Analysis of First-Cycle BE Adequacy and Major BE Deficiencies Encountered

Advancing Generic Drug Development 2024: Translating Science to Approval

Day (2), Session (6): (Ensuring Efficient and Consistent High Quality Generic Drug Development)

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Learning Objectives

- To explain the factors that could impact first-cycle bioequivalence (BE) adequacy based on observed BE deficiencies
- To identify recommendations that could potentially improve first-cycle BE adequacy

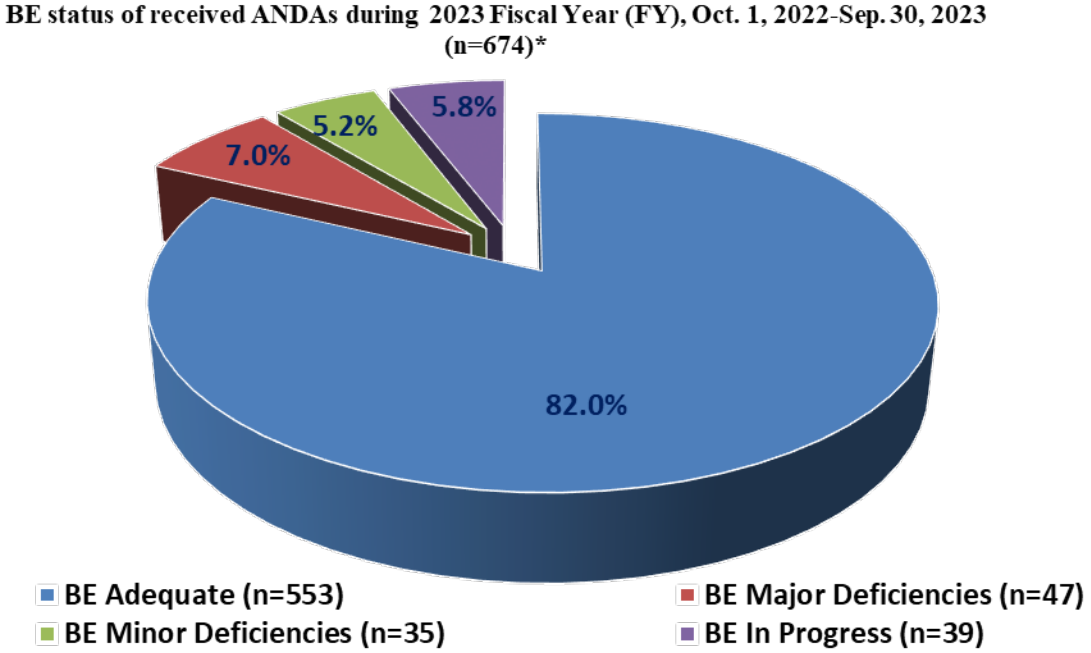
Outline

- Purpose
- Analysis of first-cycle BE adequacy rate
- BE deficiency types encountered
- Recommendations for improving first- cycle BE adequacy
- Summary

Purpose

- First-cycle BE adequacy can be key to minimizing the time to approval
- Given the above, we would like to share with you the first-cycle BE adequacy rate in GDUFA III, Year 1 along with a description of the types of deficiencies that led to an inadequate BE outcome in the first-cycle
- We hope that a description of these deficiencies along with tips on how to avoid these pitfalls may lead to first-cycle BE adequacy and thereby facilitate approval of your proposed drug product

