U.S. FOOD & DRUG ADMINISTRATION

Breach in Data Integrity: Regulatory Outcome
"Is it the end or beginning of the story"
"Remediation and Resolution"

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General Overview

- Why Does DI Matter?
- Individual-Supervisors-Personnel-Group-Unit-Corporate involvement or knowledge
- How to fix a broken or defective organization ?

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, safe and effective?
- Is data submitted to support applications, assess quality of drugs and release batches reliable, truthful, accurate, original?
- Can we be confident in providing these drugs to our patients?

Why Data Integrity Matters

If data integrity has failed, what needs fixing?

- Data integrity – illuminates state of the quality system
- Serious data integrity problems – deficient quality systems
- Quality systems require sustained effort and resources to fix.
- Changing culture; much harder than changing equipment.

Data Integrity and Quality System

What is a quality system?

- GMP requirements' central objective: a system (policies and processes) that prevents errors and defects – Pharmaceutical Quality System (PQS).
- PQS success assures an ongoing state of control.
- PQS culture means vigilance, timely action, early warning of emerging quality issues.
- Appropriate, scientifically sound decisions are made.

I forgot to record a mixing time Is this a DI issue? Am I in Trouble ?

It depends.

-What did you do ?

-Who was notified?

- Impact/Extent

- Risk

- CAPA

Key Questions
Related to any Potential DI Scenario

Who: persons, departments involved, who knew

What: happened and data was affected, extent of the problem, release/in-process/stability/ application submission testing

When: did it happen, element of time

Why: did it happens, determines gaps

Where: equipment/systems affected

How: did it happen, part of gap analysis and for how long has it been going on

Data Integrity and Quality System

Managers should establish a vigilant quality culture in which:

- Timely action prevents risks to quality
- Lifecycle adaptations address manufacturing weaknesses and continually improve systems
- Effective process performance and product quality monitoring provide early warning of emerging quality issues
- Systemic solutions are implemented rather than ineffective shortcuts
- Small problems are habitually fixed so to prevent their accumulation into costly, complex problems

Data Integrity Problems

Recent examples:

- Falsified sterility test data
- Falsified or manipulated media fill data
- Failing Results Disregarded/Invalidated without a scientifically sound justification
- Out-of-Specification results for releases, stability, application submission batches ignored, not investigated

Data Integrity Problems

What does a **regulator** do when he or she finds deficiencies like these?

What is a **firm** expected to do when data integrity problems are found (by the firm or by a regulator)?

Data Integrity Problems

What we know:

- Data was falsified.
- OOS results were not reported.
- Chromatographic parameters were altered to obtain favorable results.
- Only good results reported.
- Release batches considering only favorable results.

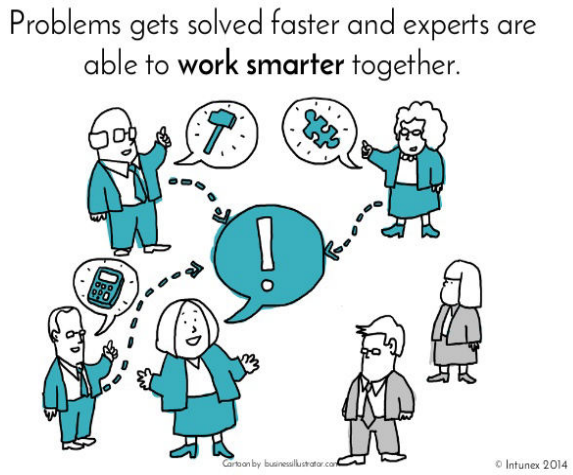
What do you do?

Data Integrity Remediation

Options

1. Leave.

2. Freeze.



3. Find root cause and remediate.

DI Remediation Recommendations

1. Hire a qualified consultant with experience in data integrity.
2. Conduct a comprehensive investigation into the extent of the inaccuracies in data record and reporting.
3. Methodology
4. Summary of laboratory/manufacturing operations
5. Interview current/former employees

DI Remediation Recommendations (cont.)

6. Assess extent: identify omissions, alterations, deletions, record destructions, non-contemporaneous records.
7. Describe all operations where DI lapses are discovered.
8. Identify the nature, scope, and root cause.
9. Comprehensive retrospective evaluation of the nature of DI testing/manufacturing deficiencies.

DI Remediation Recommendations (cont.)

10. Analysis of risk to patients, and risk posed by ongoing operations.
11. Management strategy for site, including global CAPA.
12. How firm intends to assure reliability of data generated, including analytical/manufacturing and all data submitted.

DI Remediation Recommendations (cont.)

