Introduction of Bioequivalence for Generic Drug Products

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Learning Objectives

- Refresh the concepts of pharmaceutical equivalence (PE) and bioequivalence (BE) for a generic drug product.

- Define a reference standard (RS) in abbreviated new drug application (ANDA) submission and Orange Book.

- Describe the general considerations in BE studies and Product-Specific Guidance (PSG).

- Describe the general considerations in BE studies with pharmacokinetic (PK) endpoints.

- List the drug products and their certain conditions for a waiver of the in vivo BE study requirement (Bio-waivers).

Outline

Generic Drug Products

- Therapeutical Equivalence (TE), PE, and BE
- ANDA submitted to FDA for generic drug products

Fundamental Concepts and BE Approaches

- Definition of Reference Listed Drug (RLD) and RS
- Different Types of BE Studies Recommended in PSG
- Overview and General Consideration in BE Study with PK Endpoint
- Waivers of In Vivo Testing (Biowaivers)

Generic Drugs and OGD

- Mission of the Office of Generic Drugs (OGD): "Ensuring **high-quality, affordable** generic drugs are available to the American Public."

- In the United States, 9 out of 10 prescriptions are filled by generic drugs. Compared to its brand-name (or innovator) drug product, average cost of a generic drug is 80-85% less.

21 CFR Part 314 - Generic Drugs

FDA

Pharmaceutical Equivalence (PE)	**+**	Bioequivalence (BE)	**=**	Therapeutic Equivalence (TE)
drug products in identical **dosage forms** and **route(s) of administration** that contain **identical amounts** of the identical **active drug ingredient**, that deliver identical amounts of the active ingredient over the identical dosing period, and meet the identical compendial or other applicable standard of identity, strength, quality, and purity		the absence of a significant difference in the **rate and extent** to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available **at the site of drug action** when administered at the same molar **dose under similar conditions** in an appropriately designed study		

Abbreviated New Drug Applications (ANDAs)

- ANDAs contain data which are submitted to FDA for the review and potential approval of generic drug products.

- 21 CFR 320.21(b): requires submission of evidence that the proposed drug product is **bioequivalent** to the reference listed drug or information supporting **waiver** of evidence demonstrating in vivo BE.

- 21 CFR 320.24(a)
  - FDA may require **in vivo or in vitro** testing, or both, to measure the bioavailability or establish the BE of specific drug products.
  - Applicants must conduct BE testing using the most accurate, sensitive, and reproducible approach available among those set forth in 320.24(b).

Overview and General Considerations

Fundamental Concepts and BE Approaches

Reference Drug Products

- "*Referencing Approved Drug Products in ANDA Submissions Guidance for Industry (**Oct 2020**)*": how to identify a reference listed drug (RLD) and reference standard (RS) and the basis of submission in an ANDA submission.

- **RLD**: the previously approved drug product to duplicate.

- **RS**: the specific drug product that will be used in conducting any in vivo BE testing required to support approval of ANDA.

- Basis of Submission (**BoS**): a basis for ANDA submission (including the name of RLD, dosage form and strength, and its application number) on Form FDA 356h.

Orange Book

- FDA's Approved Drug Products with Therapeutic Equivalence Evaluations

Mkt. Status	Active Ingredient	Proprietary Name	Appl. No.	Dosage Form	Route	Strength	TE Code	RLD	RS	Applicant Holder
RX	DICLOFENAC POTASSIUM	DICLOFENAC POTASSIUM	A213875	CAPSULE	ORAL	25MG	AB			AUROBINDO PHARMA LTD
RX	DICLOFENAC POTASSIUM	DICLOFENAC POTASSIUM	A204648	CAPSULE	ORAL	25MG	AB			BIONPHARMA INC
RX	DICLOFENAC POTASSIUM	DICLOFENAC POTASSIUM	A210078	CAPSULE	ORAL	25MG	AB			STRIDES PHARMA GLOBAL PTE LTD
RX	DICLOFENAC POTASSIUM	ZIPSOR	N022202	CAPSULE	ORAL	25MG	AB	RLD	RS	ASSERTIO THERAPEUTICS INC

TE evaluations Codes
- **AA, AN, AO, AP or AT**: no known or suspected BE problems.
- **AB**: actual or potential BE problems resolved with adequate in vivo or in vitro evidence supporting BE.
- **BC, BD, BE, BN, BP, BR, BS, BT, BX or B***: Drug products that FDA at this time, considers not to be therapeutically equivalent to other pharmaceutically equivalent products.

General Considerations in BE Study Design

- Release mechanism of drug substance from the drug product (e.g., immediate vs. extended release).

