

Common Bioequivalence Information Requests: Tips for Facilitating the Review Process

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Generic Drug Forum 2025
April 10, 2025

Learning Objectives

- To present deficiencies that may trigger information requests (IRs)
- To identify the actionable recommendations that could potentially avoid these deficiencies, which may reduce the number of assessment cycles to achieve BE adequacy

Outline

- Purpose
- An overview of issued IRs
- Types of observed deficiencies
- Tips for avoiding these pitfalls
- Summary

Purpose

- Under the GDUFA III commitment letter¹, FDA agreed to promote transparency and communication between FDA and ANDA applicants for improving predictability and effectiveness of the review process
- We would like to share with common themes that we observed in IRs issued in GDUFA III, Year 1
- We hope that a description of these deficiencies along with tips on how to avoid them will facilitate approval of your proposed drug product

CRL, DRL and IR²



- Complete Response Letter (CRL), “*will be issued after the complete assessment of a received ANDA by **all appropriate disciplines**.*”
- Discipline Review Letter (DRL), “*is a letter used to convey FDA’s preliminary thoughts on possible deficiencies found by **a discipline** assessor and/or assessment team.....*”
- Information Request (IR), “*is a letter.....to **request further information or a clarification** of the information already provided.....*”

Issuance and Use of an IR²

- An IR is a request for further information or clarification that is needed or would be helpful to allow completion of the discipline assessment
- FDA may issue IRs before the completion of a discipline assessment and at any time in subsequent assessment cycles
- Late Cycle Information Request (LCIR)³ issued after the mid-cycle of an original ANDA or less than 90 days from the goal date for any ANDA amendment

Findings: Issuance of an IR or LCIR

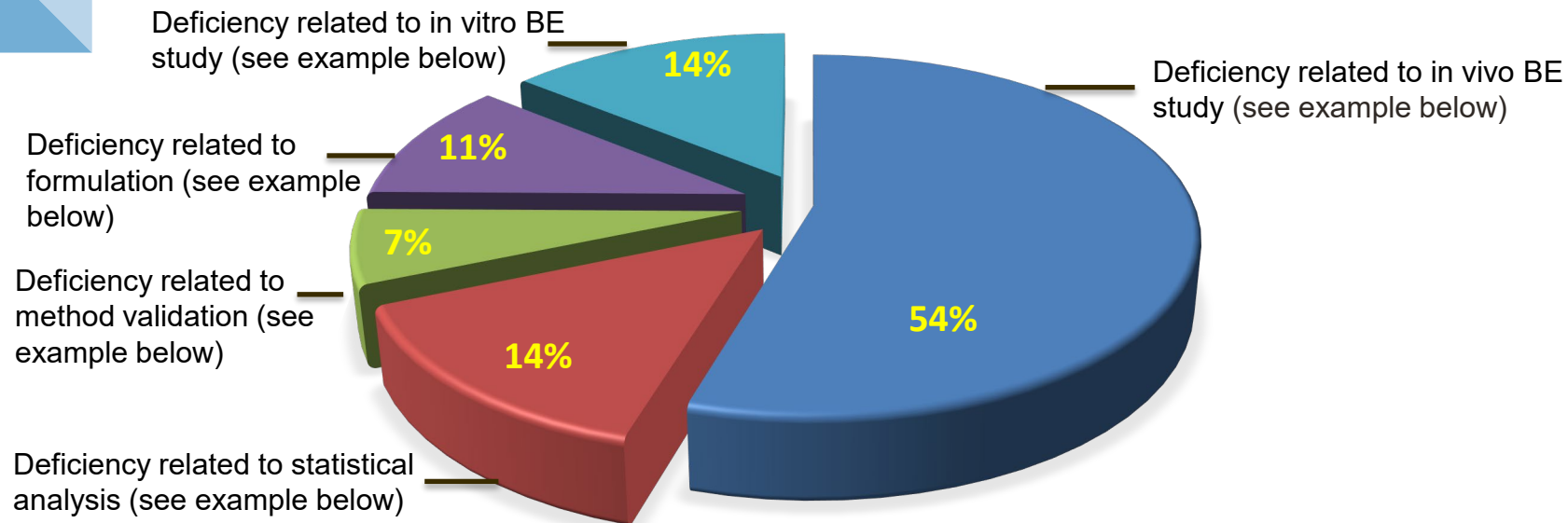
Out of ANDAs submitted during GDUFA III Year 1 and assessed by OB:

- 16.1% of ANDAs were issued BE-IRs asking for additional information/clarification, before the mid-point of the first assessment cycle
- 1.6% of ANDAs were issued BE-LCIRs, after the mid-point of the first assessment cycle

Findings: Deficiency Types in IRs

- Most issued IRs (78%) contained only one deficiency
- All issued IRs were identified as containing only minor deficiencies, except for one which contained a major deficiency

Findings: BE deficiency types listed in BE-IR/LCIR* (GDUFA III, Year 1, n=122 deficiencies)



Example for each deficiency type:

Missing the composition of non-standard FDA meal - in vivo BE
Missing information for IVRT testing (i.e., temperature) - in vitro BE
Missing SOPs -method validation
Missing information for breakdown of flavor -formulation
Missing the sequence column in SAS dataset - statistical

