Role of Data Integrity in Drug Applications

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Learning Objectives

In this presentation, you will learn:

- Impact of Data Integrity on Drug Applications
- Data Integrity Remediation Considerations
- Data Integrity Case Study from Regulatory Submission

Why Does Data Integrity Matter?

- Data provided in drug applications must be reliable and trustworthy.
- Failure to uphold data integrity could cast doubt on all information submitted in the application.
- Data integrity failures could be intentional vs. unintentional actions.
- Both are CGMP violations.

Data Integrity Applies to ALL Activities

- Data from all sites, including CDMO and CRO are assessed for integrity.

CDMO: Contract development and manufacturing organization; CRO: Contract research organization

Data Integrity Issue Indicators by Regulatory Framework

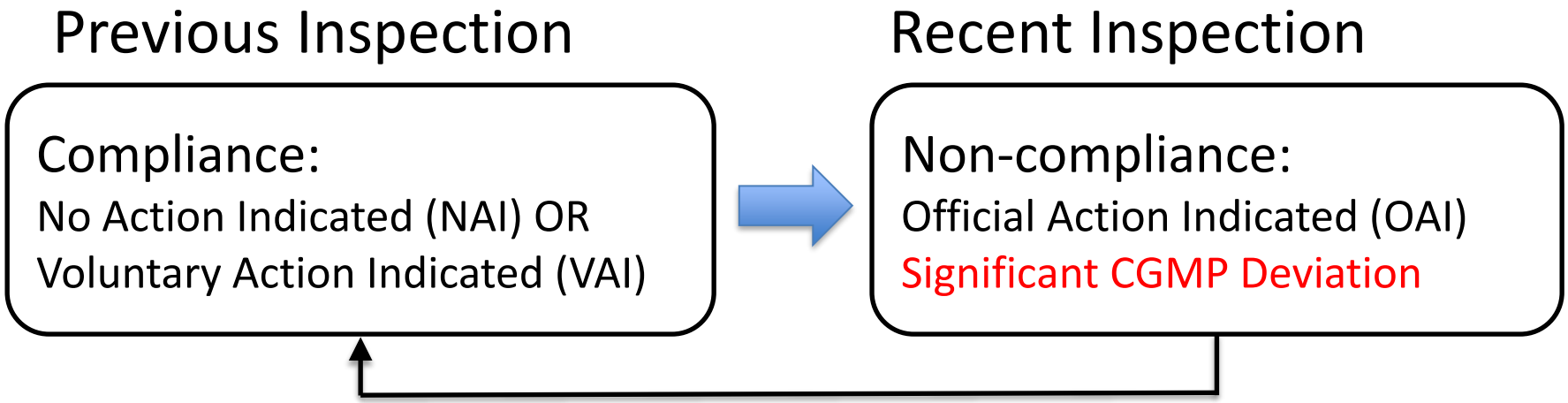
Indicators	Relevance
• Failure to investigate adequately and document OOS or aberrant results	**OOS investigation** § 211.192
• Testing into compliance • Failure to prevent unauthorized access or changes to data • Lack of audit trails for lab instruments and turning off audit trails	**Accurate and Complete Data and CGMP Records** §§ 211.22(a), 211.68, 211.188, 211.194, and 212.60(g)

OOS: Out-of-specification

Data Integrity Issue Indicators by Regulatory Framework (Continued)

Indicators	Relevance
• Failure to record activities at the time they were performed (e.g., selective omission of activities)	**Contemporaneously recorded** §§ 211.100(b) and 211.160(a)
• Failure to have controls over electronic data	**Attributable** §§ 211.101(d), 211.122, 211.186, 211.188(b)(11), and 212.50(c)(10)

Retrospective Impact to Drug Applications



"What is the extent of impacted data?"

"How systemic are the practices that affect data integrity?"

