength of the test with the reference product and (2) a single-dose, fed BE study comparing the highest strength of the test with the reference product. Because single-dose studies are considered more sensitive in addressing the primary question of BE (e.g., release of the drug substance from the drug product into the systemic circulation), multiple-dose studies are generally not recommended.

Conducting an in vivo BE study on a strength other than the highest may be appropriate for reasons of safety. Use of a lower strength for reasons of safety is generally acceptable if the following conditions are met:

[32] See footnote 2.

- Linear elimination has been documented over the therapeutic dose range.
- The recommendations in section IV.D.4 of this guidance are followed.

In other cases (such as non-linear elimination), applicants may contact the Office of Generic Drugs via a controlled correspondence if there is no applicable PSG or the proposed strength differs from what is recommended in the applicable PSG.

4. Demonstration of Bioequivalence: Additional Strengths

Additional strengths of modified-release products may be demonstrated to be bioequivalent to the corresponding reference product strengths under 21 CFR 320.24(b)(6) if all the following conditions have been met:

- The reference product demonstrates dosage form equivalence among different strengths and demonstrates similar dissolution performance across different strengths.

- The test product includes the same excipients for different strengths and the ratios of drug and excipients among different strengths of the test product is justified and appropriate for the drug release mechanism of the test product (e.g., drug and excipients of different strengths can be either proportional or not proportional in quantity).

- The additional strength of the test product has the same drug release mechanism as the strength of the test product that underwent an acceptable in vivo BE study compared to the reference product.

- Dissolution testing of all strengths is acceptable. The drug products should exhibit similar dissolution profiles between the strength on which the BE testing was conducted and other strengths, based on the similarity factor (f_2) test or other appropriate statistical approaches (e.g., a multivariate model independent approach or a model dependent approach) in at least three dissolution media (e.g., a pH of 1.2, 4.5, and 6.8).[33]

We recommend that applicants generate dissolution profiles on the test and reference products of all strengths. To note, there may be instances in which an in vivo BE study for non-proportionally formulated strengths may be necessary to demonstrate bioequivalence. The decision of the acceptability of the approach will be made during ANDA assessment based on the totality-of-evidence (in addition to the dissolution data).

5. Post-Approval Changes

Refer to FDA's guidance for industry *SUPAC-MR: Modified-Release Solid Oral Dosage Forms: Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Dissolution Testing and In Vivo Bioequivalence Documentation* (October 1997) for information

[33] In such instances, we anticipate that such approach will be adequate to demonstrate BE. See 21 CFR 320.24(b)(6).

regarding BE testing recommended for specified types of post-approval changes for modified-release dosage forms.

For post-approval changes, we recommend that applicants perform an in vitro comparison between the approved (pre-change) product and the test (post-change) product. If appropriate, we recommend that the f_2 test be used to compare dissolution profiles. If the f2 test requirements are not met, for the comparison of the dissolution profiles, applicants should use another appropriate statistical approach (e.g., a multivariate model independent approach or a model dependent approach). An in vivo BE study may be needed if dissolution profiles are not shown to be similar. When an in vivo BE study is recommended to support a post-approval change for an ANDA product, FDA recommends that applicants compare the post-change ANDA drug product to the RLD product and not to the pre-change ANDA product.

E. Chewable Tablets

Applicants should administer chewable tablets according to the directions in the RLD labeling. If the labeling states that the tablet must be chewed before swallowing, the product should be chewed when administered in BE studies. If the labeling gives the option of either chewing the product or swallowing it whole, the product should be swallowed whole, with 240 milliliters of water, when administered in BE studies. We also recommend that applicants conduct in vitro dissolution testing on intact, whole tablets of the chewable drug product.

F. Orally Disintegrating Tablets

Applicants should administer orally disintegrating tablets according to the directions in the RLD labeling. If the labeling states that the tablet may be administered with or without water, BE studies should be conducted without water.

G. Sublingual

Sublingual tablets should not be swallowed. The tablets should be placed under the tongue until they are dissolved. Follow the labeling instruction or the applicable PSG for additional information on the method of administration.

H. Transdermal

Transdermal drug products are administered to the skin and designed to deliver the drug through (rather than to) the skin. Most transdermal products are extended-release film dosage forms, more commonly known as *transdermal delivery systems*. These deliver drugs into the systemic circulation at a controlled rate for a specified duration. To demonstrate the BE of transdermal delivery system, an in vivo single-dose, two-treatment, two-period crossover BE study with PK endpoints is recommended. Studies on adhesion and skin irritation/sensitization are

recommended as well to assess the noninferiority of the generic product to the reference product.[34]

Administration of TDS products should be to the intact skin unless the labeling indicates otherwise. Transdermal delivery systems should be applied as directed unless recommended otherwise in the relevant PSGs. Reservoir transdermal delivery systems should not be cut or otherwise altered before application. Topically applied creams, gels, ointments, lotions, or other formulations intended for a systemic effect should be applied as directed over a body surface area consistent with the labeled use. Systemic BE assessments can be made for transdermal delivery systems and topical formulations. If a product can be administered interchangeably to multiple body sites, it is generally suggested that applicants use a single administration site to demonstrate BE or refer to recommendations in the applicable PSGs.

V. SPECIAL TOPICS

A number of topics that may warrant special consideration are addressed in the following subsections. If a PSG is available on FDA's Product-Specific Guidances for Generic Drug Development web page,[35] the recommendations in that PSG generally supersede those described within this section.

A. Moieties To Be Measured

1. Parent Drug Versus Metabolites

The parent drug in the dosage form should always be measured in the biological fluids collected in BE studies, unless accurate assay quantitation is not possible using state-of-the-art-technology. We generally recommend that applicants measure only the parent drug, rather than metabolites, because 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. Primary metabolite(s), formed directly from the parent compound, should be measured if they (1) are formed substantially through presystemic metabolism (gut wall or gut lumen metabolism) and (2) contribute significantly to the safety and/or efficacy of the product. This approach should be used for all drug products, including prodrugs. We recommend that applicants analyze the parent drug measured in these BE studies using a confidence interval approach. Applicants can use the metabolite data to provide supportive evidence of a comparable therapeutic outcome.