Status of ANDAs Submitted During GDUFA III, Year 1



82 ANDAs were found to have either a major (n=47) or minor (n=35) inadequate BE deficiency outcome

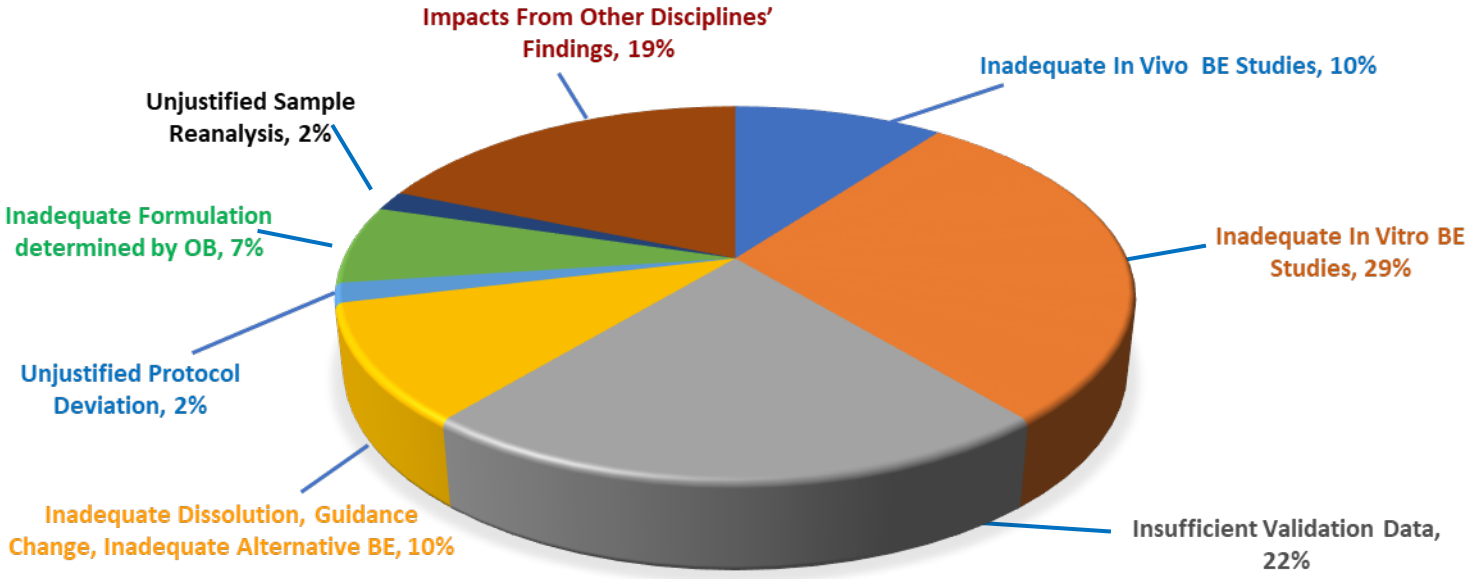
*Data presented here includes 674 ANDAs (total 729 submitted ANDAs -48 Refuse to Receive ANDAs -7 reviewed by other disciplines) as of 07/25/2024

First Cycle BE Adequacy Rate and Types of BE Deficiencies Encountered (GDUFA III, Year 1)

First Cycle BE Adequacy Rate (N=635)		
	First-cycle BE adequate	First-cycle BE inadequate
% (n)	87% (553)	13% (82)

- The first-cycle BE adequacy rate is 87% for 635 ANDAs assessed by Office of Bioequivalence (OB) with an outcome of either BE adequate/BE inadequate during 2023FY
- Out of 82 ANDAs with inadequate BE, 57% and 43% ANDAs were classified as having BE major and minor deficiency outcomes, respectively

Top Themes - BE Major Deficiencies*
(GDUFA III, Year 1, n=47 ANDAs)



Impacts From Other Disciplines' Findings Include:
Inadequate RRA (Remote regulatory Assessment) Findings
Inadequate Bio-batch due to API (Active Pharmaceutical Ingredient) Sameness Issues
Inadequate Formulation due to Excessive Excipients' Amounts Causing Safety Concerns
Inadequate Formulation due to Excipients with Unknown Safety Profiles
BE Waiver Request Denied due to Unacceptable User Interface Design

*Note:
1. N=59 deficiency themes, An BE inadequate ANDA may contain one or more deficiency themes (e.g., inadequate in vivo BE and inadequate in vitro BE study), therefore, the number of themes is greater than the surveyed BE inadequate ANDAs
2. The theme are based on Guidance for ANDA Submissions- Amendments to ANDAs Under GDUFA (July 2018)
3. Example for calculating the % of each theme: deficiency theme classified as inadequate in vivo BE Studies (n=6): 6/59 themes x 100% =10%

Case Scenario #1 of BE Major Deficiencies

- For a RSABE* statistical approach, both of the following conditions must be satisfied:
  1. The 95% upper confidence bound must be ≤ 0 (numbers should be kept to a minimum of four significant figures for comparison).
  2. The point estimate of the Test/Reference geometric mean ratio must fall within [0.8000, 1.2500].
- The submitted statistical results failed to meet RSABE acceptance criteria #2, i.e., applicant calculated T/R ratio as 1.25 (only two decimal places) while assessor confirmatory calculation was 1.2525 (four decimal places)
- Recommended to submit a new in vivo BE study
- **Tip:** Follow the specific recommendation for the RSABE statistical approach in the PK BE guidance (August 2021)**

