Data Integrity and Data Quality in Application Submissions

Minglei Cui, PhD
Team Leader of Division of Bioequivalence II
Office of Bioequivalence, Office of Generic Drugs, FDA

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Outline

- What is data integrity
- Importance of data integrity
- How to assure the integrity and quality of data
- Case presentations
- Advantages of early reporting
- Summary
- Future steps

What is Data Integrity?

- *Data integrity* refers to the completeness, consistency, and accuracy of data. Complete, consistent, and accurate data should be **a**ttributable, **l**egible, **c**ontemporaneously recorded, **o**riginal or a true copy, and **a**ccurate (ALCOA)

Data Integrity and Compliance With Drug CGMP Questions and Answers Guidance for Industry, FDA, Dec. 2018 (https://www.fda.gov/media/119267/download)

Importance of Data Integrity

- The integrity and quality of data in application submissions are critical concerns of FDA
- Poor data quality, whether due to sloppiness or fabricated data, has the potential to undermine the ability of FDA to provide appropriate analyses as part of the drug product approval process
- Implementation and use of a Quality Management System to data governance should ensure controls over the data lifecycle with the principles of quality risk management

Assure Data Integrity and Data Quality in Application Submission: **Guideline**

- Investigator
  - Should permit monitoring and auditing by the applicant/sponsor, and inspection by the appropriate regulatory authority.
  - Upon request of the monitor, auditor, or regulatory authority, the investigator should make available for direct access all requested study-related records.
- Applicants/sponsors may need to update processes and procedures (clinical and analytical) to ensure compliance with applicable regulations.

Assure Data Integrity and Data Quality in Application Submission (cont.): **Guideline**

- Applicants/Sponsors
  - Responsible for implementing and maintaining quality assurance and quality control systems with written SOPs.
  - Ensure that clinical studies (bioavailability and bioequivalence (BE)) are conducted and data are generated, documented, and reported in compliance with the protocol and the applicable regulatory requirements.
  - Ensure direct access to all study-related sites, source data/documents, and reports for the purpose of monitoring and auditing by the applicants, and inspection by regulatory authorities.
  - Quality control should be applied to each stage of data handling (clinical or bio-analytical) to ensure that all data are reliable and have been processed correctly.

Assure Data Integrity and Data Quality in Application Submission: **Inspection**

- Office of Study Integrity and Surveillance (OSIS), FDA
  - Evaluate information from the inspection and classify the inspection into one of three categories:
    - No Action Indicated (NAI)
    - Voluntary Action Indicated (VAI)
    - Official Action Indicated (OAI)
  - OAI classification usually means that the inspected entity must invest significant resources into correcting the objectionable conditions that FDA has identified, including any observed data integrity issues.
  - However, NAI or VAI does not necessarily mean that data is reliable

Assure Data Integrity and Data Quality in Application Submission: **Review Division**

- Determine whether data in application is reliable when classification is not OAI but have identified data integrity concern
- Request “For Cause Inspection” if found integrity concern for clinical and bio-analytical data
- Request further investigation if found data anomalies
  - Similar PK profiles and/or unusual PK trends
  - Suspected of switching test and reference products and/or making dilutions in order to make study pass

Case Studies

Case # 1

- Findings from multiple inspections at the site
  - Failure to conduct a systematic and thorough evaluation to identify and correct sources of contamination.
  - Failure to investigate data anomalies.
  - Lack of assay reproducibility between original and repeat results.
  - Assay accuracy not assured under the conditions of sample processing.
  - Biased exclusion of study data resulting in the acceptance of failed runs.
  - Failure to demonstrate the accuracy of analytical methods with appropriate validation experiments and documentation.
- Site Classification: OAI
- FDA recommended action:
  - *Perform an independent audit of the results, or*
  - *Re-assay the samples at a different facility (if retained and stable), or*
  - *Repeat the study*

Case #2

- Findings by inspections
  - Widespread falsification of dates and times in laboratory records for subject sample extractions
  - The apparent manipulation of equilibration or “prep” run samples to meet predetermined acceptance criteria
  - Lack of documentation regarding equilibration or “prep” runs preventing to conduct an adequate internal investigation to determine the extent and impact of these violations
- Site Classification: OAI
- FDA recommended action:
  - *Re-assay the samples, or*
  - *Repeat the BE study, or*
  - *Conduct a third-party audit of the study*