If the parent drug concentrations 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 the confidence interval approach for BE demonstration.

[34] Refer to the draft guidances for industry *Assessing Adhesion with Transdermal and Topical Delivery Systems for ANDAs* (October 2018) and *Assessing the Irritation and Sensitization Potential of Transdermal and Topical Delivery Systems for ANDAs* (October 2018) for details. When final, these guidances will represent the FDA's current thinking on these topics.

[35] See footnote 2.

607
608 *2. Enantiomers Versus Racemates*
609
610 For BE studies, we recommend using an achiral assay to measure the **racemate**. We recommend
611 measuring individual **enantiomers** in BE studies only when all the following conditions have
612 been met: (1) the enantiomers exhibit different PD characteristics, (2) the enantiomers exhibit
613 different PK characteristics, (3) the primary efficacy and safety activity reside with the minor
614 enantiomer, and (4) nonlinear absorption is present (as expressed by a change in the enantiomer
615 concentration ratio with change in the input rate of the drug) for at least one of the enantiomers.
616 When all these conditions are met, we recommend that applicants separately apply their BE
617 analysis to the enantiomers.
618
619 *3. Drug Products with Complex Mixtures as the Active Ingredients*
620
621 Certain drug products contain complex drug substances (e.g., active moieties or active
622 ingredients that are mixtures of multiple synthetic and/or natural source components). Some or
623 all the components of these complex drug substances cannot be fully characterized with regard to
624 chemical structure and/or biological activity. For these complex drug products, we do not
625 encourage quantification of all active or potentially active components in PK studies. Rather, we
626 recommend that applicants base BE studies on a small number of markers of rate and extent of
627 absorption. Selection of the markers should be based on the characteristics and mechanism of
628 action of the drug product. Criteria for marker selection can include the biopharmaceutics of the
629 dosage form; the amount of the moiety in the dosage form; the plasma or blood concentrations of
630 the moiety; and the biological activity of the moiety relative to other moieties in the complex
631 mixture.
632
633 **B. Long Half-Life Drugs**
634
635 For an oral immediate-release product with a long elimination half-life drug (> 24 hours),
636 applicants can conduct a single-dose, crossover study, provided an adequate washout period is
637 used. If the crossover study is problematic, applicants should conduct a BE study with a parallel
638 design. For either a crossover or parallel study, sample collection times should be adequate to
639 ensure completion of gastrointestinal transit of the drug product and absorption of the drug
640 substance (which usually occurs within approximately 2 to 3 days). Applicants can use C_{max} and
641 a suitably truncated AUC (for instance, an AUC truncated at 72 hours ($AUC_{0\text{-}72\ hr}$)) to
642 characterize peak and total drug exposure, respectively. However, sampling should ensure that
643 the complete drug absorption phase is covered and characterized. For drugs exhibiting flip-flop
644 kinetics with reported $\mathbf{t_{1/2}}$ > 24 hours, truncation of AUC may not be appropriate.
645
646 **C. First Point $\mathbf{C_{max}}$**
647
648 The first point of a concentration-time curve in a BE study, based on blood or plasma
649 measurements, is sometimes the highest point, which raises questions of bias in the estimation of
650 C_{max} because of insufficient early sampling times. A carefully conducted pilot study can enable
651 an applicant to avoid this problem.
652

In the BE study, collection of blood samples at 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 is usually sufficient to assess peak drug concentrations. Failure to include early (5- to 15-minute) sampling times leading to first time point C_{max} values may result in FDA excluding the data from affected subjects from the BE analysis.

D. Alcoholic Beverage Effects on Modified-Release Drug Products

The consumption of alcoholic beverages can affect the release of a drug substance from a modified-release formulation. The formulation can lose its modified-release characteristics, leading to a more rapid drug release and an altered systemic exposure, which can have deleterious effects on the drug's safety and/or efficacy.

FDA recommends that applicants developing certain modified-release solid oral dosage forms conduct in vitro studies to determine the potential for dose dumping in alcohol which may occur in vivo. In vitro assessments of the drug release from the drug product using media with various alcohol concentrations may be recommended. An in vivo BE study of the drug product when administered with alcohol may be appropriate in some cases. For information on specific products, we recommend that applicants consult any relevant PSG.[36]

E. Endogenous Compounds

Endogenous compounds are already present in the body either because the body produces them or because they are present in a normal diet. Because these compounds are identical to the drug that is being administered, determining the amount of drug released from the dosage form and absorbed by each subject can be difficult. We recommend that applicants measure and approximate the baseline endogenous concentrations in blood (plasma) or urine and subtract these concentrations from the total concentrations measured from each subject after the drug product is administered to achieve an estimate of the actual drug availability from the drug product. Depending on whether the endogenous compound is naturally produced by the body or is present in the diet, the recommended approaches for determining BE differ as follows:

- When the body produces the compound, we recommend that applicants measure multiple baseline concentrations from each individual subject in the time period before administration of the study drug and subtract the time-averaged baseline or time-matched baseline from post-dose concentrations for those subjects in an appropriate manner consistent with the PK properties of the drug.

- When there is a dietary intake of the compound, we recommend that applicants strictly control the intake both before and during the study. Subjects should be housed at a clinic before the study and served standardized meals containing an amount of the compound similar to that in the meals to be served on the PK sampling day.

[36] See footnote 2.

For both approaches above, we recommend that applicants determine baseline concentrations for each dosing period and perform baseline corrections that are period specific. If a baseline correction results in a negative plasma concentration value, the value should be set equal to 0 before calculating the baseline-corrected AUC. PK and statistical analyses should be performed on both uncorrected and corrected data. Determination of BE should be based on the baseline-corrected data.

