U.S. FOOD & DRUG ADMINISTRATION

Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA

Lei Zhang, Ph.D.
Deputy Director
Office of Research and Standards
Office of Generic Drugs
CDER, U.S. FDA

Nilufer Tampal, Ph.D.
Associate Director of Scientific Quality
Office of Bioequivalence
Office of Generic Drugs
CDER, U.S. FDA

February 24, 2022

SBIA Webinar

Outline

- Objectives of the webinar
- Guidance history and scope
- Guidance overview
- Major changes
- Key topic areas with questions and comments received
- Responses to selected questions/comments
- Summary
- Panel discussion and Q&A

Webinar Objectives

- Provide an overview of the revised FDA draft guidance for industry titled *"**Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA**"* (Aug 2021)
- Describe the major changes in the revised draft guidance
- Provide clarification and rationale on selected topics to address comments received through the docket
- Understand how principles described in the revised draft guidance in conjunction with product-specific guidances and other pre-submission communications facilitate generic drug development and generic drug application assessment

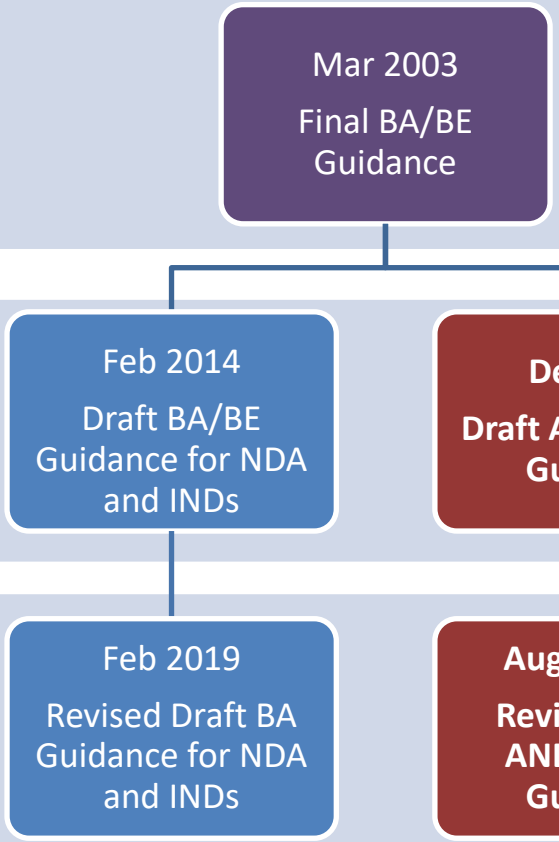
ANDA: Abbreviated new drug application

Guidance History

Covered both NDA and ANDA

Split into two guidances: One focused on new drugs and one focused on generic drugs

Both guidances have gone through revision since 2013 and 2014



Today's topic

NDA: New drug application; IND: Investigational New Drug; BA: Bioavailability; BE: Bioequivalence; PK: Pharmacokinetic

Scope of the ANDA PK BE Guidance

- Provides recommendations to applicants planning to include BE information in ANDAs and ANDA supplements
- Describes how to meet the BE requirements set forth in the Federal Food, Drug, and Cosmetic Act (FD&C Act) and FDA regulations
- Generally applicable to dosage forms intended for oral administration and to non-orally administered drug products in which **reliance on systemic exposure measures (PK endpoints) is suitable for establishing BE**, e.g., transdermal delivery systems and certain rectal and nasal drug products
- Also covers BE studies conducted during post-approval period for ANDAs

Relation to Other Relevant Guidances

- **Guidance: BA Studies for INDs and NDAs**
  - FDA recommends that applicants for INDs, NDAs, 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.
- **Product-Specific Guidances (PSGs)**
  - Reflect the FDA's current thinking and expectations on how to develop a generic drug product therapeutically equivalent to a specific reference listed drug (RLD).
  - FDA recommends ANDA applicants consult routinely published PSGs when considering the appropriate BE study and/or other studies for a proposed drug product.
  - Refer to Product-Specific Guidances for Generic Drug Development web page at https://www.fda.gov/drugs/guidances-drugs/product-specific-guidances-generic-drug-development for the most recent version of a PSG.
  - SBIA webinar on PSGs: FDA Product-Specific Guidances: Lighting the Development Pathway for Generic Drugs (May 2021)

