Data Integrity and Data Quality Issues in Abbreviated New Drug Applications

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Disclaimer:

This presentation reflects the views of the presenter and should not be construed to represent FDA's views or policies.

Learning Objectives

- ✓ Provide the fundamental principles of data integrity in Abbreviated New Drug Applications (ANDAs)
- ✓ Recognize the roles and responsibilities of sponsors, investigators, and Contact Research Organizations (CROs) in maintaining data integrity throughout the study lifecycle
- ✓ Highlight case studies, identify common data anomalies, and integrity issues
- ✓ Comprehend FDA's regulatory response to data integrity violations

Data Integrity Definition

Data integrity refers to the accuracy, completeness, and reliability of the data throughout its lifecycle. The ALOCA principles should be followed:

- **A** Attributable- Clearly linked to the person who generated it
- **L** Legible- Readable and understandable
- **C** Contemporaneous- Recorded at the time the activity was performed
- **O** Original- The first recording, or a true verified copy
- **A** Accurate- Free from errors and truthful

Ensuring data integrity is fundamental to maintaining quality, compliance, and trust in the regulatory process.

Draft FDA Guidance for Industry: Data Integrity for In Vivo Bioavailability and Bioequivalence Studies (https://www.fda.gov/media/177404/download, April 2024)

Data Integrity: Foundation for Regulatory Decision-Making and Public Health Protection

Why Data Integrity Matters

- ✓ Ensure the safety, efficacy and quality of drug product
- ✓ Supports the FDA's ability to evaluate drug applications and protect public health
- ✓ Represents a key responsibility of pharmaceutical companies and CROs

Consequences of Poor Data Quality

- ✓ Undermines the FDA's ability to conduct appropriate regulatory analyses
- ✓ May result in FDA Untitled Action Letters issued to CROs
- ✓ Can lead to medication failure or delays in access to generic drugs
- ✓ Causes loss of credibility and financial burden from repeat studies and third-party audits

FDA Notifications Regarding Data Integrity Concerns

Year	Contract Research Organization
2011	Cetero Research at Houston, USA
2016	Semler Research at Bangalore, India
2021	Panexcell Clinical Lab at Mumbai, India
2021	Synchron Research Services at Ahmedabad, India
2024	Synapse Labs. Pvt. Ltd at Pune, India
2025	Raptim Research Ltd at Mumbai, India

Notification to Pharmaceutical Companies: Clinical and Bioanalytical Studies Conducted by Panexcell Clinical Lab or Synchron Research Services Are Unacceptable

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Ensuring Data Integrity in Application Submission

Investigator Responsibilities

- ✓ Allow monitoring, auditing, and regulatory inspection
- ✓ Provide direct access to study records
- ✓ Maintain procedures to ensure integrity of study activities
- ✓ Update processes to maintain compliance

Sponsor Responsibilities

- ✓ Implement quality assurance/quality control systems and written standard operating procedures
- ✓ Ensure bioavailability /bioequivalence studies comply with protocol and regulations
- ✓ Maintain access to sites, source documents, and reports
- ✓ Apply quality control across all stages of data handling

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e6r2-good-clinical-practice-integrated-addendum-ich-e6r1

FDA Inspection Classification – Office of Study Integrity and Surveillance (OSIS)

- OSIS reviews inspection findings to assess compliance and potential data integrity concerns. Based on the evaluation, inspections are classified into three categories.

No Action Indicated (NAI)	Voluntary Action Indicated (VAI)	Official Action Indicated (OAI)
No objectionable conditions or practices observed	Objectionable conditions or practices observed	Regulatory and/or administration actions are recommended
Facility in an acceptable state of compliance	Facility can voluntarily correct deficiencies	Unacceptable state of compliance

- OAI classification indicates significant corrective actions and remediation efforts to address identified deficiencies, including data integrity issues.

