Data Integrity Case Studies

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Outline

1. What OMQ Does
2. Draft Data Integrity Guidance
3. Recent Data Integrity Case Examples
4. Questions
What OMQ Does

Office of Compliance mission:

Promote and protect the public health through strategies and actions that minimize consumer exposure to unsafe, ineffective, and poor quality drugs.

Office of Manufacturing Quality (OMQ):

We focus on the drug manufacturing aspect of this mission.
OMQ Actions
January to August 15, 2016

- Import Alerts 66-40, 16
- Import Alerts 99-32, 15
- Untitled Letters, 2
- Warning Letters Issued & Cleared, 26
- Injunctions, 3
- Pharmacy Compounding Letters, 32
- Regulatory Meetings, 17
Data Integrity

FDA continues to see a significant number of CGMP violations due to lack of data integrity.

Numerous regulatory actions result:

- Warning Letters
- Import Alerts
- Consent Decrees
New Draft Guidance

Data Integrity and Compliance with CGMP

- Question and Answer format
- Published April 2016
- Online at:

What is Data Integrity?

From the draft guidance:

“Data integrity refers to the completeness, consistency, and accuracy of data. Complete, consistent, and accurate data should be attributable, legible, contemporaneously recorded, original or a true copy, and accurate (ALCOA).”
Recent Data Integrity Case Examples

- The following 6 cases are examples from 2016 regulatory actions.
- Each touches on questions raised in the draft guidance.
Case 1: Testing on the Side

Background

• Two separate API manufactures
• During inspection each was observed to be pretesting API samples, and storing results in auxiliary folders.
• One firm labelled their auxiliary folder “Test,” the other “R&D.”
• Later, official sample runs were completed and stored in official folders.
• Extensive volume of unofficial tests
Case 1: Testing on the Side

What happened

• Firms both postulated that systemic API sample pretesting was related to system suitability problems.

• But data indicated auxiliary folders included OOS investigations/results.

• Yet “official” results/quality-release decision did not include any of this data.

• FDA issued Warning Letters to both firms.
Sidebar: System Suitability

Draft Guidance, Question 13

Q: Why has the FDA cited use of actual samples during “system suitability” or test, prep, or equilibration runs in warning letters?

A: In some situations, use of actual samples to perform system suitability testing has been used as a means of testing into compliance.
Sidebar: System Suitability

- System suitability should be performed using a qualified standard.
- If a drug sample is being used as a reference standard, it has to be fully qualified to become a reference standard, and needs to be from a different batch than the sample to be tested.
Case 1: Testing on the Side

From the guidance:

“We would consider it a violative practice to use an actual sample in test, prep, or equilibration runs as a means of disguising testing into compliance”

Takeaway:

Only test your actual samples after you’ve performed system suitability with a qualified standard.
Case 2: Those Pesky Impurities

Background:

• API manufacturer.
• Firm had process problems.
• Problems led to OOS levels of residual solvent impurities in the finished API.
Case 2: Those Pesky Impurities

What Happened Next

• Firm routinely manipulated chromatograms and deleted impurity peaks so product appeared to be within specifications.

• Analyst even admitted to substituting a reference standard chromatogram instead of testing a sample.

• Warning Letter and Import Alert
A Note on Impurities

• Impurity specifications, even in fractions of a percent, can matter to patient health.

• From ICH Q3C Guidance:
  “Drug products should contain no higher levels of residual solvents than can be supported by safety data.”

• In this case, the data for known genotoxic/carcinogenic impurities were manipulated.
Case 2: Those Pesky Impurities

Takeaway

• When evaluating impurities, consult ICH Q3 guidance documents, as well as any monograph and product specific requirements.

• If you have problems with impurities, whether due to process problems or raw materials, they should be addressed.

• Data manipulation does not solve the problem.
Case 3: A Stitch in Time

Background

• Two API manufacturers.
• Both used audit trails on their electronic analytical equipment.
• Both reported passing results.
Case 3: A Stitch in Time

What happened

• On inspection, FDA investigators found data manipulation signs in audit trails.
• Analysts deleted data and retested samples.
• Analysts even altered computer clock settings to backdate analytical tests.
• Lab personnel admitted falsification of data when presented with audit trails.
A Note on Audit Trail Review

Draft DI Guidance Question 7

Q: How often should audit trails be reviewed?
A: FDA recommends that audit trails that capture changes to critical data be reviewed with each record and before final approval of the record. Audit trails subject to regular review should include, but are not limited to, the following: the change history of finished product test results, changes to sample run sequences, changes to sample identification, and changes to critical process parameters.
Case 3: A Stitch in Time

Takeaway

• In these cases, audit trail review would have caught manipulation before FDA inspection.
• Audit trails should be reviewed prior to product release.
• Verify that runs are done properly; also look for anomalies as signs of a larger problem.
• This can help ensure test results used to release drugs are accurate.
A Note on Shared Passwords

From one of the previous cases:

“Quality Control (QC) analysts used administrator privileges and passwords to manipulate your high performance liquid chromatography (HPLC) computer clock to alter the recorded chronology of laboratory testing events.”
A Note on Shared Passwords

Draft Guidance, Question 4

Q: How should access to CGMP computer systems be restricted?

