Data Integrity Issues in Bioequivalence Studies

Nilufer Tampal, PhD

Acting Associate Director of Scientific Quality
Office of Bioequivalence, Office of Generic Drugs, USFDA

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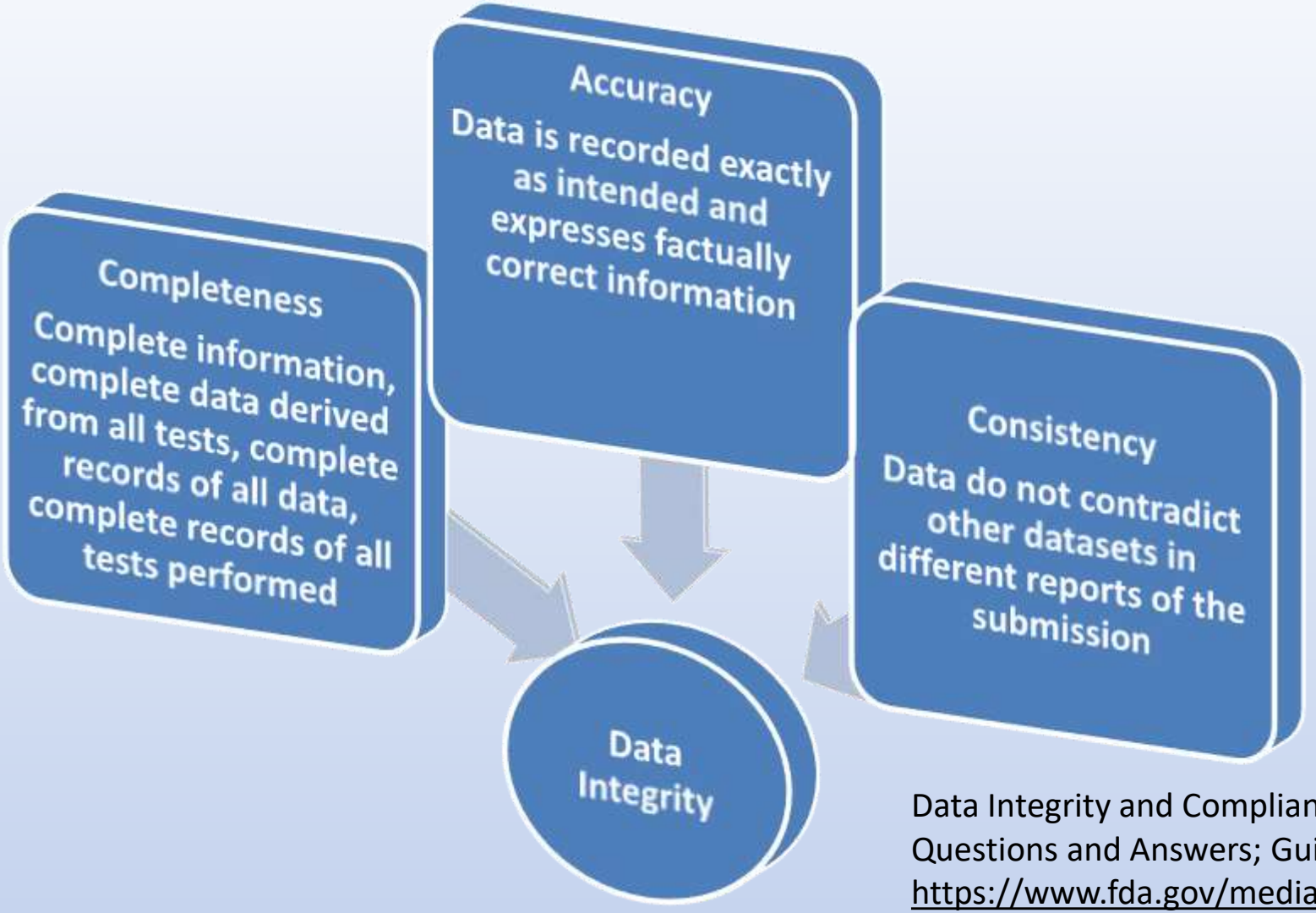
Outline

- Introduction to data integrity
- Common data integrity issues - case studies from regulatory submissions
- Recommendations for managing data integrity

Disclaimer

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

What is Data Integrity?