Case #3

- Findings by Reviewer and For Cause Inspection
  - Reviewer found unusual trend in the concentration data which triggered unannounced, “for cause” inspection
  - OSIS inspection findings:
    - Sample substitution and manipulation
    - Deliberately removing certain sample data to meet the BE criteria
    - Multiple studies affected
- Software analysis identified similar PK profiles between subjects in BE studies
- Site Classification: OAI
- FDA recommended action:
  - *Repeat all studies conducted by this contract research organizations (CRO)*

Case #4

- OSIS Inspection: VAI
- Bioanalytical Investigation (software tools and other methods):
  - Many overlapping/nearly identical concentration-time profiles (i.e., similar concentrations at all the sampling time points)
  - Distinguishable distribution pattern of T/R ratios for Cmax and AUC (i.e., distinct groups of subjects where T/R for PK parameters for individual subgroups is above or below one)
  - Subjects with overlapping PK profile appeared in the page of notebook in the freezer room
- FDA recommended action:
  - *Repeat all studies conducted by this CRO*

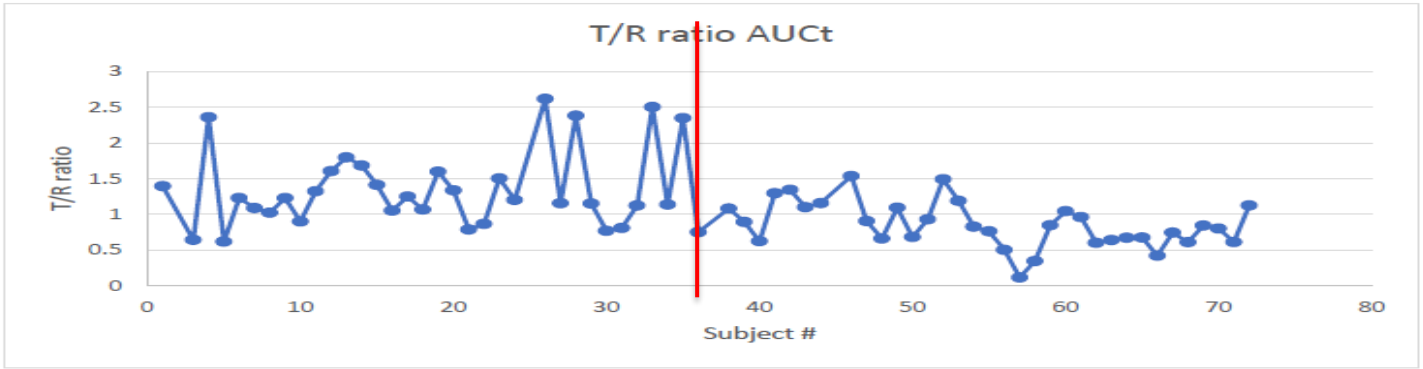
Case #4 (Hypothetical Data): Data Anomalies and Poor Documentation by Bioanalytical Investigations (Software Tools)

Subjects	Parameter	GMR Point Estimate	GMR 90%Confidence Interval	Bioequivalence Determination
	Cmax	1.42	1.2-1.7	Not BE
1 -37 (n=37)	AUC0-t	1.33	1.1-1.4	Not BE
	Cmax	0.67	0.6-0.8	Not BE
37-72 (n=35)	AUC0-t	0.7	0.61-0.81	Not BE
	Cmax	1.07	0.92-1.12	BE
Full Study	AUC0-t	1.02	0.80-1.11	BE