F. In Vitro Dissolution Testing

The following guidances for industry provide recommendations for developing a dissolution methodology, setting acceptance criteria/criterion, and applying the regulatory applications of dissolution testing:

- *Dissolution Testing of Immediate Release Solid Oral Dosage Forms* (August 1997)
- *Dissolution Testing and Acceptance Criteria for Immediate-Release Solid Oral Dosage Form Drug Products Containing High Solubility Drug Substances* (August 2018)
- *Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations* (September 1997)
- *Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation* (March 2013)

1. Immediate-Release Products

The dissolution of a drug is product specific; FDA recommends that for immediate-release drug products, applicants develop optimal discriminating dissolution methods. Applicants may also use the dissolution method set forth in any related official USP drug product monograph or in FDA's dissolution database,[37] provided that applicants submit adequate dissolution data/information supporting the discriminating ability of the USP or FDA database method being proposed for the proposed immediate-release product.

If a new dissolution method is developed, FDA recommends that the submission include the dissolution method development and validation report with the complete information/data supporting the proposed method.

2. Modified-Release Products

For modified-release drug products, FDA recommends that applicants develop specific discriminating dissolution methods. Applicants may also use the dissolution method set forth in any related official USP drug product monograph or in FDA's dissolution database,[38] provided that applicants submit adequate dissolution data supporting the discriminating ability of the USP or FDA database method being proposed.

[37] FDA's dissolution database, which describes FDA's dissolution methods, is available at http://www.accessdata.fda.gov/scripts/cder/dissolution/index.cfm.
[38] Ibid.

If a new dissolution method is developed for the modified-release drug product, FDA recommends that the submission includes the dissolution method development and validation report with the complete information/data supporting the proposed method.

Overall, the selected dissolution method and acceptance criteria should be discriminating and sensitive enough to reject batches/lots that would perform differently from the batches/lots used in the pivotal BE studies.

If applicants propose a method different from the dissolution method described in the FDA dissolution database or USP, FDA recommends that they submit data using the dissolution method described in the FDA dissolution database or USP, in addition to their proposed method, for comparison.

G. Enteral Feeding Tube

If the approved labeling for the RLD states that the product may be administered by an enteral feeding tube (e.g., a nasogastric or a gastric tube), the applicant should conduct in vitro comparative testing to compare the performance of the test product to that of the reference product; this comparative testing supports the administration of drugs via enteral feeding tubes. Refer to PSGs for individual product recommendations.[39]

[39] See footnote 2.

APPENDIX A: GENERAL DESIGN AND DATA HANDLING OF BIOEQUIVALENCE STUDIES WITH PHARMACOKINETIC ENDPOINTS

For both replicate and non-replicate in vivo bioequivalence (BE) studies with pharmacokinetic (PK) endpoints, the Food and Drug Administration (FDA) recommends the following general approaches. However, elements can be adjusted for certain drug substances and drug products.

Study conduct:

- Fasting Study: The test or reference product should be administered with about 8 ounces (240 milliliters) of water to subjects under fasting conditions (i.e., after an overnight fast of at least 10 hours).

- Fed Study: We recommend that subjects start the recommended meal 30 minutes before administration of the test or refrence product following an overnight fast of at least 10 hours. Study subjects should finish eating this meal in 30 minutes or less, and the drug product should be administered 30 minutes after start of the meal. The drug product should be administered with about 8 fluid ounces (240 milliliters) of water.

- In general, we recommend that applicants conduct fed BE studies using meals that provide the greatest effects on gastrointestinal physiology and systemic drug availability. We recommend a high-fat (approximately 50 percent of total caloric content of the meal), high-calorie (approximately 800 to 1000 kilocalories) test meal for fed BE studies. This test meal should derive approximately 150, 250, and 500 to 600 kilocalories from protein, carbohydrate, and fat, respectively.[40] The caloric breakdown of the test meal should be provided in the study report. No food should be allowed for at least 4 hours post-dose. Water may be allowed as desired except for 1 hour before to 1 hour after drug administration. Subjects should receive standardized meals scheduled at the same time in each period of the study.

- Before and during each study phase, we recommend that subjects abstain from alcohol for at least 24 hours before each study period and until after the last sample from each period has been collected.

- Generally, the highest-marketed strength can be administered as a single unit. If the highest strength is not deemed safe for healthy subjects or the general population, then the study can be performed with individuals already prescribed and taking the drug at the highest marketed strength, or alternatively, in healthy subjects or the general population using a lower strength, where appropriate. If warranted to achieve sufficient bioanalytical sensitivity, multiple units of the highest strength can be administered, provided that the total single dose remains within the labeled dose range and the total dose is safe for administration to the study subjects.

[40] An example test meal would be two eggs fried in butter, two strips of bacon, two slices of toast with butter, four ounces of hash brown potatoes, and eight ounces of whole milk. Substitutions in this test meal (e.g., beef or chicken instead of bacon) can be made as long as the meal provides a similar amount of calories from proteins, carbohydrates, and fat and has a comparable meal volume, density, and viscosity.

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

- The lot numbers of both test and reference products and the expiration date for the reference product used in the study should be stated in the study report and the applicable Bioequivalence Summary Tables. We recommend that the assayed drug content of the test product batch not differ from the reference product by more than +/- 5 percent. The applicant should include a statement of the composition of the test product and, if possible, a side-by-side comparison of the compositions of the test and reference products. Under 21 CFR 320.63, the study drug test article of the test and reference products must be retained for 5 years. For additional information, refer to the guidance for industry *Handling and Retention of BA and BE Testing Samples* (May 2004).

Sample collection and sampling times:

We recommend that under normal circumstances, applicants sample blood, rather than urine or tissue. 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 drawing blood samples at appropriate times to describe the absorption, distribution, and elimination phases of the drug. For most drugs, we recommend collecting 12 to 18 samples, including a predose sample, per subject, per dose. This sampling should continue for at least three or more terminal elimination half-lives of the drug. The exact timing for sample collection depends on factors such as the nature of the drug and the rate of input from the administered dosage form. The sample collection should be spaced in such a way that the **C_{max}**[41] and **λz** can be estimated accurately. At least three samples should be obtained during the terminal log-linear phase to obtain an accurate estimate of λz from linear regression. We recommend recording the actual clock time when samples are drawn as well as the elapsed time related to drug administration.