A: FDA recommends that you restrict the ability to alter specifications, process parameters, or manufacturing or testing methods by technical means where possible (for example, by limiting permissions to change settings or data). FDA suggests that the system administrator role, including any rights to alter files and settings, be assigned to personnel independent from those responsible for the record content.
Case 4: A Tale of Two Sets of Books

Background

- API manufacturer.
- Complaints are officially logged in a hard copy book.
- During inspection, FDA finds papers in the trash not matching the official records.
- Specifically, a second unofficial complaint log
Case 4: A Tale of Two Sets of Books

What Happened

• Discarded complaints covered sub-potent product and contamination with particles, insects, and dirt.

• None were in the official log.

• Firm admitted there were likely other unlogged “unofficial” complaints.

• Firm received Warning Letter and Import Alert.
Paper vs Electronic Records

Guidance excerpt from answer to question 2

“The requirements for record retention and review do not differ depending on the data format; paper-based and electronic data record-keeping systems are subject to the same requirements.”

Guidance excerpt from answer to question 6

“Similarly, bound paginated notebooks, stamped for official use by a document control group, allow detection of unofficial notebooks as well as of any gaps in notebook pages.”
Case 4: A Tale of Two Sets of Books

Takeaway

• Complaint information should be evaluated to determine if there are both acute and potentially systemic issues.

• Data Integrity issues found in both electronic and paper based systems.
Case 5: Broken Promises

Background

• Contract analytical testing lab
• FDA inspection finds poor lab controls, but no direct evidence of data manipulation.
• Firm commits to implementing controls (audit trails, password protection, etc.).
• FDA classifies the site as acceptable based on firm’s promises.
Case 5: Broken Promises

What Happened

• At next inspection, FDA found firm had not implemented any updated controls.
• Even though it had committed to do so.
• FDA issued Warning Letter.
• WL triggers accelerated reinspection to verify corrective actions implemented.
Case 5: Broken Promises

Takeaway

• FDA keeps records of what firms commit to.
• FDA routinely checks to see if previous commitments have been implemented.
• If a firm doesn’t follow through on previous commitments, it reduces the credibility of future promises.
• Follow through on what you say you’re going to do. It’s in everyone’s best interest.
Case 6: The C in ALCOA

Background

• Two API manufacturers.
• Both had problems completing records at time of performance.
• One had problems in the production area.
• The second in the lab.
Case 6: The C in ALCOA

What Happened

• First firm created unofficial “mock” batch records.
• Days after production firm would create/backdate the official records.
• Backdated records didn’t match the “mock” data from actual production.
• FDA issued Warning Letter.
Case 6: The C in ALCOA

What Happened

• Second firm’s microbiology lab had poor practices.
• Analyst would perform tests, but wouldn’t fill out results until days later.
• Analyst stated they filled out the records later “by memory” and when “they had time.”
• But FDA also found evidence that the tests in question might not have happened at all.
• FDA issued Warning Letter and Import Alert.
Case 6: The C in ALCOA

Takeaway

- The C in ALCOA is for “contemporaneously” recorded.
- FDA has seen firms backdating both paper and electronic records.
- Backdating records is a CGMP violation
- Backdating raises questions regarding record accuracy.
Note on Refusals

- Some recent data integrity cases have also come from inspections where information was not forthcoming.

- Two recent examples:
  - Saying something isn’t there, when it is.
  - Leading an investigator out of a lab on purpose (so lab records could then be created/backdated).
Note on Refusals

• Draft Data Integrity Guidance Question 17:
  – Q “Is the FDA investigator allowed to look at my electronic records”
  – A: “Yes. All records required under CGMP are subject to FDA inspection.”

• An escalation factor when evaluating data integrity cases is whether a firm is forthcoming during inspection

• For more information, see FDA’s Guidance on Circumstances that Constitute Delaying, Denying, Limiting, or Refusing a Drug Inspection
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Questions?