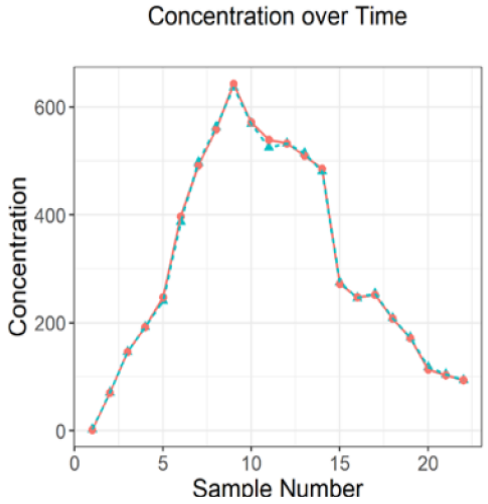
Unusual PK trends T/R ratios

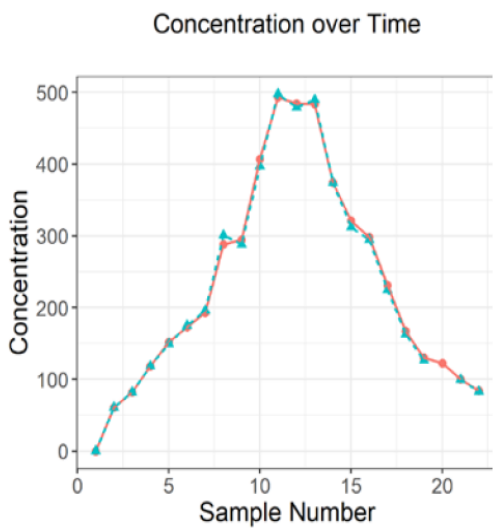
Group 1

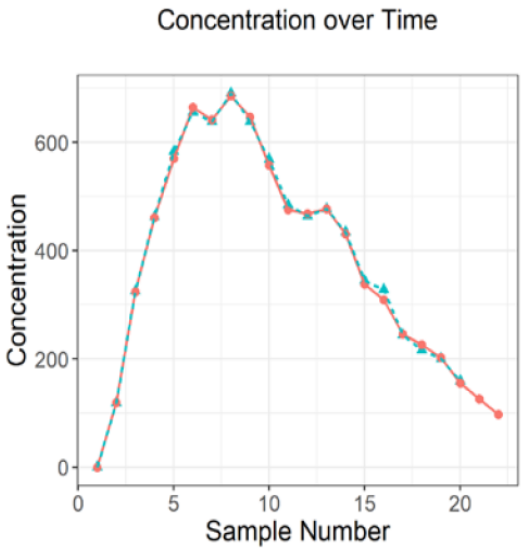
Group 2



Case #4 (Hypothetical Data): Examples: Matching Profiles for XXXX Tablets in the Notebook







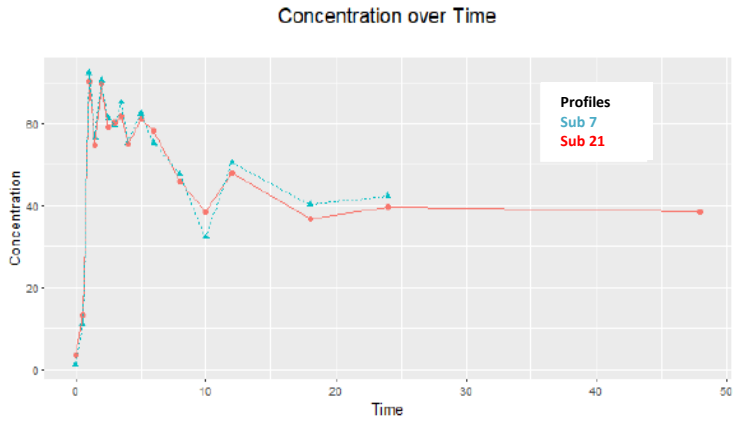
- Data showed subjects with overlapping PK pairs
- OSIS found a notebook documenting the subject pairs that had nearly identical concentration-time profiles

Case #5 (Hypothetical Data) XXXX Tablets USP

Parameter	Unscaled Lower 90% CI	Unscaled Upper 90% CI	Point Estimate	sWT	sWR	sWT sWR ratio	sWT sWR Lower 90% CI	sWT sWR Upper 90% CI
LAUCT	84.23	119.02	0.91	0.5096549	0.3121902	1.5918448	1.33	2.13
LCMAX	86.11	115.31	1.02	0.3723029	0.3921794	0.9840567	0.78	1.35

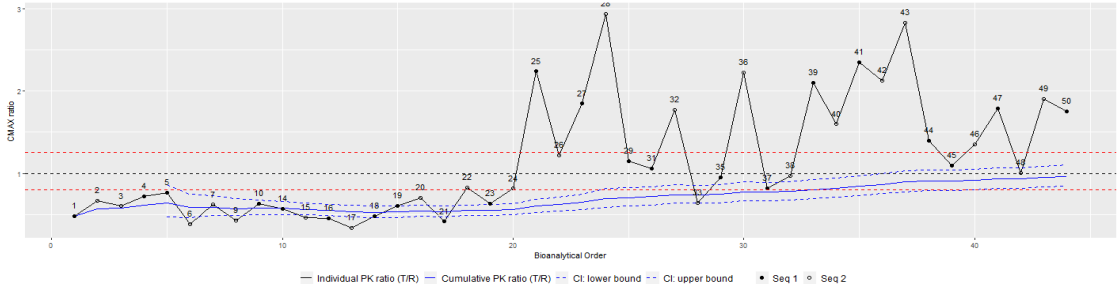
Unscaled	sWT sWR ratio	95% Upper Confidence Bound	OUTCOME
PASS	PASS	-0.055894	PASS
PASS	PASS	-0.097819	PASS