Subjects with pre-dose plasma drug concentrations:

If the pre-dose concentration is ≤ 5 percent of the C_{max} value in a subject with a pre-dose plasma concentration, applicants can include the subject's data without any adjustments in all PK measurements and calculations. We recommend that if the pre-dose value is > 5 percent of the C_{max}, applicants drop the subject from all BE study evaluations.

[41] Terms that appear in bold type are defined in the glossary at the end of this guidance.

Data deletion because of vomiting:

We recommend that data from subjects who experience vomiting during a BE study for immediate-release products be deleted from statistical analysis if that vomiting occurred at or before 2 times median $\mathbf{T_{max}}$. For modified-release products, we recommend deleting data from the analysis if a subject vomits during a period of time less than or equal to the dosing interval stated in the labeling of the product. The concentration data for the subject who vomited should be reported.

Handling of outliers:

Applicants should not remove data from the statistical analysis of BE studies solely because that data are identified as statistical outliers. Outlier data may only be removed from the BE statistical analysis if there is a real-time documentation demonstrating a protocol violation during the clinical and/or analytical phase of the BE study. Applicants should include a prospective plan in the BE study protocol for removing subjects from the BE statistical analysis (e.g., a clinician documents in a case report form that the subject did not swallow the tablet, based on a mouth check of the subject). Data from redosing studies are not considered as evidence to support removal of outlier data from the statistical analysis. Note that all subject data should be submitted and potential outliers flagged with appropriate documentation as part of the submission.

Pharmacokinetic information in submissions:

We recommend that applicants provide the following PK information in their submissions:

- Plasma or other acceptable matrix concentrations and time points (both actual and nominal sampling time points).

- Subject, period, sequence, treatment.

- Intersubject, intrasubject, and/or total variability, if available.

- For single-dose BE studies: $\mathbf{AUC_{0\text{-}t}}$, $\mathbf{AUC_{0\text{-}inf}}$, AUC truncated or partial AUCs if applicable, and C_{max}. In addition, report the following supportive information: T_{max}, K_{el} and $\mathbf{t_{1/2}}$.

- For steady-state BE studies: $\mathbf{AUC_{0\text{-}tau}}$ and $\mathbf{C_{maxSS}}$. In addition, report $\mathbf{C_{minSS}}$ (lowest concentration in a dosing interval), $\mathbf{C_{avSS}}$ (average concentration during a dosing interval), degree of fluctuation [$(C_{maxSS}\text{-}C_{minSS})/C_{avSS}$], swing [$(C_{maxSS}\text{-}C_{minSS})/C_{minSS}$], and T_{max}.

- Additional analysis may be needed in certain cases to ensure that the two products are bioequivalent.

Submission of data from in vivo bioequivalence studies:

- For information about submitting electronic datasets, including plasma concentration data (under PC domain), PK parameter data (under PP domain), and other applicable data domains for ANDA submissions, refer to the Study Data Tabulation Model Implementation Guide web page.[42]

- For the most recent version of FDA's study data guidance and technical specifications, check FDA's Study Data Standards Resources web page.[43] This page includes links to the following:

  - The guidance for industry on study data standards entitled *Providing Regulatory Submissions in Electronic Format—Standardized Study Data* (October 2020)

  - Relevant technical specifications found in the *FDA Data Standards Catalog* and the *Study Data Technical Conformance Guide*

Statistical information for AUC_{0-t}, AUC_{0-inf}, and C_{max}:

We recommend that applicants provide the following statistical information for AUC_{0-t}, AUC_{0-inf}, and C_{max}:

- Geometric means

- Arithmetic means

- Geometric mean ratios and their corresponding 90 percent confidence intervals and/or 95 percent upper confidence bound, as applicable

We also recommend that applicants provide logarithmic transformation for measures used for BE demonstration and consult the guidance for industry *Statistical Approaches to Establishing Bioequivalence* (February 2001).

Confidence interval values for unscaled average bioequivalence anaylses:

For unscaled average bioequivalence analyses, to pass a confidence interval limit of 80 to 125 percent, the rounded confidence interval value should be at least 80.00 percent and not more than 125.00. We thus recommend that when applicants evaluate the confidence interval to assess bioequivalence using an unscaled average bioequivalence analysis during the development program, applicants round confidence interval values to two digits after the decimal point.

[42] The Study Data Tabulation Model Implementation Guide web page is available on the Clinical Interchange Standards Consortium's website at https://www.cdisc.org/standards/foundational/sdtmig.

[43] FDA's Study Data Standards Resources web page is available at http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm.

Highly variable drugs:

For non-narrow therapeutic index (non-NTI) drugs exhibiting high intra-subject variability, applicants may consider using a reference-scaled average BE approach. If using this approach, the applicant should provide evidence of high variability in the PK parameters including AUC and/or C_{max} for BE assessment. For the method of statistical analysis using the reference-scaled average BE approach for highly variable drugs, refer to Appendix B and product-specific guidances for individual product recommendations.[44]

Narrow therapeutic index drugs:

Narrow therapeutic index (NTI) drugs are defined as those drugs where small differences in dose or blood concentration may lead to serious therapeutic failures and/or adverse drug reactions that are life-threatening or result in persistent or significant disability or incapacity. For BE assessment for NTI drugs, we recommend a reference-scaled average BE approach with a four-way, fully replicated, crossover design study that permits the simultaneous equivalence comparison of the mean and within-subject variability of the test and reference products.[45] For the method for statistical analysis using the reference-scaled average BE approach for NTI drugs, refer to Appendix C and product-specific guidances for individual product recommendations.[46]

[44] See the Product-Specific Guidances for Generic Drug Development web page at https://www.fda.gov/drugs/guidances-drugs/product-specific-guidances-generic-drug-development to search for published product-specific guidances.