Office of Bioequivalence Review Division: Data Integrity Assessment

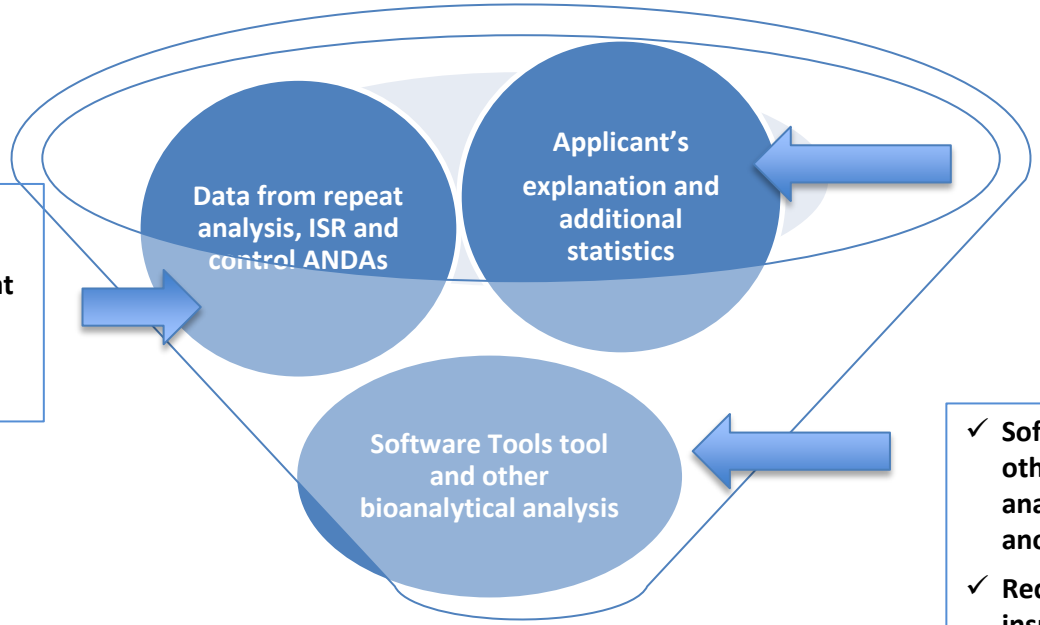
Primary Responsibilities

- ✓ Evaluate whether the data submitted in the application are reliable
- ✓ Request a “For-Cause Inspection” if potential data integrity concerns are identified
- ✓ Initiate further investigation when data anomalies are detected

Examples of Potential Data Anomalies

- ✓ Unusually similar pharmacokinetic (PK) profiles or unusual PK trends
- ✓ Suspicious of switching test and reference standard and /or making dilution to make study pass BE criteria
- ✓ Questionable repeat analysis

Systematic Investigations for Study Data



ANDAs for the same drug with bioanalysis done at other sites were used as reference (controls)

Applicants were asked to explain the observed data anomalies

- ✓ Software Tools and other bioanalytical analysis to detect data anomalies
- ✓ Requesting For-cause inspection

Systemic Data Integrity Concerns

Case Studies

Case Study #1 Data Discrepancy (Hypothetical Data)

- ✓ Suspected deliberate bias in fasting study data due to discrepancies in reported concentration values across multiple reports. For example, subject A with the reference treatment

Sampling Time Points (hr)	Reported Values in the Analytical Raw Data (μg/mL)	Reported Values in the SAS Dataset (μg/mL)	Reported Values in the Analytical Report (μg/mL)
0.25	42.207	51.966	25.894
0.5	45.979	59.054	29.532
0.75	42.937	57.244	28.596
1.0	39.014	51.872	26.067

- ✓ Corrected concentration values showed the study failed to meet bioequivalence

