Developing and Implementing Science-Based Standards in Bioequivalence Assessment

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SBIA Webinar:

FDA Product-Specific Guidances: Lighting the Development Pathway for Generic Drugs

Topics for Discussion

- Role of Abbreviated New Drug Application (ANDA) Assessors in Product-Specific Guidance (PSG) Development
- Impact of Recommendations in PSGs on ANDA Assessments: Case Studies
- Alternate Bioequivalence (BE) Approach Proposal(s) to PSG Recommendations: Case Studies
- Summary

Role of ANDA Assessors in PSG Development

- Involved in development of new PSGs and revision of existing PSGs
- Prior to publication of PSGs,
  - Ensure alignment of the PSG recommendations with current ANDA assessment practices
  - Evaluate the impact of PSG recommendations on the pending and approved ANDAs

Impact of Recommendations in PSGs on ANDA Assessments: Case Studies

Case Study 1: Revised PSG, All Applicants Requested to Submit New BE Study

Drug Product: Oral Solid Extended-Release Capsules

PSG: Single-dose, in vivo crossover fasting and fed BE studies

Reference Listed Drug (RLD) Labeling Revision:

- As a post-marketing commitment, the RLD (NDA) applicant conducted a BE study comparing administration as whole capsules and as granules sprinkled on soft food such as applesauce
- The results of this study supported the labeling revision to recommend administration of granules with one tablespoonful of applesauce, as an alternative route of administration

NDA: New Drug Application

Case Study 1 (cont.)

Evaluating Impact on BE Recommendations based on New RLD Information:

- During the ANDA assessment, ANDA assessor evaluated this new information in the RLD labeling, and proposed to revise the PSG to add fasting sprinkle-in-applesauce BE study
- There were a number of approved and pending ANDAs. None of the ANDA applicants conducted fasting sprinkle-in-applesauce BE study
- The recommendation to add the fasting sprinkle-in-applesauce study is in alignment with scientific recommendations for similar cases and Agency's BE assessment practice

Case Study 1 (cont.)

Revised PSG: Added fasting sprinkle-in-applesauce BE study

Impact on Approved and Pending ANDAs: Yes, all the applicants were requested to:

- Submit fasting sprinkle-in-applesauce BE study
- Update the labeling to include new administration method: sprinkle on applesauce

Case Study 2: Proposal to Revise PSG, No impact on pending ANDAs

Drug Product: X, Novel Oral Anticoagulant (NOAC)

PSG for Drug Product X: 2-way in vivo crossover fasting and fed BE studies in healthy subjects

PSGs for Other NOACs – Due to steep exposure-response relationships for both efficacy and safety, PSGs recommend 4-way, fully replicate crossover *in vivo* BE studies, application of average BE approach (BE limits of 80-125%), and comparison of within-subject variability (upper limit of the 90% CI ≤ 2.5)

Case Study 2 (cont.)

Evaluation of PSG Revision for Drug Product X:

- PSG was revisited to determine whether revision is needed to be consistent with other NOACs
- ANDA assessor analyzed the data from ANDAs, NDA, and literature; and determined
  - Drug product X has different physico-chemical, safety/efficacy, and intra-/inter-subject variability than other NOACs
  - Overall, less safety concerns for drug product X as compared to other NOACs
  - Risks do not appear high enough to recommend additional BE data
- ANDA assessor coordinated with relevant Offices in CDER to reach a consensus decision that 2-way crossover design is appropriate for drug product X. This avoided the need for multiple applicants conducting new in vivo BE studies, without compromising BE standards

Case Study 2 (cont.)