Regulations, Guidances, and PSGs

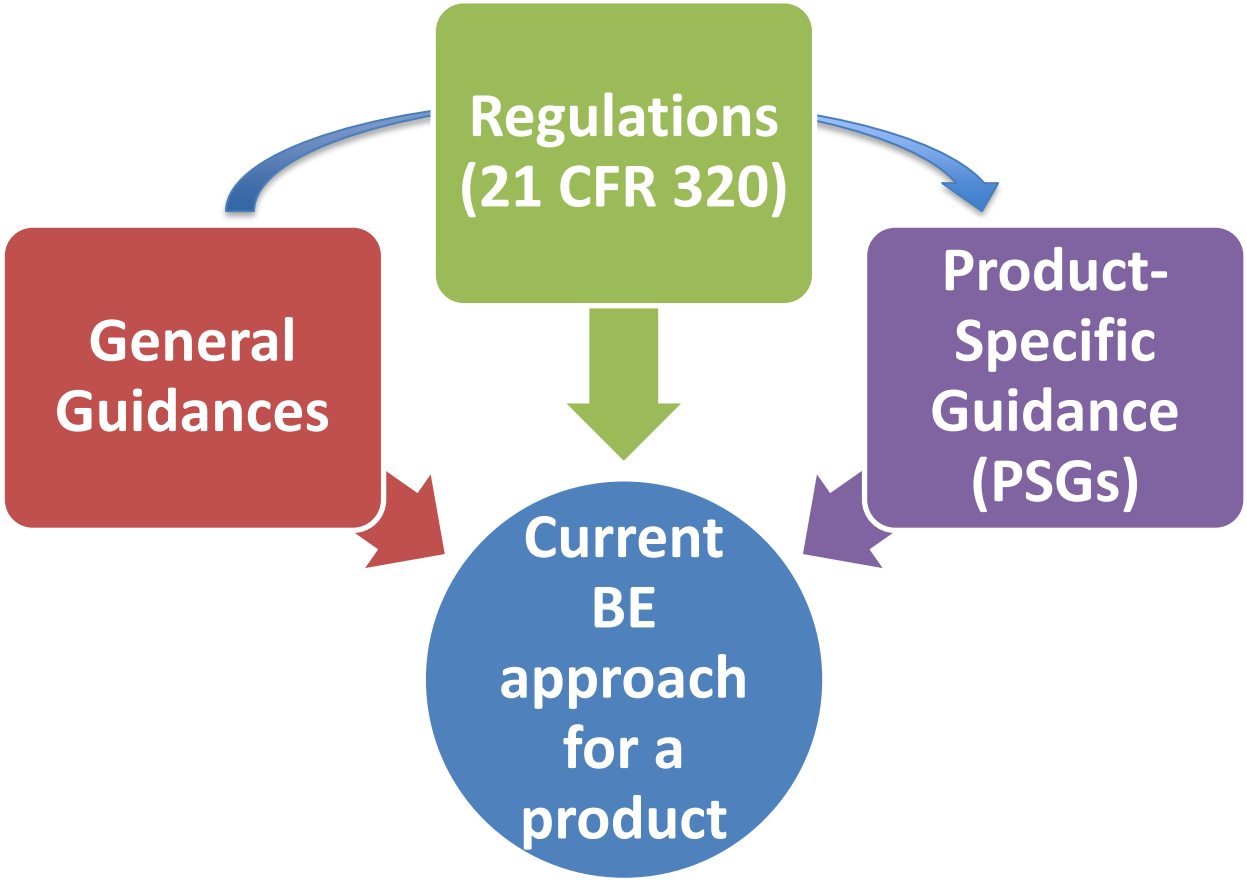


Table of Contents of 2013 and 2021 draft ANDA PK BE Guidance (1)

2013

2021

Table of Contents of 2013 and 2021 draft ANDA PK BE Guidance (2)

2013

2021

Table of Contents of 2013 and 2021 draft ANDA PK BE Guidance (3)

2013

2021

Table of Contents of 2013 and 2021 draft ANDA PK BE Guidance (4)

2013

2021

Overview of ANDA PK BE Guidance

- General BE Principles
  - *"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."*
- Both in vivo and/or in vitro methods can be used to establish BE
  - Comparative PK
  - In vitro tests predictive of human in vivo BA (in vitro-in vivo correlation (IVIVC))
  - Comparative pharmacodynamic (PD)
  - Comparative clinical endpoint
  - In vitro studies