- ✓ Critical for CROs to have a robust Quality Management System

Case Study #2: Data Anomalies

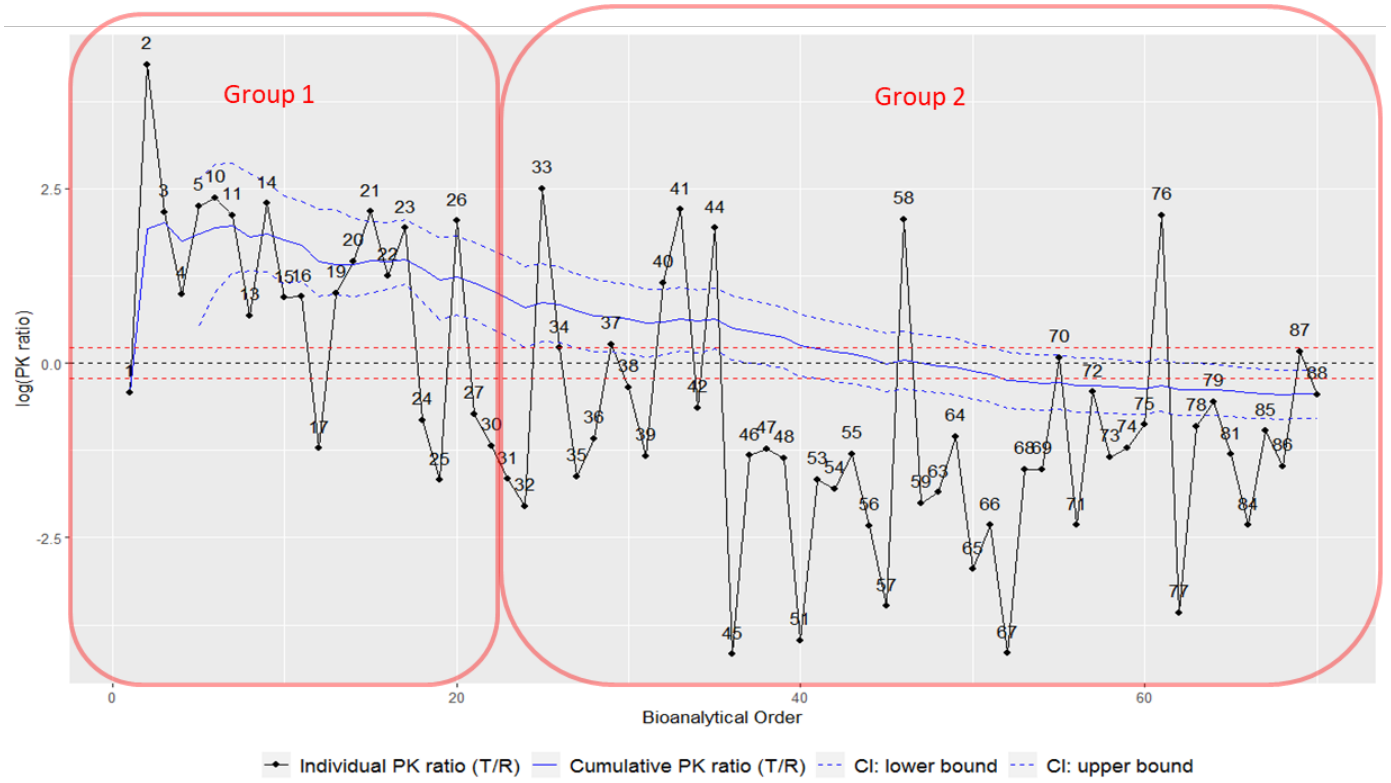
- ✓ Fasting study: two groups dosed one week apart at the same clinical site.
- ✓ Suspected switching or swapping of subjects' test or reference samples between two groups, either during dosing, sample collection, or sample analysis.

PK Parameters	Arithmetic Means Group 1 (#1- 30)		GMR T/R	Arithmetic Means Group 2 (#31- 86)		GMR T/R
	Test	Reference		Test	Reference	
Cmax (ng/mL)	1342	416	**2.86**	465	1094	**0.32**
AUC0-t hr (ng.h/mL)	3036	1227	**2.77**	1238	2730	**0.36**

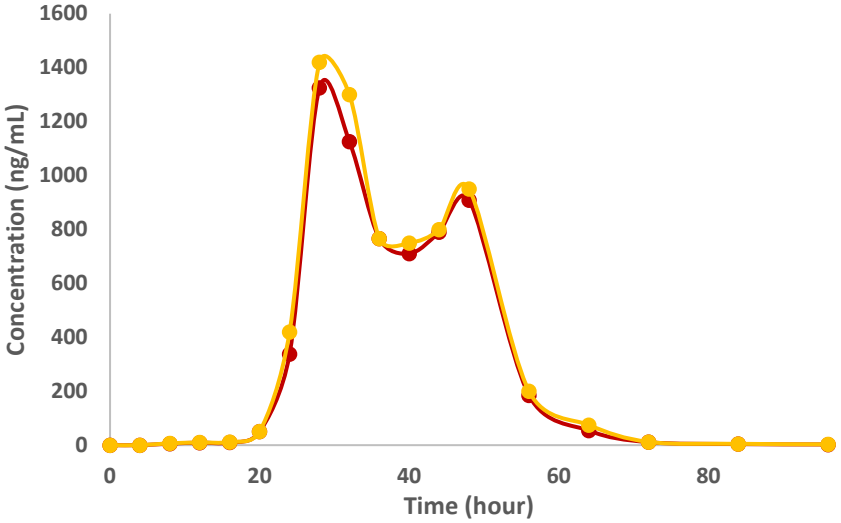
- ✓ Applicant voluntarily proposed repeating the fasting study at a different CRO site but did not provide an explanation for the differences in treatment effect between the two groups.

