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Data Integrity

September 5, 2018

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Legal Notice

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Data Integrity Overview

- Data Integrity: "The extent to which all Data are complete, consistent and accurate throughout the Data Lifecycle."

MHRA GMP Data Integrity Definitions and Guidance for Industry March 2015

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Medicines and Health Products Regulatory Authority, "MHRA GMP Data Integrity Definitions and Guidance for Industry March 2015", March 2015, https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/697053/Data_integrity_definitions_and_guidance_v2_Withdrawn.pdf

Where Have DI Concerns Been Found?

- Essentially all GMP environments:

Data integrity issues are not just found in "release testing"

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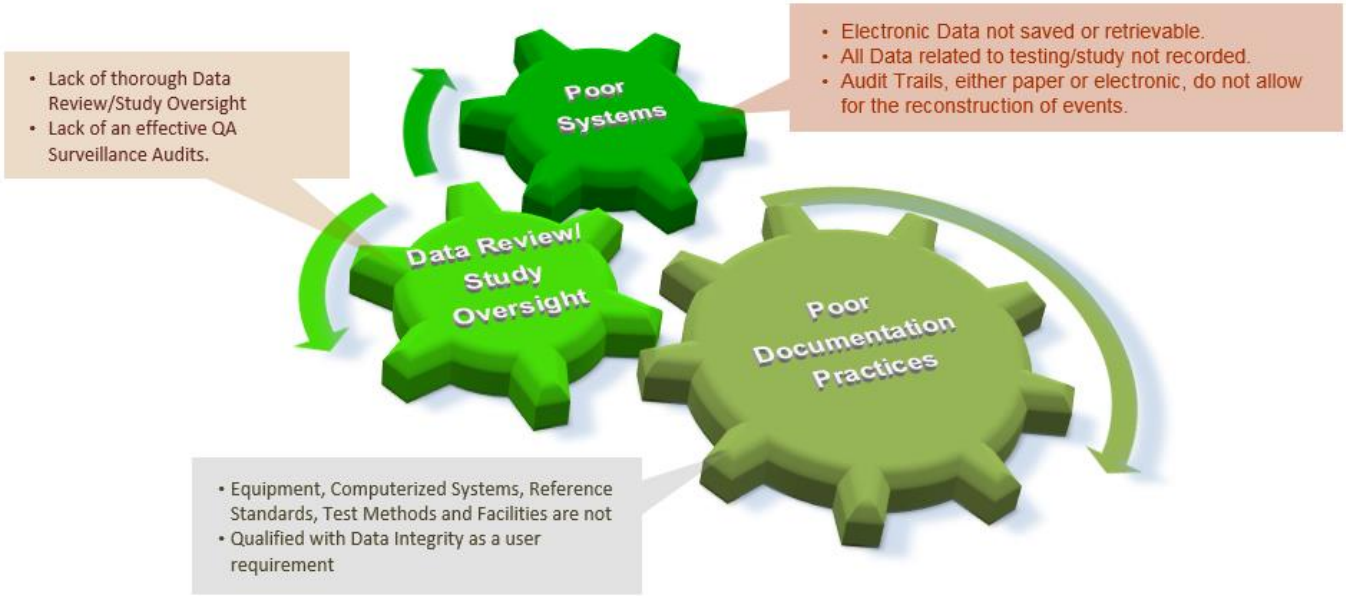
Challenges To Data Integrity