*RSABE: Reference-scaled average bioequivalence
**Draft guidance for industry Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA (August 2021)

Case Scenario #2 of BE Major Deficiencies

- **BE study unacceptable due to unacceptability of the bio-batch**
  - **OPQ's deficiency:** *"…As per "Guidance for Industry – Alternate Source of the Active Pharmaceutical Ingredient in Pending ANDAs", the original exhibit batches, including the Bio-batch, are not acceptable"…*
  - **OB's deficiency:** *"The in vivo fasting and fed BE studies conducted on the bio-batch (#xxxxx), which has not been found to be acceptable by the OPQ. Consequently, all in vivo BE studies and in vitro dissolution data in support of your waiver request for the lower strengths are also not valid. The deficiencies related to the drug product portion of your submission have been communicated to you by the OPQ, please address any outstanding deficiencies related to your drug products. Alternatively, new in vivo BE studies and in vitro dissolution testing are recommended."*
- **Tips:**
  - **Wisely select your API supplier, ensure drug product quality and stability, and maintain manufacturing site compliance**

Additional Examples of BE Major Deficiencies

Theme	BE major deficiencies	Tips that could potentially avoid the deficiency
Inadequate In vitro BE testing	Missing in vitro BE studies [Nasogastric (NG) tube testing]	Check the RLD labeling for tube usage
Insufficient Validation Data	Inadequate statistical demonstration of the discriminatory ability of the in vitro release testing (IVRT) method	Check the relevant general guidance and product-specific guidance (PSG) for identifying an appropriate statistical method (e.g., model independent approach)
Inadequate In vitro Dissolution Testing	Inadequate in vitro dissolution testing due to aged or expired batches	Conduct dissolution testing on fresh lot or ensure the test product stability at the time of the dissolution study.
Unjustified Protocol Deviations	Exclusion of concentration data of subject in BE statistical analysis without justification	Submit the investigation report with real-time evidence to support exclusion
Inadequate Formulation	The presence of FDA unapproved color additives in the formulation	Use CFR-listed color additives
Unjustified Sample Reanalysis	Repeat concentrations had high % differences from the respective original concentrations without justification	Provide justification with supporting documentation/data

Recommendations for Avoiding BE Deficiencies

Check if BE study report/data are complete and consistent before submission:

- sufficient validation report
- pre-established SOPs with scientifically sound criteria
- scientifically sound justification for any protocol deviations on the impact of BE study outcome
- inclusion of quantitative breakdown or DMF# of colorants, flavors, inks, capsule shells, etc.
- dissolution data generated using a discriminating method
- SAS data in proper format and data in SAS file match data presented in BE study report

Additional Suggestions to Increase Chances of a First-Cycle BE Adequate Outcome

- Monitor new recommendations from new/revised PSGs [i.e., original PSG includes one option (in vivo BE study) whereas revised PSG includes two options]
- For challenging issues, new study design, or complex drug products, seek the Agency's recommendation /clarification on your BE strategy prior to submission
- You may propose alternative approaches to demonstrating BE provided that they are scientifically justifiable and comply with the applicable statutes and regulations

Challenge Question #1

What was the first-cycle BE adequacy rate for ANDAs assessed by OB in FY 2023?

A. 13%

B. 57%

C. 87%

D. 82%

Challenge Question #2

In which of the following scenarios could a bio-batch still be considered acceptable?

A. API source change due to cGMP compliance issue

B. The capsule of bio-batch stained with black spots by Teflon

C. Aged bio-batch with appropriate stability data

D. The bio-batch contains FDA unapproved color additive

Summary

- Our data indicates that approximately 87% of ANDAs submitted and assessed by OB in GIII FY1 (i.e., n=553) were found BE adequate and 13% of said ANDAs (i.e., n=82) were found BE inadequate in the first-cycle BE assessment
- Out of 82 ANDAs with a BE inadequate outcome, 47 ANDAs (57%) were classified as having BE major deficiencies
- Consider the recommendations in this presentation, including engagement with the Agency through the appropriate communication channels (e.g., Controlled Correspondence or pre-ANDA meetings), to improve the chances of application attaining a first-cycle BE adequate outcome

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To bring effective and safe generic drug products to the American people is not merely a job, but a great honor. - Fang Lu Ph.D., September 25, 2024