Data Integrity and Compliance With Drug CGMP: Questions and Answers; Guidance for Industry
https://www.fda.gov/media/119267/download

Why Data Integrity Matters

- Helps to ensure the safety, efficacy, and quality of drugs
  - An important component of the industry's responsibility
- Helps to ensure FDA's ability to protect the public health
  - Making decisions on inaccurate and invalid data can have consequences

Potential Cost to the FDA (expend resources for regulatory actions)	Potential Cost to Applicants and Contract Research Organizations (CROs)	Potential Cost to Patients and Public
Advisory Action Letters, notifications to all affected applicants, rejection of data linked to the application(s) covering the length of time the violations occurred	Financial burden for conducting new studies or audits by independent third parties Reputation and credibility	Delay in patient's access to new drug treatments and affordable generic drugs Medication failure resulting in serious adverse events including death

Compromised System

System includes people, machines, and methods organized to accomplish a set of specific function*

Accidently compromised system:

- Errors in processing, execution, diagnosis
  - errors during transfer of data from one device to another
- Complacency and overconfidence

Intentionally compromised system:

- Physical action that change equipment (software), datasets, methods, etc., leading to falsification and fabrication of records and data

*ANSI definition

Commonly Encountered Issues

Examples from bioanalytical studies:

- Processing, data transfer, and transcription errors
- Incomplete reports
- Data replacement: data from acceptable runs replaced with results from reassays
- Data manipulation: swapping and mis-identifying study samples

Commonly Encountered Issues

Examples from clinical site inspections:

- Insufficient and missing case history records for study enrollment
- Incomplete and under-reporting of adverse events
- Test results with unidentified or misidentified subjects
- Unexplainable discrepancies in subject sample accountability and shipping records

Case Studies

CRO 1 - Data Discrepancies

Inconsistencies in the data identified in different sections of the submission

- Mismatch of the data in the clinical report, SAS transport files, and 'Analyst' printouts
  - Raw data was for a different applicant, conducted at the same CRO site for the same drug

Critical for CROs and Applicants to have a robust Quality Management System (QMS)

CRO 2 – Data Substitution – Intentional Bias

Analytical report did not accurately reflect the source data

- Subject sample data were projected to be accurate by overwriting the files
- For three failing QCs, the original chromatograms and data were substituted with reanalyzed QC data
- No documentation and reporting for reanalysis of failed QCs

CRO 2 – Data Substitution - Intentional Bias (continued)

Chromatogram printouts for QCs in the **original** files

Sample **2189** injected on 10/8 at 19:51
Sample **2200** injected on 10/9 at 7:34
Sample **2211** injected on 10/9 at 9:12