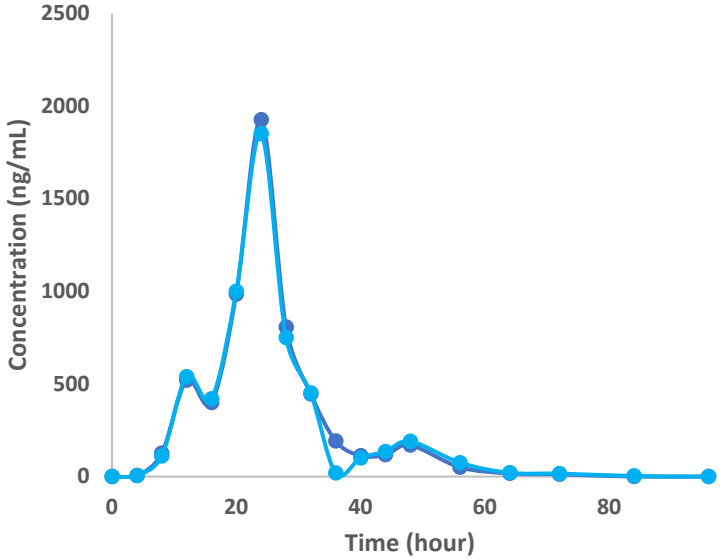
Case Study: #2: Data Anomalies

Plot of Cmax Ratio in Log Scale in the Order of Subject IDs



Case Study #2: Examples of Matching Concentration-Time Profiles in the Laboratory Notebook





- ✓ Overlapping PK profile pairs observed across subjects from two dosage groups .
- ✓ OSIS found a notebook documenting subject pairs that had nearly identical concentration-time profiles.
- ✓ Additional cases of unusual PK trend and/or overlapping profile identified at Analytical site A. OSIS recommended further Review Division investigation.
- ✓ FDA site classification: OAI

Case Study #2: Totality of Evidence By Review Division

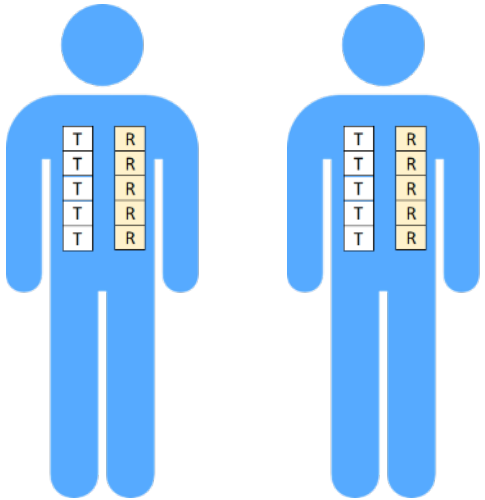
- ✓ Evaluated all ANDAs with studies conducted at Site A
- ✓ Used software tools to identify potential data anomalies
- ✓ Verified that similar observations were not present for the same product in studies conducted at other sites
- ✓ Investigated bioanalytical reports for:
  – repeat analyses
  – discrepancies across different reports
- ✓ Observed studies that failed BE with a larger number of subjects at another CRO site but passed with a smaller sample size at the affected site
- ✓ Reviewed explanations provided by the applicant and CRO for the findings

FDA Action for Case #2: Untitled Letter

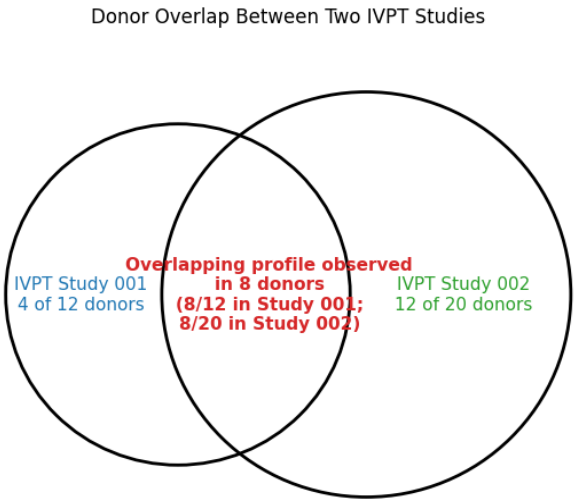
- ✓ Concluded that the reliability and validity of data generated at CRO Site A could not be ensured.
- ✓ Issued an Untitled Letter stating that studies conducted by CRO Site A were not acceptable.
- ✓ FDA publicly notified NDA and ANDA sponsors that clinical and bioanalytical studies conducted at CRO Site A were unacceptable due to data integrity concerns and must be repeated.
- ✓ Affected applications included approved, tentatively approved, and pending applications.
- ✓ Applicants were required to repeat the bioequivalence studies using different CROs
- ✓ Therapeutic equivalence ratings for approved ANDAs were changed to “BX”