Drug with high variabilities

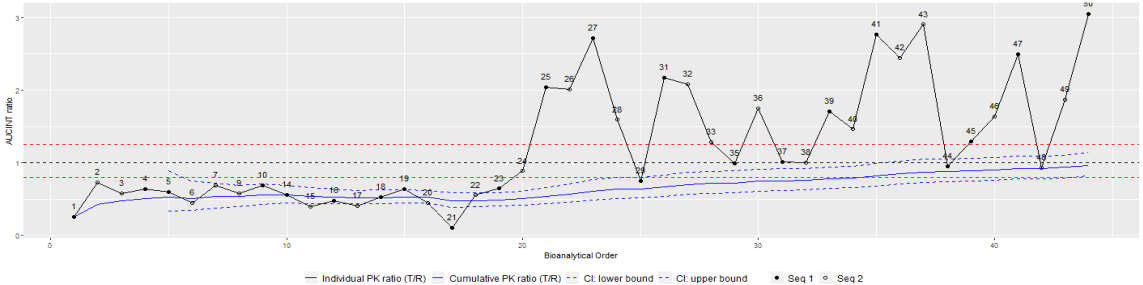


Case #5 (Hypothetical Data): XXXX Tablets-Fasting

Cmax T/R Ratio



AUC T/R Ratio



Clinical findings:

- Several subjects with identical demographics
- Case Report Forms include multiple changes, e.g., gender, study# , and dropout status

Advantages for Early Reporting of Data Integrity Issues to FDA

- An applicant most often finds itself confronting these data integrity issues post-FDA inspection.
  - Find data integrity issues post-inspection/very late in the review process
  - Result in lengthy delays in approval.
- With a proactive Quality Management System and risk-based monitoring, the applicant may discover significant data integrity issues on its own.
- Self-discovery and subsequent early reporting prior to FDA inspection help building a relationship of trust with the regulatory authority.
- Early reporting to FDA may also help an applicant determine
  - more cost-effective way/additional steps to assure the reliability of the data.

Communicating with FDA When Data Integrity Issues Arise During Clinical Trials @https://www.fdli.org/2019/05/communicating-with-fda-when-data-integrity-issues-arise-during-clinical-trials/

Summary

- Applicants and regulatory authorities work together to ensure data integrity and data quality
- Lack of data reliability would have a negative impact on the acceptability of data submitted in support of a marketing application
- A careful risk assessment should be performed by applicants to
  - Identify the areas of criticality and guide appropriate allocation of resources for oversight of all data management processes and procedures
  - Quality control should be applied to ensure that all data are reliable
- Communicate with regulatory agency as early as possible after a significant issue is identified

Future Steps: International Collaboration

- Enhance regulatory oversight to assure data integrity
- Increase the effectiveness of the regulatory authorities and better guide resource allocation for inspection coverage
- Explore better and alternative ways to detect similarities or trends arising out of fraud that is hard to be detected by on-site inspection

Important Data Integrity Guidance

- Medicines & Healthcare products Regulatory Agency (MHRA) 'GXP' Data Integrity Guidance and Definitions (https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/687246/MHRA_GxP_data_integrity_guide_March_edited_Final.pdf)

- WHO Guideline on data integrity (https://www.who.int/docs/default-source/medicines/norms-and-standards/current-projects/qas19-819-rev1-guideline-on-data-integrity.pdf)

- E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1) (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e6r2-good-clinical-practice-integrated-addendum-ich-e6r1)

- Data Integrity and Compliance With Drug CGMP Questions and Answers Guidance for Industry, FDA, Dec. 2018 (https://www.fda.gov/media/119267/download)

- Communicating with FDA When Data Integrity Issues Arise During Clinical Trials (https://www.fdli.org/2019/05/communicating-with-fda-when-data-integrity-issues-arise-during-clinical-trials/)

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Question 1

Integrity of data refers to data that is,

A. Accurate

B. Complete

C. Consistent

D. All of the above

Question 2

Applicant's self-discovery and subsequent early reporting prior to the regulatory authorities' inspection can help build a relationship of trust with the regulatory authority and help an applicant determine when it is more cost effective, what additional steps must be taken to assure FDA of the reliability of the data

A. True

B. False