Section 505(j)(8)(B)(i) of the FD&C Act. See also section 505(j)(8)(B)(ii) and 505(j)(8)(C) of the FD&C Act; 21 CFR 314.3(b); 21 CFR 320.23(b); 21 CFR 320.24(b)

Overview of ANDA PK BE Guidance

- Study design
  - Section III of the guidance
  - Appendix A: General Design and Data Handling of Bioequivalence Studies with PK Endpoints
    - Study conditions (fasting vs. fed)
    - Sample retention
    - Sample collection and sampling times (biological matrix)
    - PK information in submissions
    - Data analysis

Study Design

- Study populations
  - Healthy vs. Patients
  - Age, sex
- Study types (single dose or multiple dose, crossover or parallel, non-replicate or replicate), e.g.,
  - a two-period, two-sequence, two-treatment, single-dose crossover study design
  - a single-dose parallel study design
  - a single-dose replicate study design for BE studies
- Sample size
- Study conditions (fasting vs. fed, dose strength to be studied)
- Safety considerations

Replicate Study Design

- 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.
- A replicate design is recommended to be used under the following scenarios:
  - Highly variable drugs (Appendix B)
    - Either partial or fully replicate, reference scaled average BE
  - Narrow therapeutic index drugs (Appendix C)
    - Fully replicate, reference scaled average BE

More clarifications provided in the revised draft guidance

Fasting vs. Fed BE for Oral IR Products

Recommend Both Fasting and Fed BE Studies for All Oral Immediate Release (IR) Drug Products	
Fasting BE Studies Only	• Products should be taken on an empty stomach (per the RLD labeling) • Serious adverse events are anticipated under fed conditions
Fed BE Studies Only	• Serious adverse events are anticipated under fasting conditions

Fasting vs. Fed BE for Oral MR Products

Recommend Both Fasting and Fed BE Studies for All Oral Modified Release (MR) Drug Products, irrespective of dosing instructions in the RLD labeling	
Fasting BE Studies Only	• Serious adverse events are anticipated under fed conditions
Fed BE Studies Only	• Serious adverse events are anticipated under fasting conditions

Post-Approval Changes

- For post-approval changes generally, FDA recommends 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 reference listed drug (RLD) and not to the pre-change ANDA product.

- ***SUPAC-IR:*** *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)
- ***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)

U.S. FOOD & DRUG ADMINISTRATION

Summary of Major Changes in the Aug 2021 Draft ANDA PK BE Guidance

Major Changes (1)

- Updates and clarifies the content on Reference Listed Drug (RLD) and Reference Standard (RS) in the Orange Book and references new guidances

RLD and RS

- For 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**)
- An 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 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)

Major Changes (2)

- Expands content on “Study Population” with regard to sex (male/female) and age (pediatric and elderly)

Study Population: Sex

- 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.

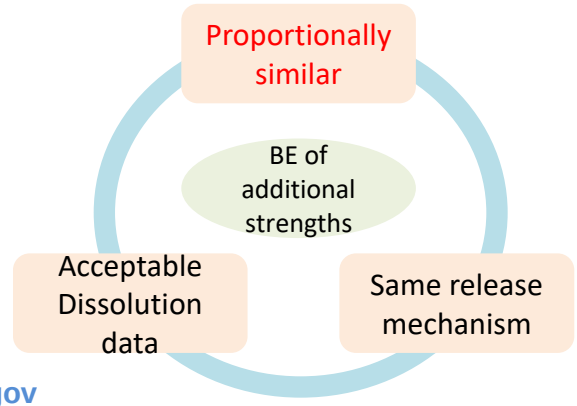
Study Population: Age

- 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.