[45] Yu L, et. al., Novel Bioequivalence Approach for Narrow Therapeutic Index Drugs. *Clin Pharm & Ther*, 97(3), 286-291, 2015.

[46] See footnote 2.

APPENDIX B: METHOD FOR STATISTICAL ANALYSIS USING THE REFERENCE-SCALED AVERAGE BIOEQUIVALENCE APPROACH: HIGHLY VARIABLE DRUGS

For highly variable drugs, a mixed scaling approach is used. Namely, the reference-scaled procedure is used for specific PK parameters that have a within subject variability of the reference product (s_{WR}) ≥ 0.294, and the two one-sided tests procedure is used for PK parameters with s_{WR} < 0.294. In other words, if AUC (**AUC_{0-t}**[47] and **AUC_{0-inf}**, as applicable) and C_{max} have different s_{WR} values, different BE analysis should be conducted.

The following are the steps that can be followed to carry out the statistical analysis for the reference-scaled average bioequivalence assessment for highly variable drugs:

Step 1. Determine s_{WR}, the within-subject standard deviation of the reference product, for the pharmacokinetic (PK) parameters including **AUC** and **C_{max}**.

a. If s_{WR} < 0.294, use the two one-sided tests procedure to determine bioequivalence (BE) for the individual PK parameter(s).

b. If $s_{WR} \geq 0.294$, use the reference-scaled procedure to determine BE for the individual PK parameter(s).

Calculation for s_{WR} can be conducted as follows:

$$s_{WR}^2 = \frac{\sum_{i=1}^{m}\sum_{j=1}^{n_i}\left(D_{ij} - \overline{D}_{i\cdot}\right)^2}{2(n-m)}$$

Where:

- i = number of sequences m used in the study

  [m=3 for partially replicate design: TRR, RTR, and RRT;
  m=2 for fully replicate design: TRTR and RTRT]

- j = number of subjects within each sequence

- T = Test product

- R = Reference product

- $D_{ij} = R_{ij1} - R_{ij2}$ (where 1 and 2 represent replicate reference treatments)

[47] Terms that appear in bold type are defined in the glossary at the end of this guidance.

- $\overline{D}_{i\cdot} = \dfrac{\sum_{j=1}^{n_i} D_{ij}}{n_i}$

- $n = \sum_{i=1}^{m} n_i$ (i.e., total number of subjects used in the study, while n_i is number of subjects used in sequence *i*)

Continue with steps 2 and 3 for PK parameters that have a $s_{WR} \geq 0.294$.

Step 2. Determine the 95% upper confidence bound[48] for:

$$\left(\bar{Y}_T - \bar{Y}_R\right)^2 - \theta s_{WR}^2$$

Where:

- $\bar{Y}_T$ and $\bar{Y}_R$ are the means of the ln-transformed PK endpoint (AUC and/or C_{max}) obtained from the BE study for the test and reference products, respectively.

- $\theta \equiv \left(\dfrac{\ln(1.25)}{\sigma_{W0}}\right)^2$ (scaled average BE limit).

- σ_{W0} = 0.25 (regulatory constant).

Step 3. For the test product to be bioequivalent to the reference product, *both* of the following conditions must be satisfied for each PK parameter tested:

a. The 95% upper confidence bound for $\left(\bar{Y}_T - \bar{Y}_R\right)^2 - \theta s_{WR}^2$ must be ≤ 0 (numbers should be kept to a minimum of four significant figures for comparsion).
b. The point estimate of the Test/Reference geometric mean ratio must fall within [0.8000, 1.2500].

Example SAS codes are presented below. It is not necessary to use SAS® if other software accomplish the same objectives.

If SAS® is used for statistical analysis, note the following:

[48] The method for obtaining the upper confidence bound is based on *Howe's Approximation I*, which is described in the following paper: WG Howe, 1974, Approximate Confidence Limits on the Mean of *X*+*Y* Where *X* and *Y* are Two Tabled Independent Random Variables, J Am Stat Assoc, 69(347):789–794.

- PROC GLM should be used for partially replicate (3-way) BE studies
- PROC MIXED should be used for fully replicate (4-way) BE studies

- **Example SAS Codes: Partial reference-replicate 3-way design**

For a BE study with the following sequence assignments in a partial reference-replicate 3-way crossover design:

	Period 1	**Period 2**	**Period 3**
Sequence 1	T	R	R
Sequence 2	R	T	R
Sequence 3	R	R	T

1. For PK parameters with a $s_{WR} \geq 0.294$, use the reference-scaled procedure to determine BE.

The following codes are an example of the determination of reference-scaled average BE for LAUCT with a partially replicate 3-way BE design:

Dataset containing TEST observations:

```
data test;
  set pk;
  if trt='T';
  latt=lauct;
run;
```

Dataset containing REFERENCE 1 observations:

```
data ref1;
  set ref;
  if (seq=1 and per=2) or (seq=2 and per=1) or (seq=3 and per=1);
  lat1r=lauct;
run;
```

Dataset containing REFERENCE 2 observations:

```
data ref2;
  set ref;
  if (seq=1 and per=3) or (seq=2 and per=3) or (seq=3 and per=2);
  lat2r=lauct;
run;
```

Define the following quantities:

T_{ij} = the observation on T for subject j within sequence i

R_{ijk} = kth observation (k = 1 or 2) on R for subject j within sequence i

$I_{ij} = T_{ij} - \frac{R_{ij1} + R_{ij2}}{2}$

$D_{ij} = R_{ij1} - R_{ij2}$

I_{ij} is the difference between a subject's (specifically, subject j within sequence i) observation on T and the mean of the subject's two observations on R, while D_{ij} is the difference between a subject's two observations on R.