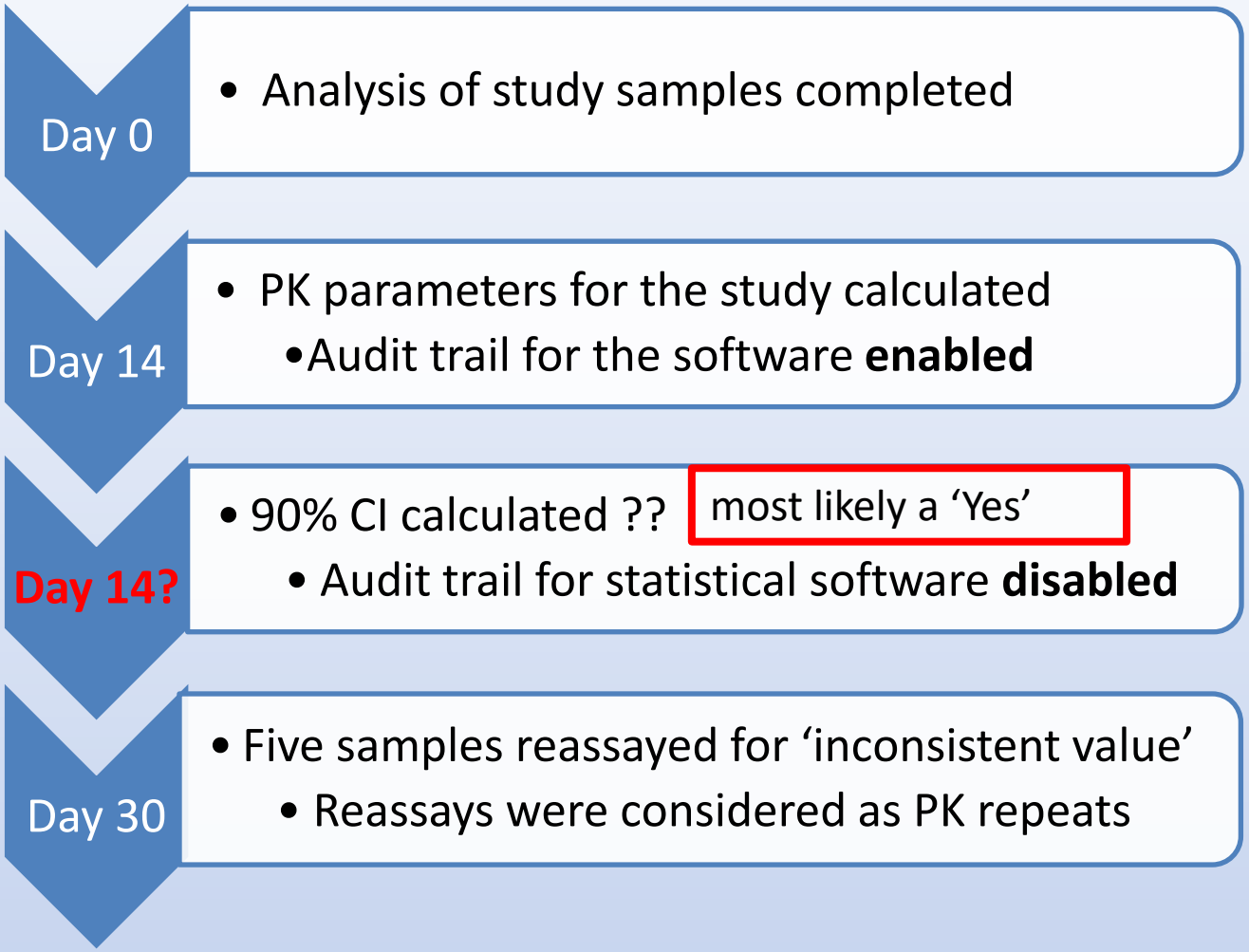
Chromatogram printouts of the **reinjected** QCs -- dates and times, out of the chronological order

Sample 2188 injected on 10/8 at 19:42
Sample 2189 injected on 10/9 at 11:11
Sample 2190 injected on 10/8 at 20:00

Sample 2199 injected on 10/9 at 07:26
Sample 2200 injected on 10/9 at 11:20
Sample 2201 injected on 10/9 at 07:43

Sample 2210 injected on 10/9 at 09:03
Sample 2211 injected on 10/9 at 11:29

CRO 3 – Suspicious Data ?