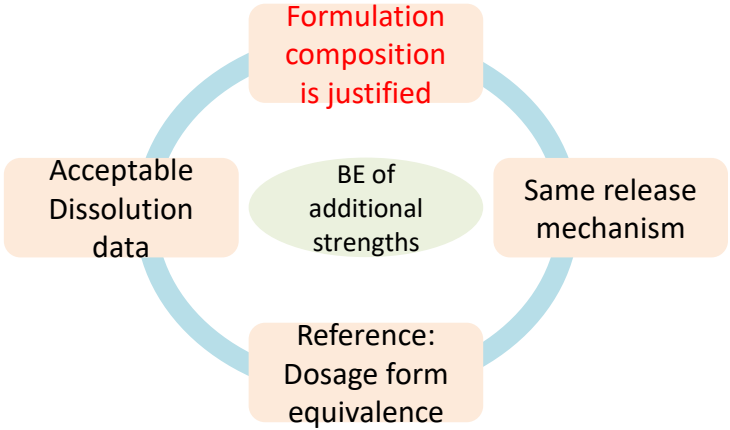
Major Changes (3)

- Modifies recommendations on how to assess proportional similarity for additional dose strengths for modified-release drug products based on formulation composition proportionality and mechanism of release

2013 Draft

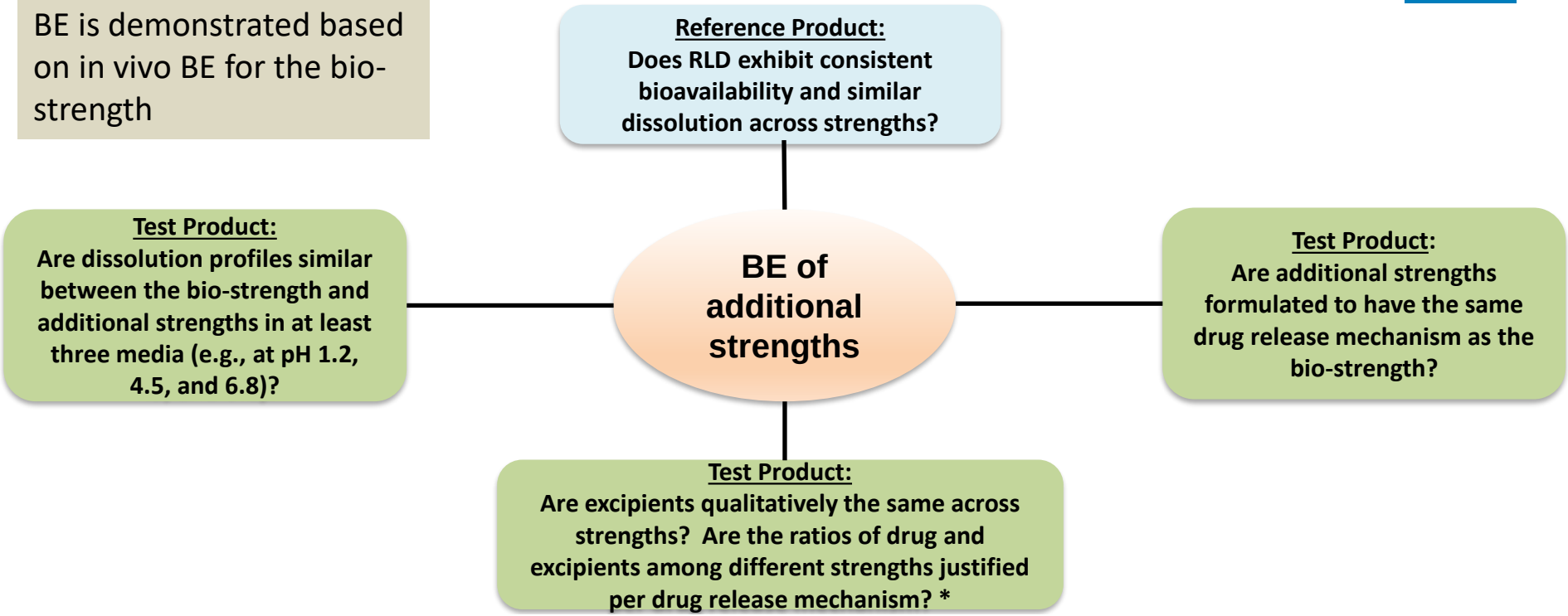


2021 Draft



Considerations in BE Demonstration for Additional Strengths of Oral MR Products

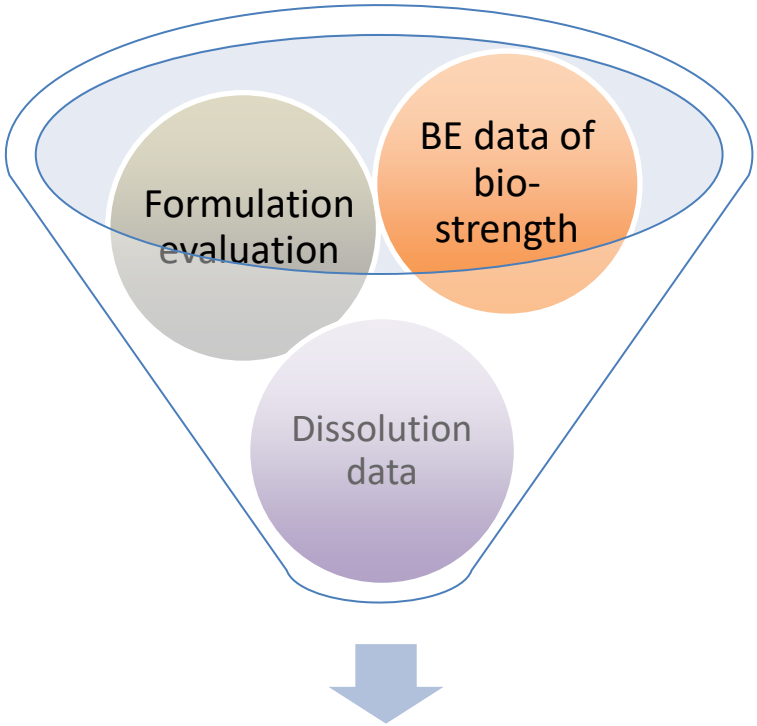
BE is demonstrated based on in vivo BE for the bio-strength



***Note**: Formulation composition proportionality may not be the only factor to determine the need for an in vivo BE study to demonstrate BE.

Modified from Sun & Wang, AAPS Webinar Dec 2020

BE Demonstration of Additional Strengths -Totality-of-Evidence



Sun & Wang, AAPS Webinar Dec 2020

Demonstration of BE for Additional Strengths: Modified Release (MR) Products

The following data may support BE for additional strengths for MR products per 21 CFR 320.24(b)(6):

- 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 (f2) 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).

Demonstration of BE for Additional Strengths: Modified Release (MR) Products

FDA recommends 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).

Major Changes (4)

- Adds sections on new dosage forms that also rely on systemic BE assessment (in addition to chewable tablets) under Section IV
  - Orally disintegrating tablets
  - Sublingual
  - Transdermal

Major Changes (5)

- Adds a section on alternative routes of administration, including products administered via a nasogastric (NG) tube or a gastric (G) tube under Section V