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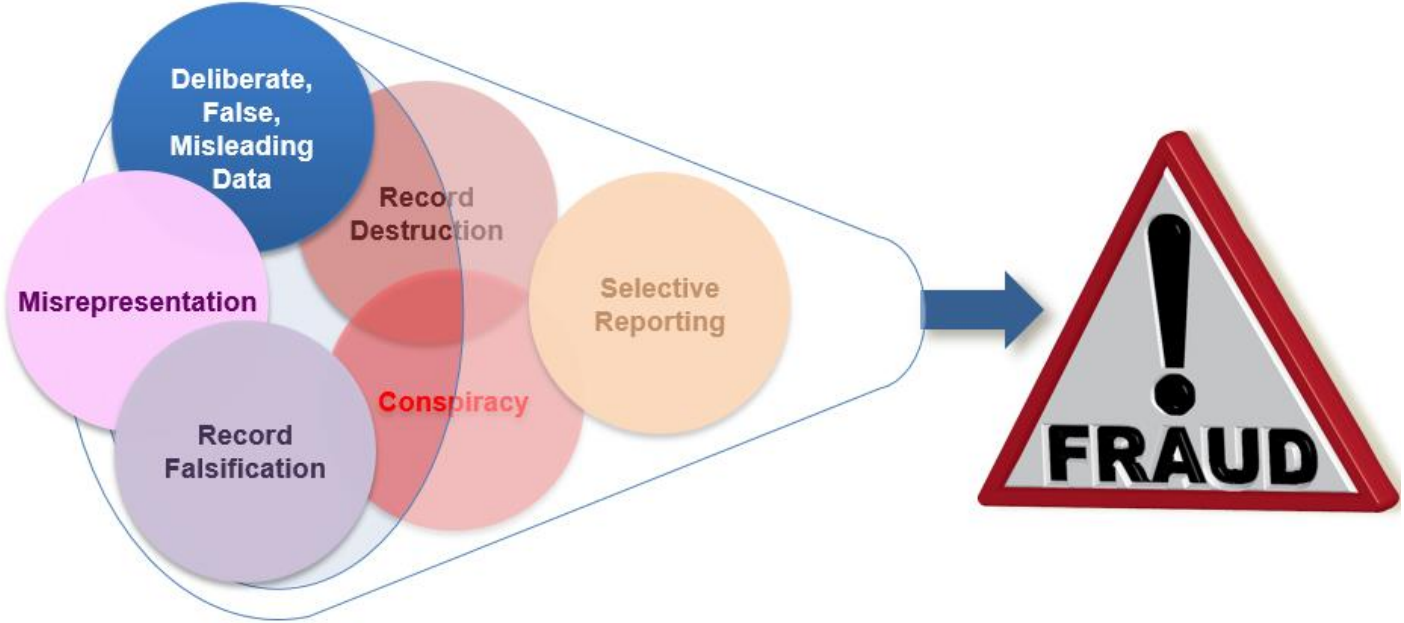
Fraud or cGMP Violations



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Fraud or cGMP Violations (Cont'd)

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Role of Culture in Data Integrity

- Attributes of Quality Culture that impact data integrity
  - Right mindset for right reason
  - Knowing the right thing to do, and doing it
  - Environment that fosters consistent and proper execution
  - A set system for identifying and resolving problems
  - Living the proactive, continuous improvement philosophy
  - Company enabled and nurtured

Role of Culture in Data Integrity (Cont'd)

- Need to hire the right people who can ensure that controls are in place
- Do not just buy new IT systems
- Ensure that there is an appropriate amount of mid-level or front line managers
- Ensure that there are no shared passwords to ensure appropriate audit trails

Data Integrity in Basic Science/Discovery - Focus on Digital Data

- Digital technologies are commonly used in life science laboratories
- If used inappropriately or without appropriate controls, can lower data quality and compromise integrity of research
- Digitation may introduce artifacts or spurious information into a representation
  - Manipulation of contrast results in misleading results
- Complex digital analyses can yield misleading results without careful monitoring and deep understanding of the digital analysis process
- Erroneous data can be rapidly multiplied and widely disseminated
- Can be manipulated more easily that other forms of data
- Particularly susceptible to distortion

National Academy of Sciences, National Academy of Engineering and Institute of Medicine; "Ensuring the Integrity, Accessibility, and Stewardship of Research Data in the Digital Age", Washington, DC: The National Academies Press, 2009, https://www.ncbi.nlm.nih.gov/books/NBK215260/, accessed June 26, 2018

Data Integrity Breaches in Preclinical Research – Notable Historic Examples

- Investigations of a contract laboratory revealed poorly conceived and carelessly executed experiments, lack of supervision and training of personnel, and inadequate record keeping = major Data Integrity issues
- Another Contract Laboratory was inspected by FDA in 1976 after whistleblower from client company reported that data was “too perfect.”

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“3-Ex Officials of Major Laboratory Convicted of Falsifying Drug Tests,” New York Times, October 21, 1983; Lyons, R.D., “F.D.A. Broadens Inquiry on Testing of New Drugs,” New York Times, November 17, 1976.