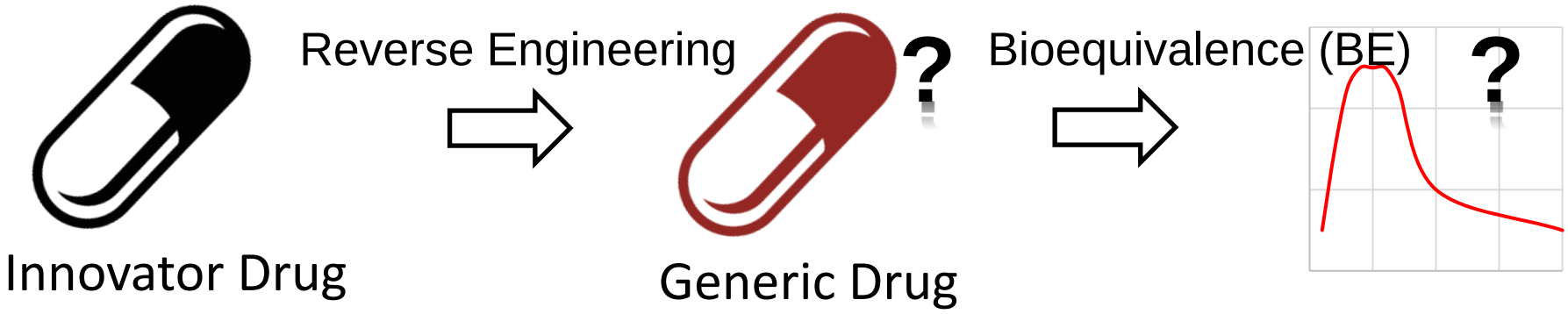
Retrospective Impact to Drug Applications (Continued)

- Industry should assess and identify which applications are impacted by failing data integrity practices.
- Industry should evaluate reliability of data submitted for review.
- Approved products

  "What is the quality of product distributed to the public?"
- Pending applications

  *"Is the data submitted in the application **Reliable?"***

Cascade Impact to Bioequivalence Study



- Data integrity failures may result in question the quality of batches used for BE studies.
- BE study outcome may therefore be in question if the quality of drug cannot be confirmed.

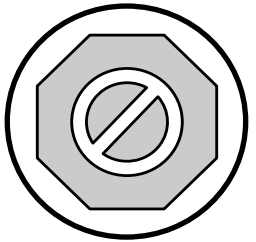
Data Integrity Remediation Considerations

Consideration I.

Comprehensive Evaluation

Consideration II.

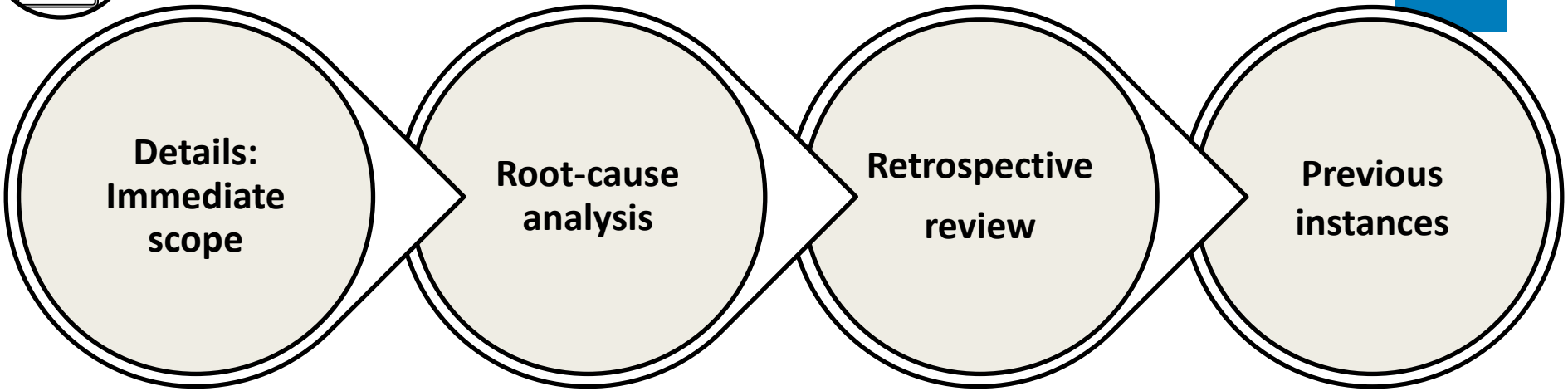
Risk-Assessment



Consideration III.

Corrective/Preventative Action (CAPA)

Consideration I. Comprehensive Evaluation



- Determine immediate scope.
- How and why did this breach happen?
- Retrospective review may find related-products impacted by this breach.
- List of previous instances.

Consideration II. Risk-Assessment

- Understand the impact of data integrity on the drug product quality for distribution.
- Conduct risk assessment of potential effect on drug product quality and application quality.
  - Choose the appropriate tool. Refer to ICH Q9.
- Determine effect on data submitted in the pending application.

Consideration III. CAPA

Corrective Action

- Establish corrective action plan based upon root-cause analysis to ensure enhanced data monitoring and/or testing in the future.
- Take steps to correct unreliable information in the application.
- Interim/long-term measures to correct the deficiencies identified during the root-cause analysis.