Determine I_{ij} and D_{ij}

```
data scavbe;
  merge test ref1 ref2;
  by seq subj;
  ilat=latt - 0.5*(lat1r+lat2r));
  dlat=lat1r-lat2r;
run;
```

Intermediate analysis - ilat

```
proc glm data=scavbe;
  class seq;
  model ilat=seq/clparm alpha=0.1;
  estimate 'average' intercept 1 seq 0.3333333333 0.3333333333
  0.3333333333;
  ods output overallanova=iglm1;
  ods output Estimates=iglm2;
  ods output NObs=iglm3;
  title1 'scaled average BE';
run;
```

From the dataset IGLM2, calculate the following:

IGLM2:

```
  pointest=exp(estimate);
  x=estimate**2-stderr**2;
  boundx=(max((abs(LowerCL)),(abs(UpperCL))))**2;
```

Intermediate analysis - dlat

```
proc glm data=scavbe;
  class seq;
  model dlat=seq;
  ods output overallanova=dglm1;
  ods output NObs=dglm3;
  title1 'scaled average BE';
run;
```

From the dataset DGLM1, calculate the following:

DGLM1:

```
dfd=df;
s2wr=ms/2;
```

From the above parameters, calculate the final 95% upper confidence bound:

```
theta=((log(1.25))/0.25)**2;
y=-theta*s2wr;
boundy=y*dfd/cinv(0.95,dfd);
sWR=sqrt(s2wr);
critbound=(x+y)+sqrt(((boundx-x)**2)+((boundy-y)**2));
```

2. For PK parameters with a s_{WR} < 0.294, use the unscaled average BE approach.

The following codes are an example of the determination of unscaled average BE for LAUCT with a partially replicate 3-way BE design:

```
PROC MIXED
  data=pk;
  CLASSES SEQ SUBJ PER TRT;
  MODEL LAUCT = SEQ PER TRT/ DDFM=SATTERTH;
  RANDOM TRT/TYPE=FA0(2) SUB=SUBJ G;
  REPEATED/GRP=TRT SUB=SUBJ;
  ESTIMATE 'T vs. R' TRT 1 -1/CL ALPHA=0.1;
  ods output Estimates=unsc1;
  title1 'unscaled BE 90% CI - guidance version';
  title2 'AUCt';
run;

data unsc1;
  set unsc1;
  unscabe_lower=exp(lower);
  unscabe_upper=exp(upper);
run;
```

- **Example SAS Codes: Fully replicate 4-period, 2-sequence, 4-way crossover design**

For a BE study with the following sequence assignments in a fully replicate 4-way crossover design:

	Period 1	**Period 2**	**Period 3**	**Period 4**
Sequence 1	T	R	T	R
Sequence 2	R	T	R	T

1. For PK parameters with a $s_{WR} \geq 0.294$, use the reference-scaled procedure to determine BE.

The following codes are an example of the determination of reference-scaled average BE for LAUCT with a fully replicate 4-way BE design:

- **Dataset containing TEST 1 observations:**

```
data test1;
  set test;
  if (seq=1 and per=1) or (seq=2 and per=2);
  lat1t=lauct;
run;
```

- **Dataset containing TEST 2 observations:**

```
data test2;
  set test;
  if (seq=1 and per=3) or (seq=2 and per=4);
  lat2t=lauct;
run;
```

- **Dataset containing REFERENCE 1 observations:**

```
data ref1;
  set ref;
  if (seq=1 and per=2) or (seq=2 and per=1);
  lat1r=lauct;
run;
```

- **Dataset containing REFERENCE 2 observations:**

```
data ref2;
  set ref;
  if (seq=1 and per=4) or (seq=2 and per=3);
  lat2r=lauct;
run;
```

The number of subjects in each sequence is n_1 and n_2 for sequences 1 and 2, respectively.

Define the following quantities:

T_{ijk} = kth observation (k = 1 or 2) on T for subject j within sequence i

R_{ijk} = kth observation (k = 1 or 2) on R for subject j within sequence i

$$I_{ij} = \frac{T_{ij1}+T_{ij2}}{2} - \frac{R_{ij1}+R_{ij2}}{2}$$

$$D_{ij} = R_{ij1} - R_{ij2}$$

I_{ij} is the difference between the mean of two observations of a subject (specifically, subject j within sequence i) on T and the mean of the subject's two observations on R, while D_{ij} is the difference between a subject's two observations on R.

Determine I_{ij} and D_{ij}

```
data scavbe;
  merge test1 test2 ref1 ref2;
  by seq subj;
  ilat=0.5*(lat1t+lat2t-lat1r-lat2r);
  dlat=lat1r-lat2r;
run;
```

Intermediate analysis – ilat

```
proc mixed data=scavbe;
  class seq;
  model ilat =seq/ddfm=satterth;
  estimate 'average' intercept 1 seq 0.5 0.5/e cl alpha=0.1;
  ods output CovParms=iout1;
  ods output Estimates=iout2;
  ods output NObs=iout3;
  title1 'scaled average BE';
  title2 'intermediate analysis - ilat, mixed';
run;
```

From the dataset IOUT2, calculate the following:

IOUT2:

```
  pointest=exp(estimate);
  x=estimate**2-stderr**2;
  boundx=(max((abs(lower)),(abs(upper))))**2;
```

Intermediate analysis – dlat

```
proc mixed data=scavbe;
  class seq;
  model dlat=seq/ddfm=satterth;
  estimate 'average' intercept 1 seq 0.5 0.5/e cl alpha=0.1;
  ods output CovParms=dout1;
  ods output Estimates=dout2;
  ods output NObs=dout3;
  title1 'scaled average BE';
  title2 'intermediate analysis - dlat, mixed';
run;
```

From the dataset DOUT1, calculate the following:

DOUT1:

```
  s2wr=estimate/2;
```

From the dataset DOUT2, calculate the following:

DOUT2:

```
  dfd=df;
```

From the above parameters, calculate the final 95% upper confidence bound:

```
theta=((log(1.25))/0.25)**2;
y=-theta*s2wr;
boundy=y*dfd/cinv(0.95,dfd);
sWR=sqrt(s2wr);
critbound=(x+y)+sqrt(((boundx-x)**2)+((boundy-y)**2));
```