  - A new draft guidance related to this topic: FDA draft guidance for industry on *Oral Drug Products Administered Via Enteral Feeding Tube: In Vitro Testing and Labeling Recommendations* (June 2021)

Major Changes (6)

- Adds a new section on **handling of outliers** in Appendix A

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.
- 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.

Major Changes (7)

- Adds two new appendices (Appendices B and C) on reference scaled average BE analyses for highly variable drugs and narrow therapeutic index drugs, respectively
  - Previously included in PSG for progesterone oral capsules and warfarin sodium oral tablets, respectively

Major Changes (8)

- Removes the section related to “Orally Administered Drugs Intended for Local Action” in the 2013 draft guidance
  - This guidance is intended to focus on PK BE studies for drugs that are systemically acting.
  - Even though the section is not included in the Aug 2021 draft guidance, the following principle is still applicable:
    - In some cases, when a drug substance produces its effects by local action in the gastrointestinal tract, it may be appropriate to determine BE using PK endpoints. In other cases, it may be appropriate to determine BE using comparative clinical endpoints, pharmacodynamic endpoints and/or suitably designed and validated in vitro studies in addition to, or instead of, measuring drug plasma concentrations.
  - In the future, separate general guidances may be developed for locally acting oral drug products and other complex drug products in addition to PSGs.