***Note:**

1. N=122 deficiencies, An IR may contain one or more deficiency (e.g., incomplete SAS datasets and missing SOP)
2. Example for calculating the % of each deficiency type: deficiency type classified as inadequate in vivo BE Studies (n=66): $66/122 \times 100\% = 54\%$

Case Scenario #1 of BE-IR deficiency related to statistical analysis



- The SAS datasets submitted in eCTD Sequence 0001, Module 5, were incomplete (a mock deficiency):
 1. *Based on your study report, a total of 1800 samples were analyzed. However, both adpc.xpt and pc.xpt files only contain 1700 rows. Many samples have concentrations of analyte in the bioanalytical report, but the values were not included in the SAS datasets*
 2. *The SAS.xpt datasets for your BE studies did NOT include the column of actual sampling time and period (1,2,3,4)*
- **Tip:** Please verify your datasets (adpc.xpt and adpp.xpt) and include accurate and complete information with all analyzed data

Case scenario #2 of **BE-IR deficiency related to formulation**



- **Example deficiency:** *Color ink was used in the capsule shell of your test product. However, we can not locate the composition table of color ink used in your test product. Please provide the missing information*
- **Tip:** Submit quantitative breakdown or DMF# of colorants, flavors, inks, capsule shells, etc.

Case scenario #3 of BE-LCIR deficiency related to in vitro study



- **Example deficiency:** *The method used in the IVRT studies including testing for the filter optimization. Please provide detailed information of the filter used in filter optimization testing including but not limit to, sharp and pore size*
- **Tips:**
 - Suggest submitting a complete written response to the LCIR by due date
 - Avoid including the gratuitous information not requested by FDA in the response, which may have an impact on the pre-set goal date

Additional examples of BE-IR deficiencies

Deficiency Type	BE-IR deficiencies	Tips that could potentially avoid the deficiency
Related to In vivo BE study	Exclusion of concentration data of subject in BE statistical analysis without justification	Submit the investigation report with real-time evidence to support exclusion
Related to statistical analysis	Statistical datasets are not in CDISC compliant format	Check the information submitted is in line with the requirements before submission
Related to In vitro Testing	Discrepancy between the in vitro testing date in the summary table and the study report	Verify that accurate information were entered in summary table or study report
Related to Formulation	Clarify the units (mg/mL or mg/5 mL) of excipient listed in the formulation	Verify the accuracy of the components and composition table
Related to method validation	Not able to locate SOPs for bioanalytical method validation	Provide the SOP that was effective at the time of bioanalytical method validation

Considerations to increase chances of a first-cycle BE adequate outcome

- Agency strongly encourages applicants to submit high quality, complete applications
- Generally, the number and magnitude of deficiencies that FDA identifies in an application correlate to the number of assessment cycles²
- Application quality and applicant responsiveness are key factors in whether IRs have maximized value for a particular application

Recommendations for avoiding IR deficiencies

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

- Provide the study date, number, study site name, and address
- Include pre-established SOPs with appropriate criteria
- Submit scientifically sound justification for any protocol deviations on the impact of BE study outcome
- Enter accurate and correct information (e.g., expiry date and testing date) when preparing summary tables and verify consistency between summary tables and the study report (i.e., Case Report Form, Certificate of Analysis)
- Ensure SAS data are in appropriate format and data in SAS file match data presented in BE study report

Tips for responding to an IR or LCIR

- Suggest providing a complete written response to an IR/LCIR by the response due date or earlier. A partial response, facsimile, or e-mail response will not be accepted
- Recommend including the appropriate attachment(s) along with the cover letter for your submission to help FDA ensure that your submission is properly triaged and assigned to the appropriate discipline

Challenge Question #1

What % of ANDAs assessed by OB in GDUFA III, Year 1 were issued IRs/LCIRs asking for clarification/additional information?

- A. 8%
- B. 18%
- C. 28%
- D. 38%

Challenge Question #2



In which of the following scenarios could an IR/LCIR be considered to have maximized value for a particular application?

- A. Providing a complete written response to an IR/LCIR by the response due date
- B. If resolved, using an IR/LCIR could lead to BE adequacy in the current assessment cycle.
- C. Application quality and applicant responsiveness
- D. All of above

Summary

- Out of ANDAs assessed by OB in GIII FY1, ~18% ANDAs were issued BE-IRs/LCIRs in the first review cycle asking for additional information /clarification
- Application quality and applicant responsiveness to IR are key factors to improve the chances of application attaining a BE adequate outcome

Acknowledgments



- **Dr. Srilaxmi Musunuri**, Project Manager of DBPM/OB/OGD
- **Dr. Utpal Munshi**, Director of DBI/OB/OGD
- **Dr. Rong Wang**, Associate Director of DBI/OB/OGD
- **Dr. Bing Li**, Associate Director of OB/OGD
- **Dr. Partha Roy**, Director of OB/OGD
- **All OB Assessors and Project Managers**



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., April 10, 2025

Useful Regulatory Reference Resources

1. GDUFA III Commitment Letter:
<https://www.fda.gov/media/153631/download?attachment>
2. Guidance for industry: [Information Requests and Discipline Review Letters under GDUFA](#) (October 2022)
3. MAPP: [Issuance of Information Requests and/or Discipline Review Letters for ANDAs](#) (October 2022)