Data Integrity Issues in Today’s Complex and Global Manufacturing Supply Chain: Regulatory Perspective

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Data Integrity Breaches on Inspection

- Ensuring data integrity is an important component of industry’s responsibility to ensure the safety, efficacy, and quality of drugs, and of FDA’s ability to protect public health.

- Increasing rate of FDA observing practices at facilities that undermine the veracity of data generated

- Practices implicate both marketed product and exhibit / bio batches manufactured for the application
Recent Warning Letters

- Lack of controlled access to computer systems
- “Trial” HPLC injections
- Trial injections in stand alone equipment, outside a quality structure
- Deleted data
- Not recording activities contemporaneously
- Backdating
- Fabricating data
- Copying existing data as new data
- Discarding or deleting results with no justification and re-running/retesting samples to present better results
- Disabled audit trail feature
Recent Warning Letters

- Releasing failing product as if it had passed
- Testing into compliance
- Not saving electronic or hard copy data that would confirm the failing results
- Inadequate out of specification investigation
- Inadequate CAPAs
- Root cause lacking scientific evidence
Myths about data integrity breaches

- Only QC issues in the laboratory.
- Only seen in HPLC chromatography or GC equipment.
- Only one person doing the wrong thing is responsible.
- Senior and corporate management are not responsible and could not have known.
- Only one system is affected.
- Just a matter of improving an SOP, having a training session, or firing an employee.
- **There is NO correlation between DI occurring at a firm and the investigator doing the inspection.**
Why Data Integrity Matters

Data integrity breaches cast doubt on all results and records.

• Can we trust what we see during an inspection?
• Are drugs within specification?
• Is data submitted in applications to FDA reliable and truthful?
• Can we be confident in providing these drugs to patients?
What happens when DI is found?

- Concurrent and parallel assessments between ORA, OMQ, and OPQ.
- Assessments focus on corrective actions to prevent recurrence as well as remediation efforts to determine impact to completed activities (e.g., released product, submitted data, etc...)

Manufacturing and testing of approved products for distribution

What is the quality of distributed product?

Effective CAPA to prevent recurrence?

Bad data integrity practices

Better data integrity practices

Is the submitted data reliable?

Manufacturing and testing for exhibit / bio batches
Data Reliability Application Assessment

• OPQ evaluates findings, responses, and corrective actions to determine if:
  
  • Sufficient demonstration of the veracity of application data generated by the facility
  
  • Provided confidence that pending applications impacted are reviewable (i.e. the data reviewed will lead to meaningful decisions).
Data Integrity Remediation

Options

1. Leave.
2. Freeze.
3. Find root cause and remediate.
Remediation – Step 1

FDA requires a **comprehensive evaluation** of data integrity deficiencies.

**Expectations:**
- Detailed description of strategies and procedures for finding scope of problem
- Comprehensive, thorough, and complete evaluation
- List of records, applications, and other documents that have been/will be examined

**Scope:**
- People
- Systems – involved in the data integrity breach and other related systems that could have the same problems:
  - raw materials, components and ingredients
  - testing records
  - production and process records
  - equipment

Third-party consultants may be needed.
“...a comprehensive evaluation of the extent of the inaccuracy of the reported data. As part of your comprehensive evaluation, provide a detailed action plan to investigate the extent of the deficient documentation practices. . .”

~ recent FDA warning letter
Comprehensive Evaluation

Examine organizational structure and personnel responsibilities:

Who and what is the real source of the problem?

Temptation is to blame one employee or a small group of employees.

- Firing people who were not responsible for creating the problem will not help.
Risk assessment of potential effect on drug product quality and application quality

Determine effect of deficient documentation practices on the quality of the drug product released for distribution.

Issues:

- Were out-of-specification (OOS) drugs shipped?
- If yes, what is the impact on patients?
- Even if no OOS drugs were shipped, it is important to maintain appropriate preventative controls.

Determine effect on pending application data:

- Can I trust my development data to support the manufacturing process and drug product quality?
- Can I trust the submission batch data supporting bioequivalence and stability?
“…A **management strategy** that includes the details of your global **corrective action and preventative action plan**.”

Describe the actions you have taken or will take, such as contacting your customers, recalling product, conducting additional testing, adding lots to your stability programs to assure stability, monitoring of complaints and/or other steps to assure the quality of the product manufactured under the violative conditions.”

~ FDA Warning Letter, March 2015
Management Strategy

“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
Key elements of a Corrective Action and Preventative Action Plan:

- analysis of findings
- consultant’s recommendations
- corrective actions taken
- timetable
- identification of responsible persons
- procedures for monitoring the plan
Management Strategy 3

*Clear accountability* for data integrity in the future.

Consider implementing an enhanced ethics program.

Data integrity problems are not always intentional – sometimes they result from poorly controlled systems.
What is the goal of a successful remediation?

Reconstruct the manufacturing process and product quality testing through records to provide certainty that there is no:

• false data
• omission of data
• hiding of data
• substitution of data

Re-establish FDA’s confidence in the data under review in applications
Points to Consider on Application Data

The domino effect of loss in trust and confidence in reliability of application data:

- DMF adequacy
- Stability batches
- Clinical/BE batches

How does FDA know what we’re approving?

How do you know what you are making?
Closing Thoughts

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

Application review process is built upon the premise that the information presented for review is reliable.

Data integrated is needed to continue improve access to safe, quality, effective medicine.
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