Summary of Major Changes

- Updates and clarifies the content on Reference Listed Drug (RLD) and Reference Standard (RS) in the Orange Book and references new guidances
- Expands content on “Study Population” with regard to sex (male/female) and age (pediatric and elderly)
- Modifies recommendations on how to assess proportional similarity for additional dose strengths for modified-release drug products based on mechanism of release and dissolution profile similarity
- Adds sections on new dosage forms that also rely on systemic BE assessment (i.e., orally disintegrating tablets, sublingual, and transdermal)
- Adds a section on alternative routes of administration, including products administered via a nasogastric (NG) tube or a gastric (G) tube
- Adds a new section on handling of outliers in Appendix A
- Adds two new appendices (Appendices B and C) on reference scaled average BE analyses for highly variable drugs and narrow therapeutic index drugs, respectively
- Removes the section related to “Orally Administered Drugs Intended for Local Action” from the 2013 draft guidance

Key Topic Areas with Questions and Comments Received

Approximately 20 comments received

- Expand the scope of the guidance to include complex formulations
- Study populations
- BE studies with regard to food
- T_{max} comparison
- Additional strength waiver for IR
- BE demonstration for additional strengths of MR products
- Alcohol dose dumping
- Guidance on sample retention

Responses to Comments/Questions Received (1)

- Expands the scope of the guidance to include complex formulations like inhalation products, liposomal products, and vaginal creams

- Response: This guidance focuses on PK endpoint BE studies. The principle can be used to guide complex products if PK endpoint BE study is being used for BE demonstration. However, these complex products will contain additional data needed to support BE especially if they are locally acting. Currently, the PSG may be the best source to understand FDA's current thinking and expectations on how to develop a generic drug product therapeutically equivalent to their respective RLDs.

Responses to Comments/Questions Received (2)

- Can FDA provide further insights as to how FDA is defining “non-smoking”? Does non-smoking mean a subject that has never smoked or does it also include a subject that was a previous smoker or has had history of smoking but has stopped for a duration of time prior to the study?
- Response: Subjects who have never smoked are preferred. Subjects who have had history of smoking but have stopped for a duration of time (e.g., at least a year) prior to the study may be acceptable, especially for drugs that are not substrates of enzymes that are induced by smoking, e.g., CYP1A1, CYP1A2 or CYP2E1.

Responses to Comments/Questions Received (3)

- Is a statistical comparison required for T_{max} or is the magnitude of difference a subjective evaluation?

- Response: No, statistical comparison is not required for T_{max}. The T_{max} assessment is not subjective. Several approaches may be taken to evaluate the impact of significance of T_{max} difference of the Test and Reference products including clinical consideration. If the rapid onset is important, partial AUC may be calculated and subject to statistical comparison.

Responses to Comments/Questions Received (4)

- Line 813: “refer to guidance for industry on *Handling and Retention of BA and BE Testing Samples* (May 2004)”
  - Reference a more recent guidance for industry: *Compliance Policy for the Quantity of Bioavailability and Bioequivalence Samples Retained Under 21 CFR 320.38(c)* issued in Aug 2020

- Response: This comment is noted. The new guidance published in Aug 2020 clarifies the number of Test and Reference products to be retained under 21 CFR 320.38. This ANDA PK BE guidance does not touch on that aspect. Here, the ANDA PK BE guidance specifies the length of the time the samples need to be maintained per 21 CFR 320.63. The proper guidance is cited related to sample retention pertaining to this ANDA PK BE guidance.

Summary and Suggestion

- The ANDA PK BE guidance is the key resource for ANDA applicants where PK BE studies are used to support BE
- Refer to general guidances or PSGs for BE approaches for a specific product
- Submit questions via controlled correspondences (CCs) if need FDA's input before the study
- FDA provides multiple communication channels (such as CCs, product-development meetings, pre-submission meetings, mid-cycle review meetings, post-complete response letter meetings) at various stages to address industry's questions for generic drug development and regulatory approval

FDA's guidance for industry Controlled Correspondence Related to Generic Drug Development (December 2020)
FDA's guidance for industry Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA (November 2020)
FDA's guidance for industry Post-Complete Response Letter Meetings Between FDA and ANDA Applicants (December 2018)

Resources (1)

- FDA Guidances Webpage: https://www.fda.gov/drugs/guidance-compliance-regulatory information/guidances-drugs
- Guidance for Industry: Referencing Approved Drug Products in ANDA Submissions (Oct 2020)
- Guidance for Industry: Statistical Approaches to Establishing Bioequivalence (Feb 2001)
- Guidance for Industry: Bioanalytical Method Validation (May 2018)
- Guidance for Industry: M9 Biopharmaceutics Classification System-Based Biowaivers (May 2021)

Resources (2)