*"A detailed corrective action plan that describes how you intend to ensure the **reliability** and **completeness** of all the data you generate including analytical data, manufacturing records, and all data submitted to FDA".*

FDA Warning Letter, July 2019

Consideration III. CAPA (Continued)

Preventative Action

- Outline organizational structure roles and responsibilities.
- **Culture** determines quality outcomes.

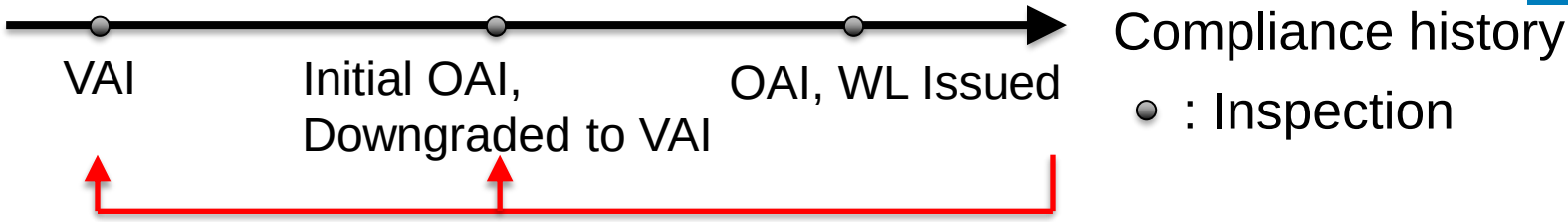
CAPA should be directed to both the facility systems AND the application data.

Reinstate FDA's Confidence in Data

- Remediation activities include improving the **QMS**, **culture**, and **retraining staff**.
- Establishing data reliability is pivotal for effective decision making.
- Remediation implicates both marketed product and those products pending approval.

QMS: Quality management system

Case Study



Significant Violations:

*"The site failed to thoroughly review **unexplained discrepancies**."*

*"The site generated **false and misleading data**."*

*"The site conducted preliminary testing prior to testing on the official system (e.g., **Trial injection**)."*

VAI: Voluntary action indicated; OAI: Official action indicated

Remediation Plans

As a remediation plan for pending applications, the site

- Assessed drug applications for DI impact.
- Conducted root-cause analysis on OOS/OOTs.
- Submitted their corrective actions, as well as internal data integrity audit report for pending applications.

OOS: Out-of-specification; OOT: Out-of-trend

Totality of Concerns From Inspection and DI Audit Report Assessment

DI audit report assessment by FDA revealed that

- ✓ The DI impact assessment failed to determine **immediate scope** of data integrity impact and related products, as well as the validity of results.
- ✓ Firm's root-cause analysis concluded with **"No Product Impact"** despite invalidation of OOS/OOT, replacement of failing test results without conducting risk-assessments, and trial injections.
- ✓ No **independent** DI audit conducted.

Regulatory Actions on Drug Applications

- The manufacturing facility lacked the necessary controls to assure the data in support of pending applications.
- Applications received complete response (CR) actions due to the inability to establish the reliability of submitted data, including the bioequivalence study.
- Applicants were also asked to **use a newly manufactured bio-batch** to demonstrate **bioequivalence to the RLD**.

RLD: Reference listed drug

Key Takeaways

- **Key Takeaway 1**

  Data integrity breaches impact both the availability of marketed products as well as the approvability of new products.

- **Key Takeaway 2**

  Data integrity breaches result in questioning the quality information for CMC and BE batches.

- **Key Takeaway 3**

  ✓ Comprehensive evaluation on data integrity (Consideration I)
  ✓ Risk-assessment and control (Consideration II)
  ✓ Corrective action and quality culture (Consideration III)

Challenge Question #1

True / False

Substantial evidence of efficacy of the drug under review may be questioned when the data to demonstrate the quality of that drug is not reliable.

Challenge Question #2

Which of the following statements is true?

A. Data integrity applies to all sites, including CDMO and CRO.

B. The firm may contract with a qualified, 3rd party data integrity consultant to assist in correcting the problems.

C. Preventative actions are established to evaluate cultural factors such as management pressure, opportunity, and rationalization.

D. Data integrity practices implicate both marketed product and exhibit/bio-batches manufactured for applications.

E. All of the above.

Closing Thought

"Without changing our patterns of thought, we will not be able to solve the problems that we created with our current patterns of thought."

- Albert Einstein

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Questions?

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