

Culture of Quality: Data Integrity and CGMP Compliance

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Learning Objectives

- Understand data integrity as part of CGMP compliance requirement and its impact on application review
- Discuss the critical role of a firm's management in creating a quality culture that supports data integrity
- Define the role of OPQ/OPMA (Office of Pharmaceutical Manufacturing Assessment) in data integrity assessment

Data Integrity and CGMP



- CGMP: **Systems** that assure proper design, monitoring, and control of processes and facilities
- **Data integrity** – the *completeness*, *consistency*, and *accuracy* of data
- ALCOA: Attributable, legible, contemporaneously recorded, original or a true copy, and accurate
- Data integrity breach is a violation of CGMP → **adulterated drug**
 - Under U.S. law, adulterated drug subject to detention
 - Generally, significant CGMP issues require re-inspection



Data Integrity Critical to Application Review

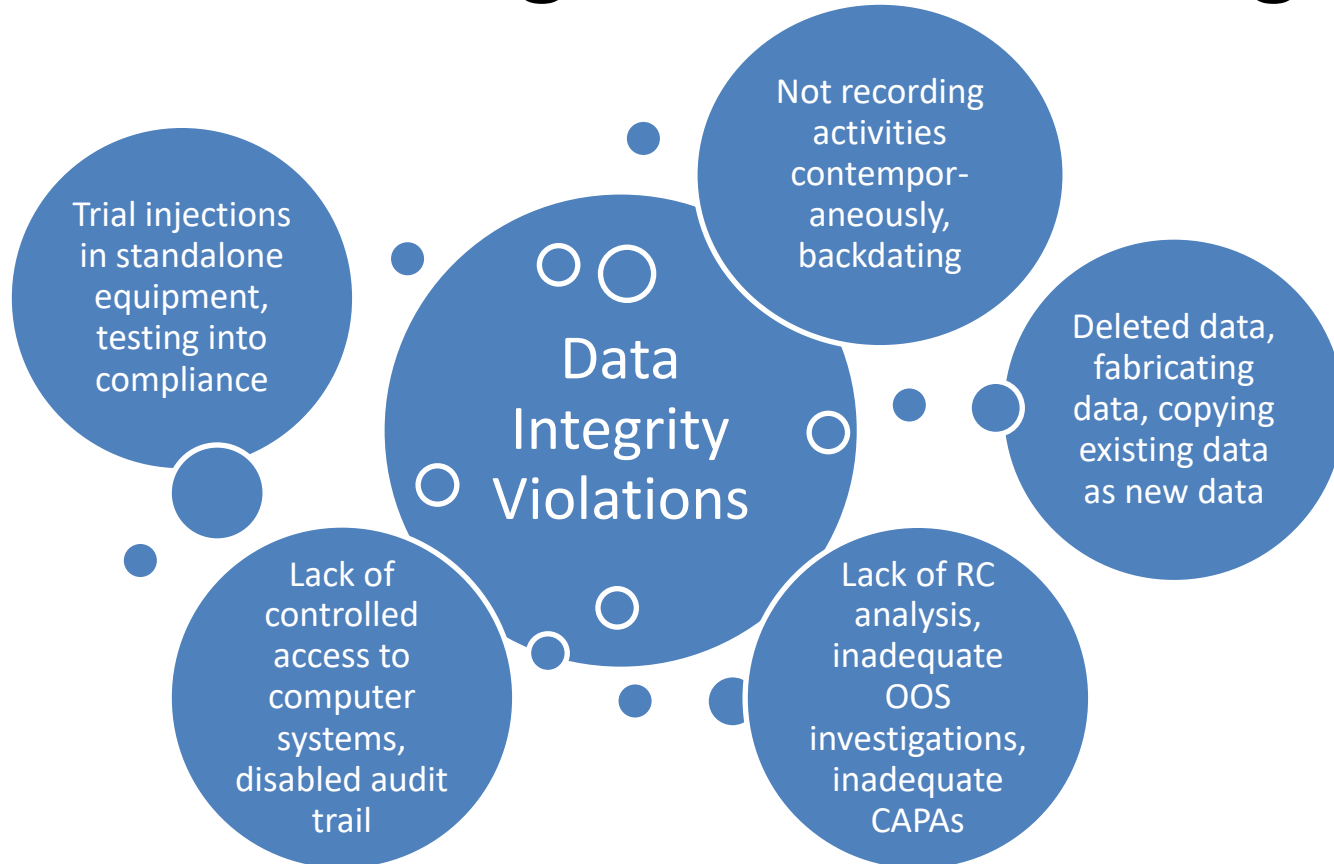
- FDA must have confidence that application data is a true and reliable representation of drug quality
- **Industry:** Responsibility to ensure the safety, efficacy, and quality of drugs
- **FDA:** Ability to protect public health
- **Public:** Breach in data integrity breaks trust

