

# 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.

# Data Integrity Issue Indicators by Regulatory Framework



Indicators	Relevance
<ul style="list-style-type: none"><li>• Failure to investigate adequately and document OOS or aberrant results</li></ul>	<b>OOS investigation</b> § 211.192
<ul style="list-style-type: none"><li>• Testing into compliance</li><li>• Failure to prevent unauthorized access or changes to data</li><li>• Lack of audit trails for lab instruments and turning off audit trails</li></ul>	<b>Accurate and Complete Data and CGMP Records</b> §§ 211.22(a), 211.68, 211.188, 211.194, and 212.60(g)

# Data Integrity Issue Indicators by Regulatory Framework (Continued)



Indicators	Relevance
<ul style="list-style-type: none"><li>Failure to record activities at the time they were performed (e.g., selective omission of activities)</li></ul>	<b>Contemporaneously recorded</b> §§ 211.100(b) and 211.160(a)
<ul style="list-style-type: none"><li>Failure to have controls over electronic data</li></ul>	<b>Attributable</b> §§ 211.101(d), 211.122, 211.186, 211.188(b)(11), and 212.50(c)(10)

# Retrospective Impact to Drug Applications



## Previous Inspection

Compliance:  
No Action Indicated (NAI) OR  
Voluntary Action Indicated (VAI)



## Recent Inspection

Non-compliance:  
Official Action Indicated (OAI)  
**Significant CGMP Deviation**



*“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.

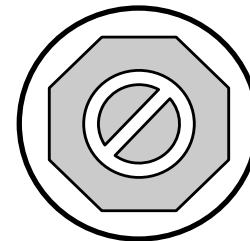
# Data Integrity Remediation Considerations



**Consideration I.**  
Comprehensive  
Evaluation



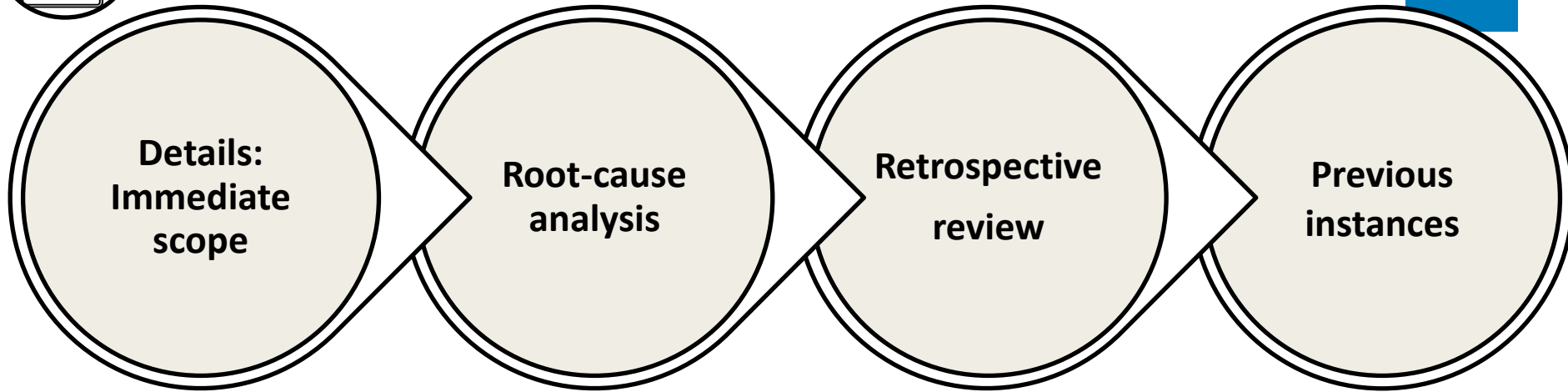
**Consideration II.**  
Risk-Assessment



**Consideration III.**  
Corrective/Preventative  
Action (CAPA)



# Consideration I. Comprehensive Evaluation



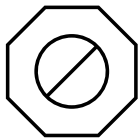
- Determine immediate scope.
- How and why did this breach happen?
- Retrospective review may find related-products impacted by this breach.
- List of previous instances.



## 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

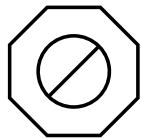


### Corrective Action

- 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.

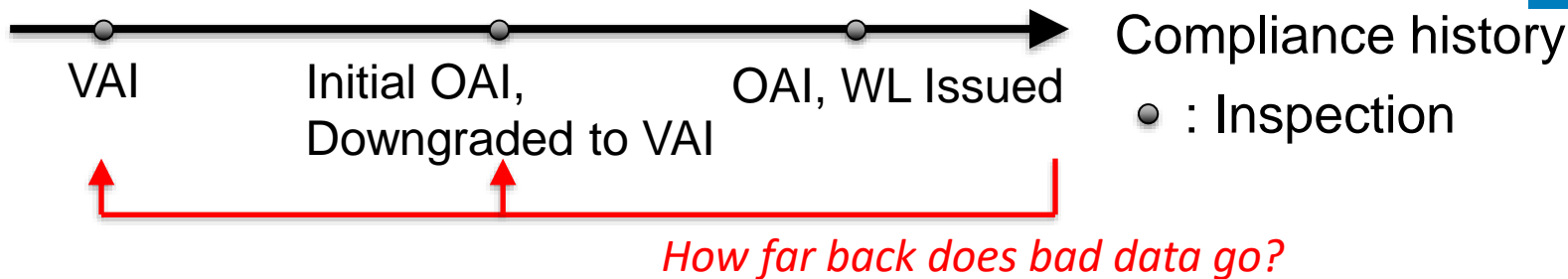
**CAPA** should be directed to both the facility systems  
AND the application data.

# 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.

# 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**).”*



# 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.

# 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**.

# 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*

# Questions?

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