13. Comprehensive description of the root causes.
14. Present evidence that the scope is commensurate with the DI findings and risk assessment.
15. Are individuals involved in DI lapses still able to influence CGMP related or drug application data?
16. Interim/Long Term Measures.
17. Update Report.

Remediation – Step 1

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

Third-party consultants highly recommended, not required. Necessary to have experience in:

- assessing data integrity
- crafting remediation plans
- regulatory agencies' expectations
- must be qualified and impartial

Comprehensive Evaluation 1

*"…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

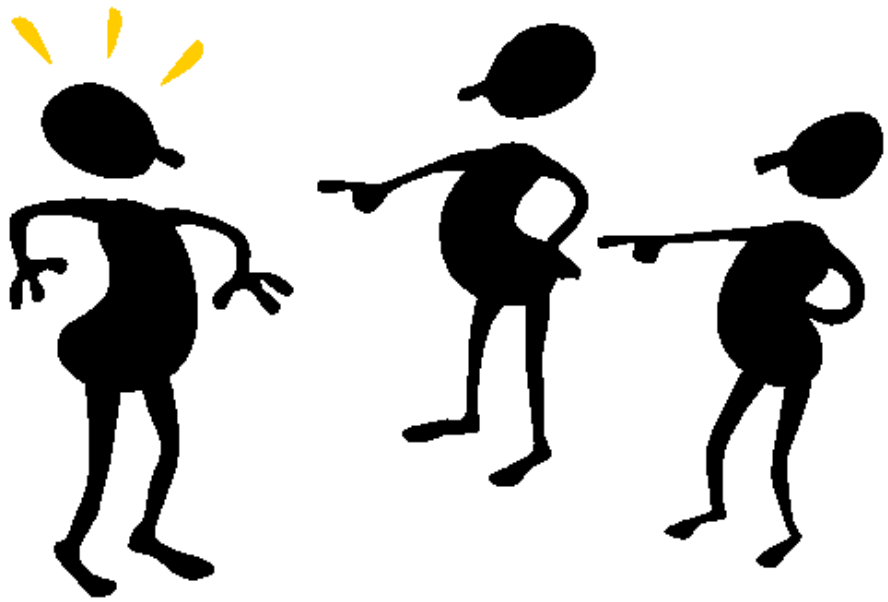
Comprehensive Evaluation 2

Examine organizational structure and personnel responsibilities:

- Nature of management's involvement
- Standard Operating Procedures
- Contract agreements

Comprehensive Evaluation 3

- 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.



Comprehensive Evaluation 4

What is FDA looking for in a comprehensive evaluation?

- 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

Comprehensive Evaluation 5

Scope of evaluation

- People – interview people identified by FDA and by consultant.
- 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

Remediation – Step 2

Risk assessment of potential effect on drug product 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.

Remediation – Step 3

"…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

Management Strategy 2

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.

Data Integrity Remediation Goals

What is the goal of a successful remediation?

We want **you** and the regulators to be able to reconstruct the manufacturing process through records.

We want certainty there is no:

- false data
- omission of data
- hiding of data
- substitution of data

Data Integrity

Applications for FDA approval of new drugs and generics

- FDA investigators may focus on “submission batches.”
- Data integrity breaches in application data can be particularly difficult for companies. Put controls in place to avoid this at all costs.

Data Integrity Remediation

Last step in the journey – re-inspection

- Investigators will look at corrective actions.
- Failure to implement corrective actions as promised may:
  - prevent FDA from lifting an import alert
  - create uncertainty about drug applications

If You Find a Data Integrity Problem

- Disclose it to regulators. FDA is much more willing to work with firms that voluntarily disclose and commit to fixing problems.
- Determine the scope of the problem and commit to voluntary remediation.

Closing Thoughts

- Data integrity is in everyone's interest.
- Patients' interests and the firms' interests are very well aligned.
- Interruption of drug supply is difficult for:
  - the firm
  - patients
  - regulators

More Closing Thoughts

Unreliable data

- difficult to achieve efficient, reliable, and robust systems
- risk of regulatory action

"I intend to make Alcoa the safest company in America. I intend to go for zero injuries."

— Paul O'Neil, former Alcoa CEO

Alcoa focused on reducing workplace injuries resulted in better managed and more efficient facilities.

Last Word

O'Neil's focus on safety created change that rippled through the whole culture.

- focus on worker safety
- examination of inefficient processes

Same is true for data integrity.

- zero-tolerance approach to data integrity
- benefits beyond patient safety

Good data can help illuminate whether operations are efficient and under control

Questions?

FDA compliance information online:
www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm081992.htm

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