- Intended site of action (e.g., systemic vs. local acting drugs).

- Formulation design and composition (e.g., tablet vs. injection).

- Ability to measure drug availability systemically or at the site of action (e.g., plasma concentration vs. drug levels in the aqueous humor).

- Available in vivo and in vitro BE tests (e.g., dissolution test, in vitro binding test and in vitro skin permeation test).

Product-Specific Guidance (PSG) for Generic Drug Development

- [PSG](#): Agency's current scientific thinking on the most sensitive, accurate and reproducible approach to demonstrate BE of a generic product to a RS product (published in a quarterly manner).

- May recommend in vivo BE studies, in vitro BE studies or a combination of both.

- May also recommend a waiver route.

- Scientific justifications are needed if the applicant's proposed BE approaches deviate from PSG's recommendations.

# 21 CFR 320.24(b) - Types of Evidence to Establish Bioequivalence

- In vivo and in vitro approaches for the systemically acting drugs:
  - In vivo test in humans measuring active ingredient/active metabolite in appropriate biological fluid as a function of time (i.e., a comparative **pharmacokinetic [PK] study**).
  - In vitro test that has been correlated with and is predictive of human in vivo bioavailability data.
  - In vivo test in humans in which the acute pharmacological effect is measured (i.e., a comparative pharmacodynamic study).
  - Well-controlled clinical trails (e.g., BE study with comparative clinical endpoints).
  - In vitro test (e.g., a comparative dissolution test).
  - Any other method deemed adequate by the Agency.

Study Design for BE Studies with PK Endpoint

- "*Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted under an ANDA*" (**Aug 2021**): how to meet the BE requirements set forth in FDA regulations.

- Standard design: randomized, two-period, two-sequence, single-dose **cross-over** design.

- Alternative design: **parallel** design (substance with very long half-lives) and **replicate** design (partial and full).
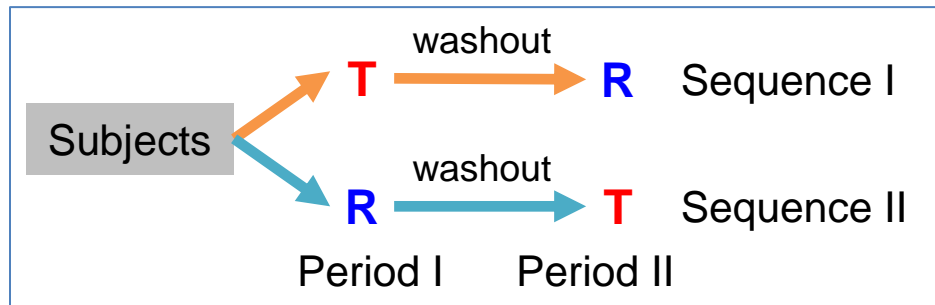
Study Design for BE Studies with PK Endpoint

- Two single-dose cross-over PK studies usually recommended for both immediate- and modified-release drug products:
  - One under **fasting** conditions: the most sensitive and accurate way to evaluate the formulation.
  - One under **fed** conditions: to assure the drug product performs the same way in the presence of high-fat, high-calories meal.
- Most studies use healthy normal male and female subjects; patients if there are safety issues.

- The subject number should be based on appropriate sample size calculation ($\geq$ 12 for general representive).

Analytical Considerations for BE Studies

- "*Bioanalytical Method Validation Guidance for Industry"* (**May 2018**): how to ensure the bioanalytical quality of BE data report.

- Standard Operating Protocols (**SOP**s) related to validation and analysis.

- Pre-study bioanalytical method **validation**:
  - Selectivity, specificity and sensitivity
  - Linearity, recovery, accuracy and precision
  - Long- and short-term storage stability
  - Dilution effects

- Study sample analysis with **quality** controls.

- Incurred sample reanalysis (ISR) to verify the **reproducibility**.

PK and Statistical analysis

- "*Statistical Approaches to Establishing Bioequivalence*" (**Feb 2001**): to provide equivalence criteria in analyzing in vivo or in vitro BE studies.

- PK parameters
  - **C_{max}**: the maximum observed concentration; trends to have higher variability; and need adequate sampling time points.
  - **AUC_{0-t}**: a measure of the total exposure of drug to the body up to the last sampling time.
  - **$AUC_{0-\infty}$**: a theoretical measure of the total exposure of drug to the body from administration till all the drug is eliminated.

PK and Statistical analysis

- Use ANOVA with two one-sided tests procedure to statistically analyze BE study data.

- **Average BE**: assess the variation in the average T and R difference among individuals; BE criteria are that the 90% confidence interval of AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} must fall within 80.00 to 125.00%.