Study failed to meet the BE limits using the original concentrations

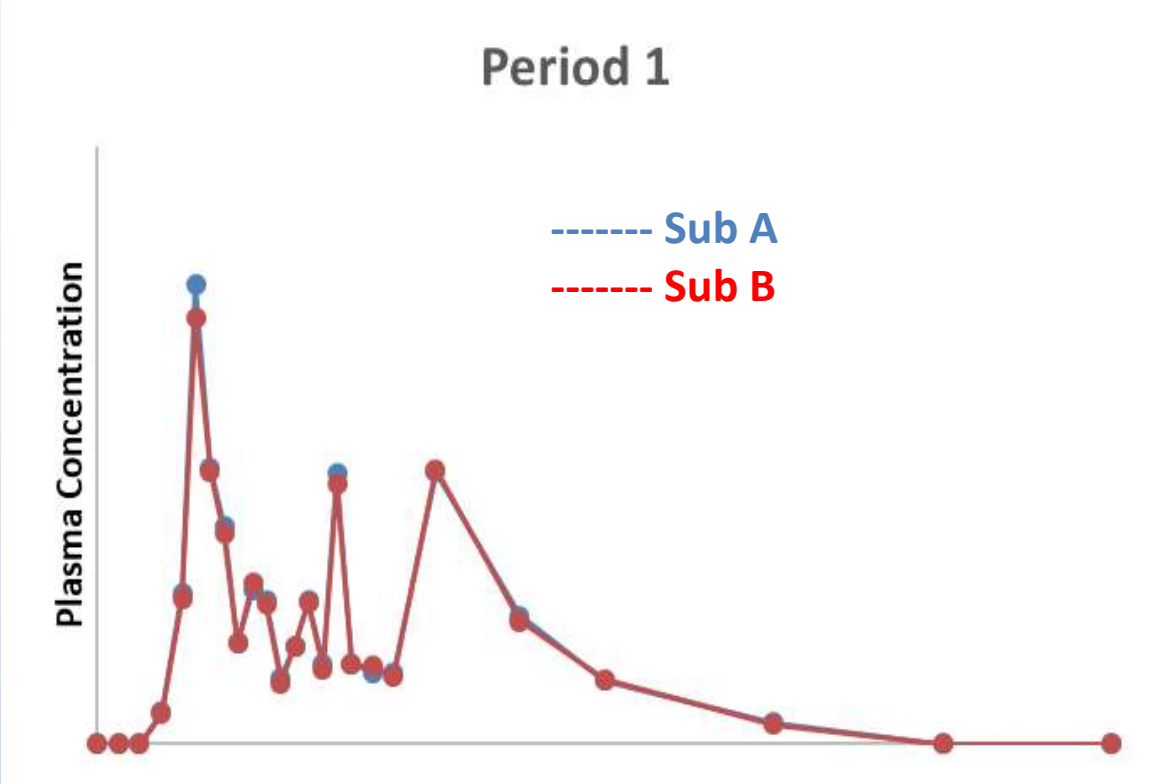
The decision to reassay the five samples biased the BE study outcome