Revised PSG: **Kept 2-way crossover design**, recommended additional clinical laboratory tests for inclusion criteria to ensure subject safety

Impact on Pending ANDAs: None

Alternate BE Approach Proposal(s) to PSG Recommendations: Case Studies

Case Study 3: Alternate BE approach

Drug Product: Topical Cream

PSG: Comparative clinical endpoint BE study

Applicant's Proposed Approach:

- Submitted a Pre-ANDA meeting request and **proposed an alternate in vitro approach** to demonstrate BE

Agency's Evaluation and Decision:

- Based on the submitted information, the **applicant's proposal** to use alternative BE approach was **deemed acceptable**
- The applicant submitted its ANDA with proposed in vitro BE approach, and subsequently the PSG was revised

Case Study 4: Alternate Study Population

Drug Product: Anticancer

PSG: In vivo BE study in cancer patients

Applicant's Proposed Approach:

- Submitted a Bio-IND proposing BE study in healthy subjects
- To support their proposal, the applicant provided the results of a number of studies conducted in healthy subjects performed in other countries

Agency's Evaluation and Decision:

- **Newly reported BE study data** indicated it is **safe to conduct BE studies in healthy subjects at the lowest feasible clinical dose**
- The applicant's proposal to conduct BE study in healthy subjects was deemed acceptable, and subsequently the PSG was revised

Bio-IND : Bio Investigational New Drug Application

Case Study 5: Alternate BE Study Design

Drug Product: Multiple

PSGs: In vivo **2-way crossover** BE studies

Query Pathway: Controlled Correspondences

Applicants' Proposed Approach:

- **Single moiety or fixed dose combination drug products:** Partial or fully replicate design, based on high variability observed in pilot BE studies
  - Data from all periods will be used for BE evaluation for all analytes
  - For fixed dose combination drug products, in some cases, proposal was to use data from
    - ✓ Only 1st two periods for BE evaluation for analyte 1
    - ✓ From all periods for BE evaluation for analyte 2

Case Study 5 (cont.)

Agency's Evaluation and Decision:

- Partial or fully replicate design may be used, but a reference-scaled BE analysis approach should only be applied to specific pharmacokinetic metrics that exhibit a high within-subject variability (≥30%) for the reference product in the pivotal BE study
- Use of partial or fully replicate study designs are generally acceptable alternatives for all PSGs that recommend two-period crossover studies
  - Applicants should consider if there are any safety concerns with additional dosing periods

Case Study 6: Alternate BE Approach for Lower Strengths

Drug Product: Extended-Release Solid Oral Dosage

PSG: In vivo BE studies on the highest strength. The lower two strengths may be deemed bioequivalent to the corresponding strengths of the reference product based on (i) acceptable BE studies on the highest strength, (ii) acceptable in vitro dissolution testing of all strengths, and (iii) proportional similarity of the formulation across all strengths

Query Pathway: Controlled Correspondence

Case Study 6 (cont.)

Applicant's Proposed Approach:

- All strengths (e.g., 10 mg, 15 mg, and 30 mg) of the **proposed generic drug product will not be developed as proportionally similar**, however, all strengths will have the **same qualitative composition**. Therefore, a **dosage strength equivalence assessment study was proposed** to meet requirements of the PSG
- In vivo BE studies on the highest strength (30 mg) and dissolution testing on all strengths will be conducted as per PSG
- Dose proportionality study design:
  - 3-way, single-dose, crossover in healthy subjects under fasting conditions
  - Each subject will receive different strengths (10 mg, 15 mg, and 30 mg) of test product at the same dose (i.e., 3 x 10 mg, 2 x 15 mg, and 1 x 30 mg) in a crossover way

Case Study 6 (cont.)

Agency's Evaluation and Decision:

- The RLD applicant also demonstrated dosage form equivalence among different strengths using similar approach
- The **applicant's proposal** to submit the ANDA using the proposed approach to demonstrate BE for the two lower strengths was **deemed reasonable**

Summary

- PSGs provide scientific recommendations in guiding industry to efficiently develop generic drug products
- PSGs describe the Agency's current thinking on a specific product and serve as guidelines for ANDA assessors in the evaluation of BE studies in ANDA submissions
- ANDA assessors employ a science-based approach in the assessment of BE study
- The applicants may use an alternative approach for their BE study, if it is scientifically justified, and satisfies the requirements of the applicable statutes and regulations
- The applicants are encouraged to discuss their alternative BE approach through appropriate pathways, such as Pre-ANDA meetings, controlled correspondences, general correspondences, etc.

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