> **The definition of BE**
>
> the absence of a significant different in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or alternative becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study.

Waivers of In Vivo Testing (Biowaivers)

- 21 CFR 320.22- a waiver of the in vivo BE study requirement maybe granted for the following products provided that certain conditions are met.

1) <u>Parenteral</u> solution for injection
   - if Qualitatively (Q1) and Quantitatively (Q2) the same as the RLD.

2) <u>Otic or ophthalmic</u> solution
   - if Q1/Q2 the same as the RLD.

3) <u>Oral/Topical/Nasal solution, elixir, syrup, tincture, a solution for aerosolization or nebulization or similar other solubilized forms</u>
   - if the formulation has the same API in the same concentration and dosage form as the RLD and does not contain any inactive ingredients affecting the drug absorption or availability.

Waivers of In Vivo Testing (Biowaivers)

4) Drug Efficacy Study Implementation (DESI)-effective drug products
   - The effectiveness of drugs that had been approved only for safety between 1938 and 1962 in U.S.
   - Determined to be efficacious by DESI panel.
   - A drug as either effective for its labeled indications or lacking substantial evidence of effectiveness for its labeled indications.
   - published in the Federal Register.
   - adequate dissolution data is required.

Waivers of In Vivo Testing (Biowaivers)

5) Biopharmaceutics Classification System (BCS)-based biowaivers
   – "M9 BCS-Based Biowaivers" (May 2021).
   – BCS: a scientific approach based on the aqueous solubility and intestinal permeability characteristics of the drug substance(s).
   – BCS Class I: high solubility, high permeability.
   – BCS Class III: high solubility, low permeability.

Demonstration of BE: Additional Strengths

6) <u>Non-biostudy strengths</u> of solid dosage forms
   - <u>Immediate-Release Products</u>: waived under 21 CFR 320.22(d)(2)
     - adequate in vivo BE study on the bio-strength.
     - adequate in vitro dissolution test across all strengths.
     - proportional similarity of the formulations across all strengths.
   - <u>Modified-Release Products</u>: demonstrated to be BE under 21 CFR 320.24(b)(6)
     - adequate in vivo BE study on the bio-strength.
     - adequate in vitro dissolution test across all strengths in at least three dissolution media (a pH of 1.2, 4.5 and 6.8).
     - Q1 sameness; Q2 similarity with justification (proportional as well as non-proportionally formulated strengths); same drug release mechanism across all strengths.

Summary

- A generic drug must be **PE** and **BE** (and thus TE) to the brand-name drug product.
- Related regulations and resources for development of generic drug products (e.g., **PSG**, Orange Book and Guidance Documents for Industry) are available to the public.
- **Comparative PK studies** (e.g., single-dose, cross-over BE studies) are mostly used for BE demonstration of systemically absorbed generic drug products.
- The applicants can request waivers of in vivo BE studies if their **bio-waiver** drug products meet FDA criteria.

Challenge Question #1

Which of the following study design is recommended for BE studies of a drug substance with a very long half-life?

A. Single-dose, Two-way cross-over Study Design

B. Single-dose, Parallel Study Design

C. Single-dose, Replicate Study Design

D. None of the above

Challenge Question #1

FDA

Which of the following study design is recommended for BE studies of a drug substance with a very long half-life?

A. Single-dose, Two-way cross-over Study Design

B. Single-dose, Parallel Study Design

C. Single-dose, Replicate Study Design

D. None of the above

Challenge Question #2

Which of the following drug product can NOT be considered for a biowaiver (waiver of in vivo testing)?

A. Parental solution for injection which is Q1/Q2 the same as RLD

B. Otic solution which is Q1/Q2 the same as RLD

C. Drug Efficacy Study Implementation (DESI)-effective drug products

D. Non-biostudy strengths of solid dosage forms with inadequate BE studies on the bio-strength

Challenge Question #2

Which of the following drug product can NOT be considered for a biowaiver (waiver of in vivo testing)?

A. Parental solution for injection which is Q1/Q2 the same as RLD

B. Otic solution which is Q1/Q2 the same as RLD

C. Drug Efficacy Study Implementation (DESI)-effective drug products

D. **Non-biostudy strengths of solid dosage forms with inadequate BE studies on the bio-strength**

Resources

- *Referencing Approved Drug Products in ANDA Submissions Guidance for Industry* (**Oct 2020**)

- *Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted under an ANDA* (**Aug 2021**)

- *Bioanalytical Method Validation Guidance for Industry* (**May 2018**)

- *Statistical Approaches to Establishing Bioequivalence* (**Feb 2001**)

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