FDA's CGMP Data Inspection



- All records under CGMP subject to FDA inspection
- Allowed to conduct authorized inspection, review, and copying of records, including
 - Copying of electronic data (211.180(c) and 212.110(a),(b))
 - In lieu of an inspection (section 704(a)(4) of the FD&C Act)
- Increasingly observed CGMP violations involving data integrity during inspections
 - For example, in FY 2020, 57 citations* related to 211.68(b): Appropriate controls shall be exercised over computer systems
 - FDA's continued focus on data management and data integrity, particularly for electronic data

Recent Warning Letters Involving DI



Myths about Data Integrity Breaches



- Only QC issues in the laboratory
- Only one system is affected
- Only one person doing the wrong thing is responsible
- Senior management not responsible, could not have known
- Just a matter of improving an SOP, having a training session, or firing an employee

Reality of Firms with DI Violations



- **A lack of basic laboratory controls** to prevent changes to electronic data
- **Routinely** re-tested samples without justification and deleted analytical data
- **Systemic data manipulation across facility**, including actions taken by **multiple analysts**, on **multiple pieces of testing equipment**, and for **multiple drugs**



The Importance of Quality Culture

- Firms should implement **meaningful and effective strategies** to manage data integrity risks
- **Management's involvement essential** in preventing and correcting DI problems
- It is the role of **management with executive responsibility** to create a **quality culture** that supports data integrity
- Without management support, quality systems can break down and lead to CGMP noncompliance

Case Example: A Deficient Quality Culture

- **Quality unit** aware of lack of controls in computer systems but failed to correct problems
- **Quality system** inadequate to ensure integrity of data generated at facilities
- **Site senior management** failed to take sufficient action to prevent recurrence of DI problems
- **Systemic** data manipulation and other CGMP violations at **multiple sites**

Effective Quality Culture

- Where employees understand that **data integrity** is an *organizational core value*
- Where employees are *encouraged to identify and promptly report* data integrity issues
- *Clear accountability* for data integrity in the organizational structure
- Consider implementing an enhanced **ethics** program

Effective Management Strategy



- Data integrity problems are not always intentional – sometimes they result from poorly controlled systems
- “As part of your corrective action and preventative action plan, describe the actions you...will take, such as **revising procedures, implementing new controls, training, or re-training personnel**, or other steps to prevent the recurrence of CGMP violations, including breaches of data integrity.”

FDA Warning Letter, March 2015

OPMA's Role in Data Reliability Assessment



- DI issues may be identified during surveillance inspections, pre-approval inspections, or in submitted application data
- Concurrent and parallel assessments between ORA, OC/OMQ (DI impact on distributed commercial products), and OPQ/OPMA (DI impact on pending applications)
- Assessments focus on corrective actions to prevent recurrence
- As well as remediation efforts to determine impact on completed activities (e.g., released product, submitted data)

ORA: Office of Regulatory Affairs

OC/OMQ: Office of Compliance/Office of Manufacturing Quality

OPQ/OPMA: Office of Pharmaceutical Quality/Office of Pharmaceutical Manufacturing Assessment

Collaborative Data Integrity Assessment



- For pending applications, OPMA evaluates DI findings, responses, and corrective actions to determine if
 - Sufficient demonstration of accuracy of application data
 - Confidence that pending applications impacted are reviewable
 - Quality of BE batch be confirmed; if not, repeat BE studies using material of reliable quality may be indicated
- OPMA actively collaborates with internal review disciplines (OPQ and OGD/OB) to resolve DI questions and determine whether BE batch was impacted / a new BE study is warranted
- ***Collaborations and knowledge sharing are key***

Summary

- Data integrity is a requirement of CGMP – DI breaches can mean adulterated drug
- Management role is critical in creating a quality culture that supports data integrity
- Evaluation of data integrity is a crucial aspect of OPMA's application review
- OPMA actively collaborates with internal review disciplines (OPQ and OGD/OB) to resolve DI questions

Challenge Question #1

Which of the statements are true?

- A. Applicants are ultimately accountable for the integrity and quality of the data in ANDAs
- B. Testing site management is responsible for the integrity and quality of the data generated at the site

C. Both A and B

Challenge Question #2

Which of the following statements is **NOT** true?

- A. Data integrity refers to the completeness, consistency, and accuracy of data
- B. Data integrity breach is a violation of CGMP
- C. Senior management is not responsible for and could not have known about data integrity breaches
- D. An effective quality culture is where employees understand that data integrity is an organizational core value and employees are encouraged to identify and promptly report data integrity issues

Closing Thought



Are you satisfied with your company's
quality culture to support data
integrity?

Questions?

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