Case Study #3 Overlapping Data Observed Across Two Applications for Drug Product X

Example of Skin Donor #1 and #2

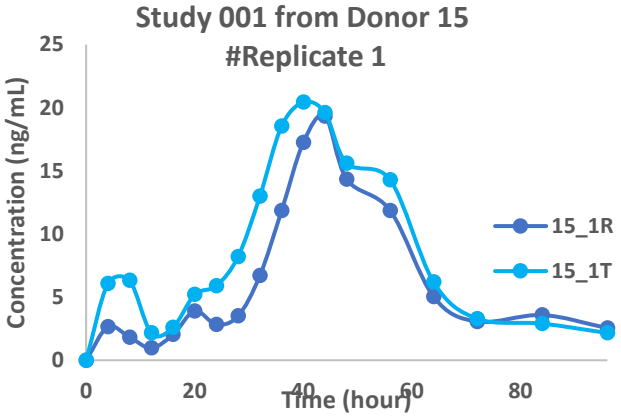


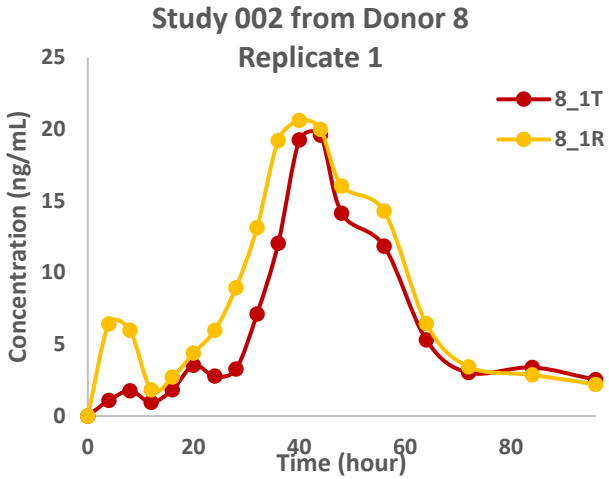
Five replicate skin sections each of test and reference standard per donor were evaluated.

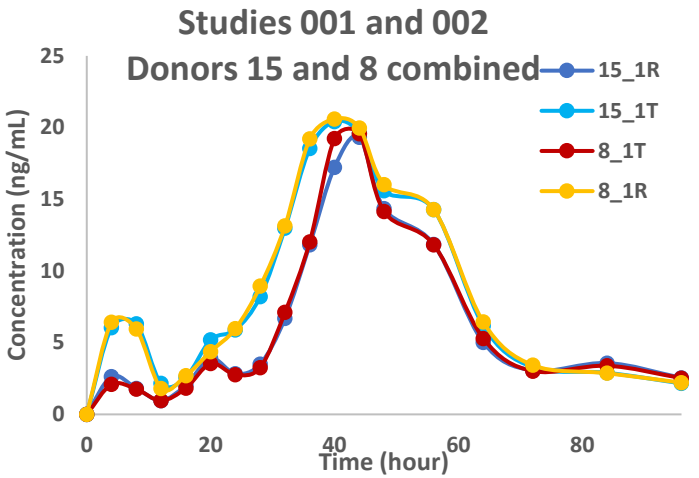


- ✓ Nearly identical IVPT profiles (point-to-point overlap) observed across multiple donor pairs
- ✓ Observed in studies supporting two different sponsors' applications conducted at the same analytical site (Site B)

Case Study #3 Cross-Study Profile Comparison Examples







- ✓ For-Cause OSIS Inspection findings: OAI
- ✓ FDA Actions:
  - Required applicants to repeat the in vitro bioequivalence studies using different CROs
  - Change the therapeutic equivalence rating to "BX" for the approved ANDAs.

Summary

- ✓ A multi-disciplinary approach is crucial in identifying systemic data integrity concerns.
- ✓ The FDA expects that all data submitted in ANDAs be reliable and accurate. Poor data integrity imposes a significant cost and burden on the agency through increased review time and follow-up.
- ✓ Data integrity violations have serious consequences. Applicants and CROs should implement robust quality management systems and maintain compliance to prevent data integrity issues and ensure the reliability of submitted data throughout the study lifecycle.

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