Bridging the Difference: Bioequivalence Assessments for Suitability Petitions

SBIA 2022: Advancing Generic Drug Development: Translating Science to Approval

Day 2, Session 8: Enabling Generics: Changes to Suitability Petitions in GDUFA III

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Learning Objectives

- Describe what changes for an abbreviated new drug application (ANDA) can be made under a suitability petition.
- Discuss bioequivalence (BE) determination for ANDAs with an approved suitability petition regarding additional strengths of a drug product that are not part of the original reference listed drug (RLD).

Suitability Petitions Submitted for ANDAs

- An ANDA must be same as RLD:
  - Active ingredient(s)
  - Dosage form
  - Strength
  - Route of administration
  - Conditions of use and Labeling (with certain exceptions)

- Applicant may submit an ANDA for a drug product that is not the same as RLD
  - Submission of a petition under 505 (j)(2)(C) of the FD&C Act for differences between RLD and intended generic product is required prior to ANDA submission
  - Known as a **Suitability Petition**

Differences to a Drug Product Allowed by Suitability Petitions

- Different route of administration
- Different dosage form
- Different strength
- One active ingredient is substituted for one active ingredients in a combination drug

Case Study 1-Oral Tablets

Background

- RLD has two approved strengths: 500 mg and 750 mg
- The 750 mg strength is the reference standard (RS)
- Therapeutic Equivalence (TE) code: 'AA' (no known or suspected BE problems)
  - Both the 500 mg and 750 mg are DESI (drug efficacy study implementation) drugs
  - DESI drugs were approved between 1938-1962 for safety only but were later evaluated for effectiveness after 1962.
  - Waiver of in-vivo BE testing can be granted to DESI drugs pursuant to 21 CFR 320.22(c) if there is comparable dissolution data to the reference product.
- Current applicant has approved suitability petition for the **addition** of a 1,000 mg strength

Applicant's Assertion

- Applicant requested an *in-vivo* BE study waiver for 1,000 mg strength based on :
  - DESI designation of 500 mg and 750 mg strengths
    - 21 CFR § 320.22(c)*
  - Formulation proportionality
  - Comparable dissolution data
  - Claim of highly soluble and permeable drug product

*FDA shall waive the requirement for the submission of evidence measuring the in vivo bioavailability or demonstrating the in vivo bioequivalence of a solid oral dosage form (other than a delayed release or extended-release dosage form) of a drug product determined to be effective for at least one indication in a Drug Efficacy Study Implementation notice or which is identical, related, or similar to such a drug product under 310.6

Bioequivalence Evaluation

Supportive Evidence

- Compositionally proportional formulation between the 1,000 mg strength and 500 mg and 750 mg strengths
- Comparable *in-vitro* dissolution between 1,000 mg strength and 500 mg and 750 mg strengths

Unsupportive Evidence

- Drug product not shown to be highly soluble and permeable
- I*n-vivo* evidence of dose-proportionality from innovator was not performed.

Final Decision

- **Not Granted:** Waiver of bioequivalence in-vivo studies for the 1,000 mg strength (requested under suitability petition)

- Lack of adequate information to support BE:
  - DESI designation covers the strengths of RLD/RS only (500 mg and 750 mg)
  - Dose proportionality studies from the innovator were not performed
  - The drug product is not highly soluble or permeable

- **Instead, recommended fasting and fed BE studies - 1000 mg strength vs. 2 X 500 mg strength RLD/RS**

Case Study 2-Oral Tablets

Background

- RLD has two approved strengths: 50 mg and 100 mg
- The 100 mg strength is the RS
- TE code: ‘AB’ for the 50 mg and 100 mg strengths
- Applicant has approved suitability petition for **addition** of a 25 mg strength

Applicant's Assertion

- Requested *in-vivo* BE study waiver of 25 mg strength based on:
  - Formulation: 25 mg strength compositionally proportional to 50 mg and 100 mg strength
  - Comparable *in-vitro* dissolution data between 25 mg strength to 50 mg and 100 mg strengths
  - Acceptable BE studies conducted on 100 mg strength (RS)

Bioequivalence Evaluation

- Formulation of 25 mg strength deemed acceptable
- Acceptable fasting and fed BE studies on 100 mg strength (RS)
- Comparable *in-vitro* dissolution data between 25 mg, 50 mg and 100 mg
- Dose proportionality studies performed by innovator

Final Decision

- **Granted**: Waiver of BE *in-vivo* studies for 25 mg strength (requested under suitability petition)
  - Acceptable BE studies conducted on 100 mg strength (RS)
  - Comparable dissolution data
  - Compositionally proportional to 50 mg and 100 mg strengths

Summary

- Suitability petitions submitted for different strengths entails addition of strengths not included within the RLD strengths.

- Waiver of in-vivo BE study requirements for addition of non-RLD strengths relies on strong BE evidence

Challenge Question #1

Suitability petitions allow for the following except:

A. Different dosage form

B. Different strength

C. Different indication

D. Different route of administration

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Questions?

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