- PSGs for Generic Drug Development: https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm
- Guidance for Industry on Bioequivalence Recommendations for Specific Products (June 2010)
- SBIA webinar on PSGs: FDA Product-Specific Guidances: Lighting the Development Pathway for Generic Drugs
- FDA Product Specific Guidance Snapshot


FDA
U.S. FOOD & DRUG
ADMINISTRATION

BE Studies with PK Endpoints for Drugs Submitted Under an ANDA

February 24, 2022

Welcome

- Recording posted within 5 working days: www.fda.gov/cdersbialearn
- Download the slides at right
- Evaluation & Certificate **available for 2 weeks only (3/10/2022)**
- Certificate of attendance supports CEs from SOCRA, RAPS, SQA and ACRP **(download upon completion of survey)**
  - Details: www.fda.gov/cdersbia
- Additional tutorials available through: www.fda.gov/cderlearn

Get the Latest Regulatory Updates & Notifications for SBIA Webinars & Conferences

LinkedIn

Twitter

YouTube

SCAN ME

Hold phone camera to the image

Today's Presenters

Lei Zhang, PhD

Deputy Director

Office of Research and Standards (ORS)
Office of Generic Drugs (OGD) | CDER

Nilufer Tampal, PhD

Associate Director of Scientific Quality

Office of Bioequivalence (OB)
OGD | CDER

Panel Discussion

Moderator:

Lanyan (Lucy) Fang, PhD
Deputy Director
Division of Quantitative Methods and Modeling (DQMM)
Office of Research and Standards (ORS)
Office of Generic Drugs (OGD)

David Coppersmith, JD
Regulatory Counsel
Office of Generic Drug Policy (OGDP) | OGD

Myong-Jin Kim, PharmD
Division Director
Division of Therapeutic Performance II (DTP II)
ORS | OGD

Lei Zhang, PhD

Bing Li, PhD
Associate Director for Science
OB | OGD

Robert Lionberger, PhD
Director, ORS | OGD

Diana Vivian, PhD
Acting Associate Director
Division of Bioequivalence II (DBII) | OB | OGD

Liang Zhao, PhD
Division Director
DQMM | ORS | OGD

Nilufer Tampal, PhD

Panel Question 1

Can you comment on:

- How do FDA develop product-specific guidances (PSGs) in alignment with the general guidance?
- What if there are differences in recommendations between PSG and the general guidance?

Panel Question 2

Docket Comment: *Current FDA guidance recommends both fasting and fed BE for immediate release oral drugs. This is not aligned with other regulatory agencies.*

- What is your perspective on this comment received in the docket?

Panel Question 3

The revised guidance recommends applicants to include similar proportions of males and females in the study or provide a justification supporting the use of a single-sex population

- What are FDA's considerations that lead to this revision to recommend including the justifications for not including subjects of both sexes in a BE study?

Panel Question 4

The revised guidance recommends applicants to include as many subjects as possible at or above age 60 or provide justification if no subject at or above age 60 is included in the BE study if the drug product is predominantly intended for use in the elderly.

- What are FDA's considerations that lead to this revision to recommend including the justifications for not including older adult (elderly) subjects in a BE study?

Panel Question 5

The revised guidance recommends applicants to justify that the BE study results obtained from adult subjects are relevant to the pediatric population if the drug product is predominantly intended for use in pediatric patients younger than 6 years

- What are FDA's considerations that lead to this revision to recommend including the justifications for results obtained from adult subjects are relevant to the pediatric population for certain products?

Q&A and Resources

Click for:

- Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA
- Bioequivalence Recommendations for Specific Products
- Product-Specific Guidances for Generic Drug Development (main page)

Additional questions or comments? Email: CDERSBIA@fda.hhs.gov

Open Q&A begins shortly – type your questions in the Q&A pod now.

Click Here for Evaluation and Certificate

Learn about other resources from CDER Small Business & Industry Assistance:
Visit Our Website!

Closing Remarks

Robert Lionberger, PhD

Director

Office of Research and Standards (ORS)
Office of Generic Drugs (OGD)

SBIA Closing

- Recording posted within 5 working days: www.fda.gov/cdersbialearn
- Certificate of attendance supports CEs from SOCRA, RAPS, SQA and ACRP **(download upon completion of survey)**
  - Details: www.fda.gov/cdersbia
- Additional tutorials available through: www.fda.gov/cderlearn

Evaluation & Certificate

available for 2 weeks only (3/10/2022)