Compromised Data Integrity in Clinical Investigations – 3 Major Categories

ALTERED DATA

- Overwriting of electronic data
- Manipulation of integrations to achieve passing result

OMITTED DATA

- Selective reporting of data
- Undocumented sample "trial" injections

MANUFACTURED DATA

- Creation of replacement or "dummy" ECG test results
- Copying an existing injection sequence, then changing the name of the sequence and the name of the injections along with the integration of the peaks.

Examples of DI Observations in Manufacturing Systems

- User names/password sharing
  - PLCs controlling a tableting machine designed to accept only 5 different user names/passwords being used by as many as 30 different operators.
  - Work stations controlling production operations without time-outs and lock-outs, resulting in shared access such that determination of who actually entered operational commands is unknown.
- Entries in hard copy batch record
  - Entries in the hard copy batch record are not made contemporaneously.
  - Inaccurate entries in hard copy batch records with regard to start and end times of certain operations.

Examples of DI Observations in Manufacturing Systems (Cont'd)

- Discarding raw data
  - Calculations, notes, visual inspection results are written on loose papers or sticky notes.
  - Unofficial batch records found torn in half in the trash. Some show failing in-process test results.
- Access rights inappropriate
  - Inappropriate access rights for batch release in enterprise software systems like SAP.
- Records are too perfect
  - Too few product complaints, deviations, or OOS results for the volume of production. (Too good to be true?)
  - Records look too perfect, e.g., in-process test records, yield calculations, and packaging reconciliations. (Too good to be true?)

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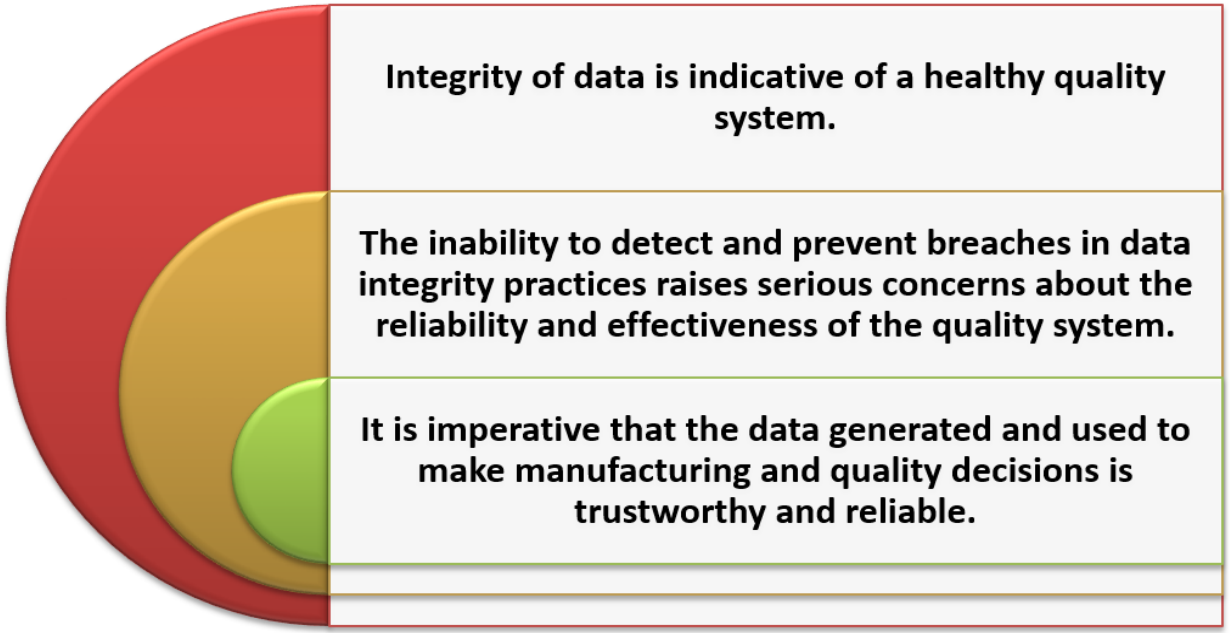
Regulator's Perspective



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Rosa, C., "Regulatory Perspective Data Integrity (2017)," presented at the 2017 PDA/FDA Joint Regulatory Conference, September 11, 2017

THANK YOU

Frances M. Zipp, President and CEO
Lachman Consultants
1600 Stewart Ave.
Westbury, NY 11590
frances.zipp@lachmanconsultants.com
(516) 222-6222

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