2. For PK parameters with a < 0.294, use the unscaled average BE approach.

The following codes are an example of the determination of unscaled average BE for LAUCT with a fully replicate 4-way BE design:

```
PROC MIXED
  data=pk;
  CLASSES SEQ SUBJ PER TRT;
  MODEL LAUCT = SEQ PER TRT/ DDFM=SATTERTH;
  RANDOM TRT/TYPE=FA0(2) SUB=SUBJ G;
  REPEATED/GRP=TRT SUB=SUBJ;
  ESTIMATE 'T vs. R' TRT 1 -1/CL ALPHA=0.1;
  ods output Estimates=unsc1;
  title1 'unscaled BE 90% CI - guidance version';
  title2 'AUCt';
run;

data unsc1;
  set unsc1;
  unscabe_lower=exp(lower);
  unscabe_upper=exp(upper);
run;
```

APPENDIX C: METHOD FOR STATISTICAL ANALYSIS USING THE REFERENCE-SCALED AVERAGE BIOEQUIVALENCE APPROACH: NARROW THERAPEUTIC INDEX DRUGS

For narrow therapeutic index (NTI) drugs, the study should be a fully replicated, 4-way crossover design to scale the bioequivalence limit to the variability of the reference product and to simultaneously compare the mean and within-subject variability of the test and reference products. The procedure described below includes both reference scaling and unscaled analysis and they are combined to ensure that for NTI drugs the BE limits do not exceed 80.00%-125.00%.

The following are the steps that can be followed to carry out the statistical analysis for the reference scaled average bioequivalence for narrow therapeutic index drugs:

Step 1. Determine s_{WR}, the estimate of within-subject standard deviation of the reference product, for the PK parameters including **AUC**[49] and **C_{max}**.

Calculation for s_{WR} can be conducted as follows:

$$s_{WR}^2 = \frac{\sum_{i=1}^{m}\sum_{j=1}^{n_i}\left(D_{ij} - \overline{D}_{i\cdot}\right)^2}{2(n-m)}$$

Where:

- i = number of sequences m used in the study

  [m=2 for fully replicate design: TRTR and RTRT]

- j = number of subjects within each sequence

- T = Test product

- R = Reference product

- $D_{ij} = R_{ij1} - R_{ij2}$ (where 1 and 2 represent replicate reference treatments)

- $\overline{D}_{i\cdot} = \frac{\sum_{j=1}^{n_i} D_{ij}}{n_i}$

[49] Terms that appear in bold type are defined in the glossary at the end of this guidance.

- $n = \sum_{i=1}^{m} n_i$ (i.e., total number of subjects used in the study, while n_i is number of subjects used in sequence *i*)

Step 2. Use the referenced-scaled procedure to determine BE for individual PK parameter(s).

Determine the 95% upper confidence bound[50] for:

$$\left(\overline{Y_T} - \overline{Y}_R\right)^2 - \theta\, s_{WR}^2$$

Where:

- $\overline{Y_T}$ and $\overline{Y_R}$ are the means of the ln-transformed PK endpoint (AUC and/or C_{max}) obtained from the BE study for the test and reference products, respectively
- $\theta \equiv \left(\frac{\ln(\Delta)}{\sigma_{W0}}\right)^2$ (scaled average BE limit)
- and $\sigma_{W0} = 0.10$ (regulatory constant), $\Delta = 1./0.9$ (approximately=1.11111, the upper BE limit)

Step 3. Use the unscaled average bioequivalence procedure to determine BE for individual PK parameter(s).

Step 4. Calculate the 90% confidence interval of the ratio of the within subject standard deviation of test product to reference product σ_{WT}/σ_{WR} . The upper limit of the 90% confidence interval for σ_{WT}/σ_{WR} will be evaluated to determine if σ_{WT} and σ_{WR} are comparable.

The $(1-\alpha)100\%$ CI for $\frac{\sigma_{WT}}{\sigma_{WR}}$ is given by

$$\left(\frac{s_{WT}/s_{WR}}{\sqrt{F_{\frac{\alpha}{2}}(\nu_1,\nu_2)}}, \frac{s_{WT}/s_{WR}}{\sqrt{F_{1-\frac{\alpha}{2}}(\nu_1,\nu_2)}}\right)$$

Where:

[50] The method of obtaining the upper confidence bound is based on Howe's Approximation I, which is described in the following paper: WG Howe, 1974, Approximate Confidence Limits on the Mean of *X*+*Y* Where *X* and *Y* are Two Tabled Independent Random Variables, J Am Stat Assoc, 69 (347):789–794.

- s_{WT} is the estimate of σ_{WT} with ν_1 as the degree of freedom
- s_{WR} is the estimate of σ_{WR} with ν_2 as the degree of freedom
- $F_{\alpha/2,\nu_1,\nu_2}$ is the value of the F-distribution with ν_1 (numerator) and ν_2 (denominator) degrees of freedom that has probability of $\alpha/2$ to its right.
- $F_{1-\alpha/2,\nu_1,\nu_2}$ is the value of the F-distribution with ν_1 (numerator) and ν_2 (denominator) degrees of freedom that has probability of 1-$\alpha/2$ to its right.
- here $\alpha = 0.1$.

Step 5. For the test product to be bioequivalent to the reference product, the following conditions must be satisfied for each PK parameter tested:

a. The 95% upper confidence bound for $\left(\bar{Y}_T - \bar{Y}_R\right)^2 - \theta s_{WR}^2$ must be ≤ 0 (numbers should be kept to a minimum of four significant figures for comparison).

b. Regular unscaled bioequivalence limits of 80.00%-125.00% should be passed.

c. The proposed requirement for the upper limit of the 90% equal-tails confidence interval for σ_{WT}/σ_{WR} is less than or equal to 2.500.

Example SAS codes are presented below. It is not necessary to use SAS® if other software accomplish the same objectives.

If SAS® is used for statistical analysis, PROC MIXED should be used for fully replicate 4-way crossover BE studies.