Emerging Theme in Data Integrity

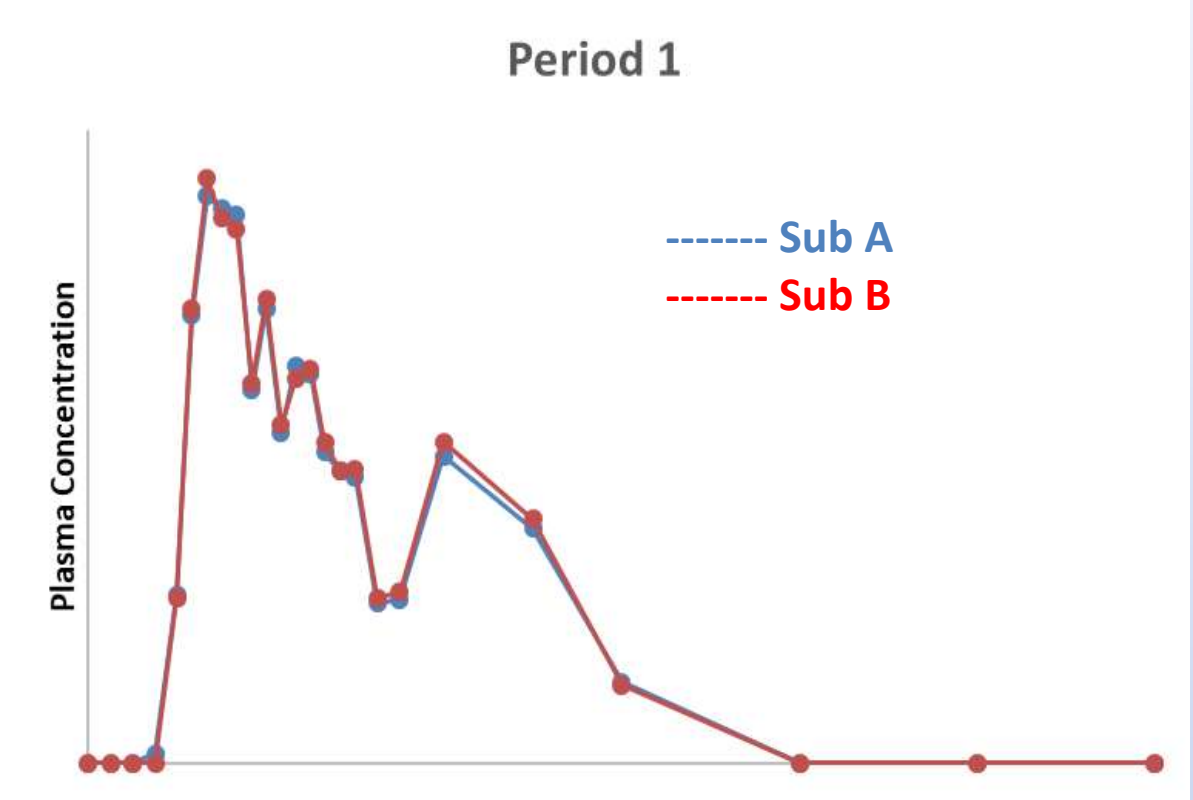
CRO 4 – Anomalous Data

Overlapping Profiles of Subject Pairs

Analyte 1

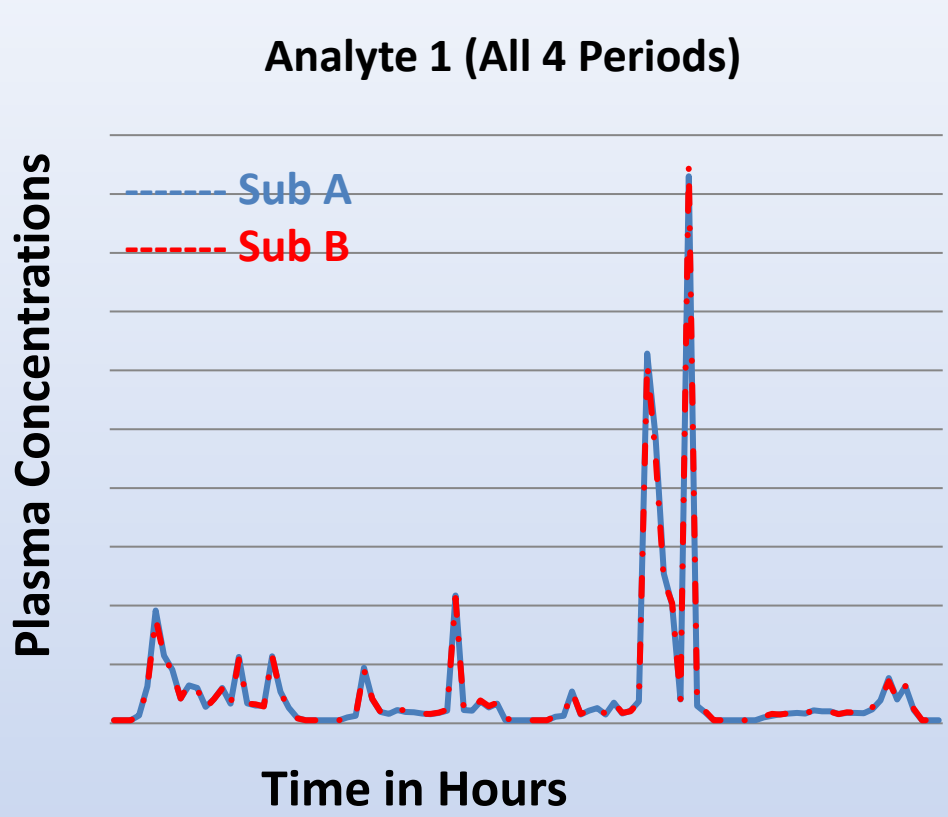


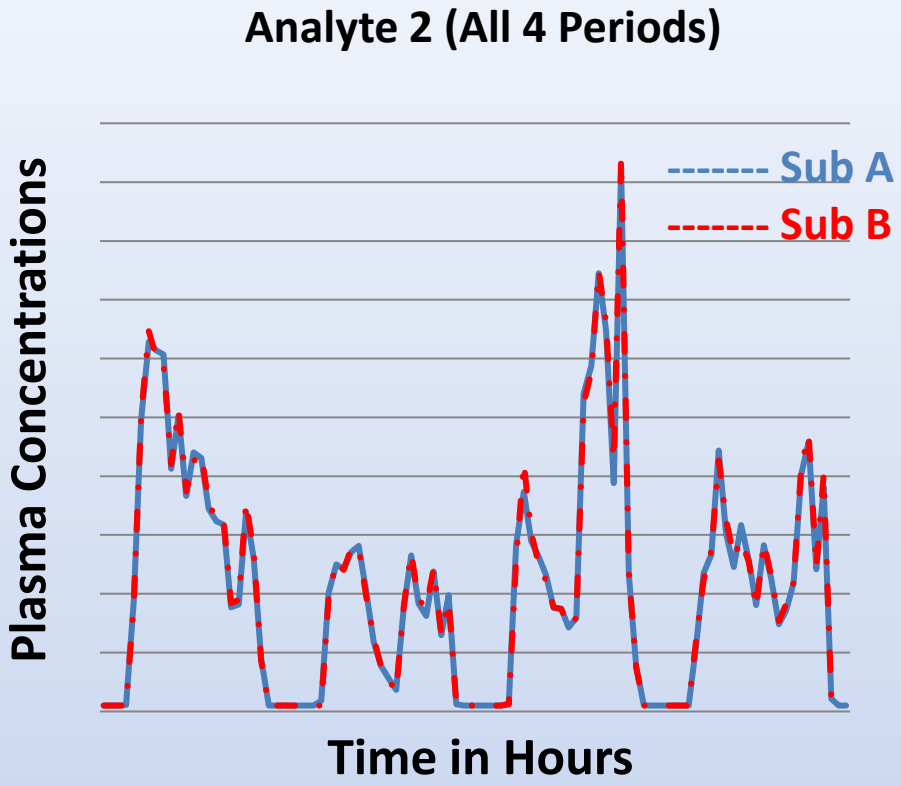
Analyte 2



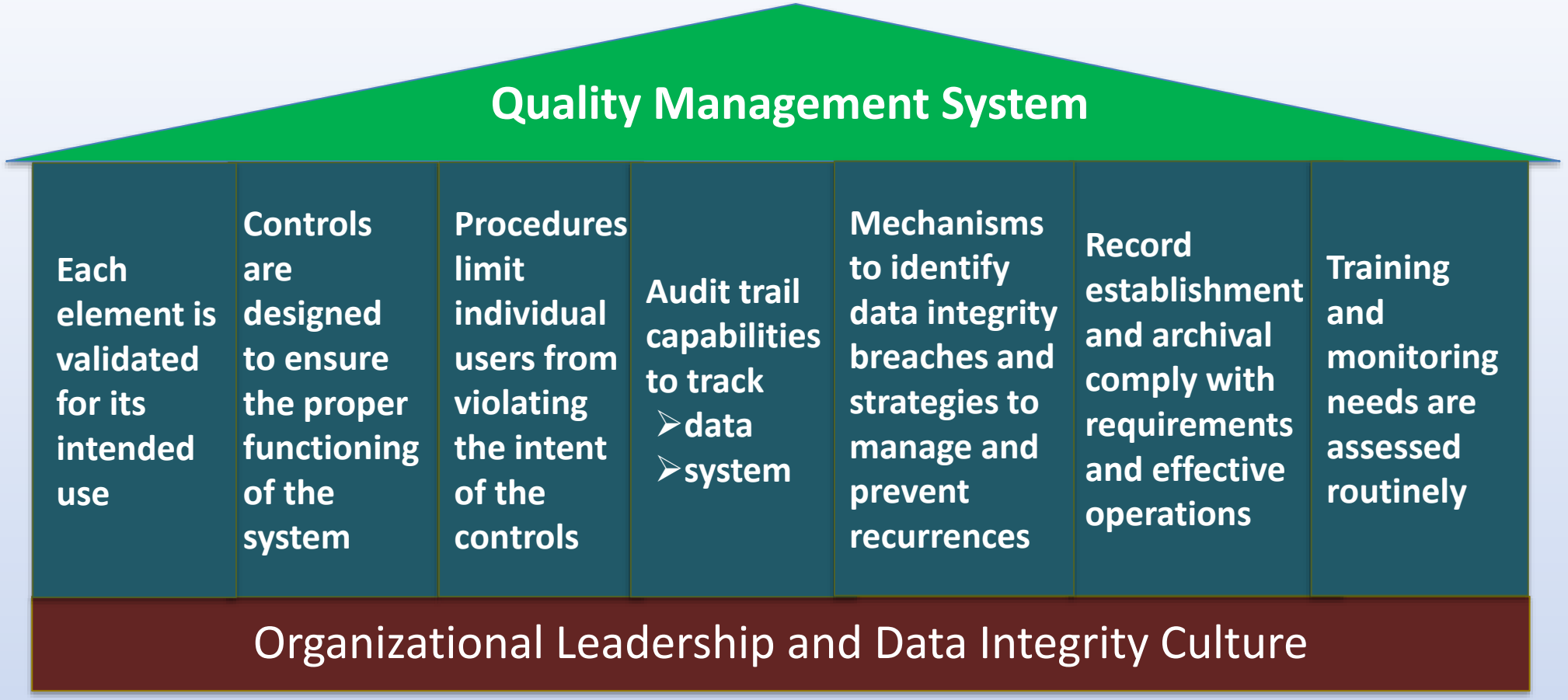
CRO 4 – Anomalous Data (continued)

Overlapping Profiles of Subject Pairs





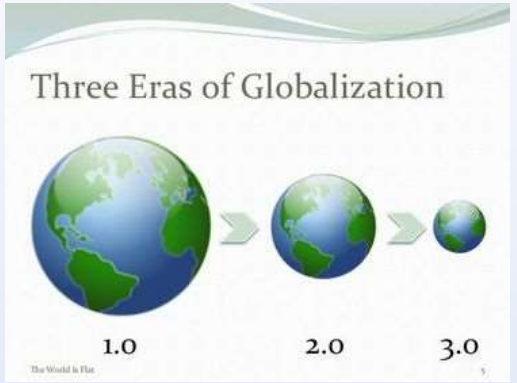
What's Next – Build and Implement a Robust System



Looking to a Future of Global Quality

- A leveled playing field for Data Integrity culture
  - Individuals and small organizations drove Globalization 3.0
  - Growing number of individual testing facilities increased

    FDA's involvement for ensuring compliance



- Applicants and CROs share the same goal of **'Patient First'** as the FDA
  - Intentional commitment to ensure integrity of data
    - Data integrity should not be left to chance
  - Implement robust Quality Management Systems
    - Shared responsibility to ensure all data submitted are complete and accurate

Achieving data integrity is essential to protecting public health

Question 1

Integrity of data refers to data that is,

A. Accurate

B. Complete

C. Consistent

D. All of the above

Question 2

When data integrity is compromised there may be a potential cost to the Applicants and not the CROs

A. True

B. False


THANK YOU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