- **<u>Example SAS Codes: Fully replicate 4-period, 2-sequence, 4-way crossover design</u>**

For a BE study with the following sequence assignments in a fully replicate 4-way crossover design:

	Period 1	**Period 2**	**Period 3**	**Period 4**
Sequence 1	T	R	T	R
Sequence 2	R	T	R	T

The following codes are an example of the determination of reference-scaled average BE for LAUCT. Assume that the datasets TEST and REF, have already been created, with TEST having all the test observations and REF having all the reference observations.

Dataset containing TEST 1 observations:

```
data test1;
 set test;
 if (seq=1 and per=1) or (seq=2 and per=2);
 lat1t=lauct;
run;
```

Dataset containing TEST 2 observations:

```
data test2;
  set test;
  if (seq=1 and per=3) or (seq=2 and per=4);
  lat2t=lauct;
run;
```

Dataset containing REFERENCE 1 observations:

```
data ref1;
  set ref;
  if (seq=1 and per=2) or (seq=2 and per=1);
  lat1r=lauct;
run;
```

Dataset containing REFERENCE 2 observations:

```
data ref2;
  set ref;
  if (seq=1 and per=4) or (seq=2 and per=3);
  lat2r=lauct;
run;
```

The number of subjects in each sequence is n_1 and n_2 for sequences 1 and 2, respectively.

Define the following quantities:

$T_{ijk} = k^{th}$ observation (k = 1 or 2) on T for subject j within sequence i

$R_{ijk} = k^{th}$ observation (k = 1 or 2) on R for subject j within sequence i

$$I_{ij} = \frac{T_{ij1} + T_{ij2}}{2} - \frac{R_{ij1} + R_{ij2}}{2}$$

and

$$D_{ij} = R_{ij1} - R_{ij2}$$

I_{ij} is the difference between the mean of a subject's (specifically subject j within sequence i) two observations on T and the mean of the subject's two observations on R, while D_{ij} is the difference between a subject's two observations on R.

Determine I_{ij} and D_{ij}

```
data scavbe;
  merge test1 test2 ref1 ref2;
  by seq subj;
  ilat=0.5*(lat1t+lat2t-lat1r-lat2r);
  dlat=lat1r-lat2r;
run;
```

Intermediate analysis - ilat

```
proc mixed data=scavbe;
  class seq;
  model ilat =seq/ddfm=satterth;
  estimate 'average' intercept 1 seq 0.5 0.5/e cl alpha=0.1;
  ods output CovParms=iout1;
  ods output Estimates=iout2;
  ods output NObs=iout3;
  title1 'scaled average BE';
  title2 'intermediate analysis - ilat, mixed';
run;
```

From the dataset IOUT2, calculate the following:

IOUT2:

```
pointest=exp(estimate);
x=estimate**2-stderr**2;
boundx=(max((abs(lower)),(abs(upper))))**2;
```

Intermediate analysis - dlat

```
proc mixed data=scavbe;
  class seq;
  model dlat=seq/ddfm=satterth;
  estimate 'average' intercept 1 seq 0.5 0.5/e cl alpha=0.1;
  ods output CovParms=dout1;
  ods output Estimates=dout2;
  ods output NObs=dout3;
  title1 'scaled average BE';
  title2 'intermediate analysis - dlat, mixed';
run;
```

From the dataset DOUT1, calculate the following:

DOUT1:

```
  s2wr=estimate/2;
```

From the dataset DOUT2, calculate the following:

DOUT2:

```
  dfd=df;
```

From the above parameters, calculate the final 95% upper confidence bound:

```
theta=((log(1.11111))/0.1)**2;
y=-theta*s2wr;
boundy=y*dfd/cinv(0.95,dfd);
sWR=sqrt(s2wr);
```

```
critbound=(x+y)+sqrt(((boundx-x)**2)+((boundy-y)**2));
```

Calculation of unscaled 90% bioequivalence confidence intervals:

```
PROC MIXED data=pk;
CLASSES SEQ SUBJ PER TRT;
MODEL LAUCT = SEQ PER TRT/ DDFM=SATTERTH;
RANDOM TRT/TYPE=FA0(2) SUB=SUBJ G;
REPEATED/GRP=TRT SUB=SUBJ;
ESTIMATE 'T vs. R' TRT 1 -1/CL ALPHA=0.1;
ods output Estimates=unsc1;
title1 'unscaled BE 90% CI - guidance version';
title2 'AUCt';
run;

data unsc1;
  set unsc1;
  unscabe_lower=exp(lower);
  unscabe_upper=exp(upper);
run;
```

GLOSSARY

AUC	Area under the curve
$AUC_{0\text{-}inf}$	Area under the curve extrapolated to infinity
$AUC_{0\text{-}t}$	Area under the curve from time zero to the last measurable time point
$AUC_{0\text{-}tau}$	Area under the curve for one dosing interval at steady state
C_{avSS}	Average plasma concentration at steady state
C_{max}	Maximum plasma concentration
C_{maxSS}	Maximum plasma concentrations during the dosing interval at steady state
C_{minSS}	Minimum plasma concentrations at steady state
Enantiomers	Two stereoisomers (molecules that are identical in atomic constitution and bonding but different in the three-dimensional arrangement of the atoms) that are related to each other by a reflection; they are mirror images of each other, which are nonsuperimposable. Every stereocenter in one has the opposite configuration in the other. Two compounds that are enantiomers of each other have the same physical properties, except for the direction in which they rotate the polarized light and how they interact with different optical isomers of other compounds.
pAUC	Area under the curve between two specific time points
λ_z	Terminal or elimination rate constant
Racemate	A racemate is optically inactive. Because the two isomers rotate plane-polarized light in opposite directions, they cancel out; therefore, a racemic mixture does not rotate plane-polarized light. In contrast to two separate enantiomers, which generally have identical physical properties, a racemate often has different properties compared to either one of the pure enantiomers. Different melting points and solubilities are very common, but differing boiling points are also possible. Pharmaceuticals can be available as a racemate or as a pure enantiomer, which might have different potencies.
T_{max}	Time to maximum observed plasma concentration
$t_{1/2}$	Half-life