CDER Office of Compliance

Thomas J. Cosgrove
Office of Manufacturing Quality Director

An Introduction to Data Integrity and Meeting the CMP Requirements
Indian Pharmaceutical Alliance
21st Century Manufacturing Vision

“A maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high quality drugs without extensive regulatory oversight.”

Dr. Janet Woodcock
Director, FDA Center for Drug Evaluation and Research
Office of Compliance Structure

Office of Drug Security, Integrity and Response (ODSIR)
Office of Manufacturing Quality (OMQ)
Office of Scientific Investigations (OSI)
Office of Unapproved Drugs and Labeling Compliance (OUDLC)
Office of Program and Regulatory Operations (OPRO)
Compliance & Enforcement Actions

- Consent decrees
- Import alerts
- Seizures
- Warning letters
- Clinical investigator disqualifications
- Criminal indictments/convictions

Unapproved drugs
Health fraud
Data integrity
CGMP violations
GCP violations
Compliance/OMQ Actions


- Import Alerts, 21
- Untitled Letters, 6
- Warning Letters, 23
- Injunctions, 2
OMQ Primary Considerations

Is the drug “adulterated”?  
- Food, Drug & Cosmetic Act  
- FDA regulations at 21 CFR 210 & 211  
- API standards set forth in ICH Q7

Most important? Patient risk  
- High risk ➔ FDA takes quick action.  
- Sub or super-potent  
- Contamination  
- Sterility concerns  
- Other defects
Dilemma: Lack of Reliable Information

**Case 1:** Failure occurs. Cause, required corrective actions, and impact on patients are well defined and understood.

**Case 2:** Adverse event triggers FDA inspection. Investigator finds that lab records are unreliable.
- Results have been deleted or replaced.
- Some results not recorded.
- Many analyses were performed without audit trails.
Will FDA Issue an Import Alert?

CGMP Import Alert issued if:

• Violation could cause drug quality defect with potential adverse patient health consequences
• Repeat violations
• Refusal or delay of an inspection
• Significant data integrity violations
Data Integrity

CGMP = minimum requirements

Data integrity underpins CGMP

Lapses obscure other problems

Tip of iceberg
What is Data Integrity?

*Data integrity* = requirements for complete, consistent, and accurate data.

The concept of data integrity underpins CGMPs.

Applies to CGMP and Good Clinical Practice (ICH E6).

**ALCOA**

- **Attributable**
- **Legible**
- **Contemporaneous**
- **Original or true copy**
- **Accurate**
What is Data Integrity?

Important Concepts:

- Metadata
- Audit Trail
- Static vs. dynamic records
- Backup datasets
- System validation
Data Integrity: Not a New Concept

Principles from the paper-and-ink era still apply. US Code of Federal Regulations requirements:

- backup data are exact and complete, and secure from alteration, inadvertent erasures, or loss (211.68)
- data is stored to prevent deterioration or loss (212.110(b))
- certain activities are documented at the time of performance and that laboratory controls be scientifically sound (211.100 and 211.160)
- true copies or other accurate reproductions of the original records (211.180)
- complete information, complete data derived from all tests, complete record of all data, and complete records of all tests performed. (211.188, 211.194, and 212.60(g))
API – ICH Q7

Computerized Systems (5.4)

– GMP-related computerized systems should be validated.
– The depth and scope of validation depends on the diversity, complexity, and criticality of the computerized application.
– Appropriate installation and operational qualifications should demonstrate the suitability of computer hardware and software to perform assigned tasks.
Incidents related to computerized systems that could affect the quality of intermediates or APIs or the reliability of records or test results should be recorded and investigated.
More on ICH Q7

Computerized Systems (5.4)

• Changes to computerized systems should be made according to a change procedure and should be formally authorized, documented, and tested.

• Records should be kept of all changes, including modifications and enhancements to the hardware, software, and any other critical component of the system.

• These records should demonstrate that the system is maintained in a validated state.
Common Data Integrity Failures

- lack of controlled access to computer systems
- not reporting “trial” chromatographic injections
  - trial injections in stand-alone equipment
  - no Quality Unit data review
- deleting data
- not recording activities contemporaneously
- backdating
More Data Integrity Failures

- fabricating data
- copying existing data as new data
- re-running samples
- releasing failed product
- testing into compliance
- not saving electronic or hard copy data

Why would firms tolerate this behavior?
Why is data integrity important?

- Breaches may conceal risks to patients.
- FDA depends on reliability of information to ensure drug quality.
- A data integrity breach (records, electronic) breaks confidence between regulator and regulated.
- FDA relies on firms to do the right thing when we are not there.
- Without reliable data, CDER vision cannot be realized.
Why is Data Integrity Important?

Data integrity: Good for patients, good for business

- Enhances and sustains brand
- Provides basis for management oversight of systems and processes
- Without reliable and accurate data, building efficient and robust systems is difficult (or impossible).
- Reduces risk of Import Alert or Warning Letter
- Competitive advantages for individual firms and regions of the world
Failures Cited in Recent Warning Letters

• Failed analytic results hidden, time/date settings manipulated, analyses re-integrated to achieve passing results; blank logbooks filled out during inspection. *January 2016*

• Routine re-testing of analytic data and deleting original results; systematic disabling of system audit trails. *December 2015*
Failures Cited in Recent Warning Letters

- Previously undisclosed laboratory conducting “off book” CGMP analyses. November 2015
- Substitution of results following failing lab results; failure to record critical values at time activities were performed in cases involving highly potent drugs. November 2015
- Uncontrolled access to data systems and no audit trails. November 2015
Failures Cited in Recent Warning Letters

• Completed batch production records days after operations ended. Also released lots before Quality Unit approvals. *July 2015*

• Failure to maintain original manufacturing data, contained in “rough notes.” *July 2015*
Failures Cited in Recent Warning Letters

• Failure to control access to data systems, July 2015

• Fabricated impurity data, June 2015

• Failure to maintain backup chromatograms that would provide “dynamic” data, May 2015

• Failure to maintain access controls, May 2015
Failures Cited in Recent Warning Letters

- Altered results of identity tests. *April 2015*
- Lack of access controls to prevent manipulation of data. *April 2015*
- Lack of audit trails for lab instruments. *April 2015*
- Turning off audit trail. *April 2015*
Failures Cited in Recent Warning Letters

• Failure to exercise controls over data systems. Analysts could delete lab results. *March 2015*

• Trial HPLC injections and retests of samples without reporting original results. *March 2015*
Failures Cited in Recent Warning Letters

• Failure to retain HPLC raw data. *February 2015*

• Selective discarding of HPLC data. *February 2015*

• Failure to prevent unauthorized access or changes to data. *February 2015*
Failures Cited in Recent Warning Letters

• Trial HPLC injections, disregarding test results, and reporting only results from additional tests. *January 2015*

• Unreported product failures, labeled “trial” HPLC injections. Similar failures for gas chromatography, ultra violet spectroscopy and moisture analyses. *January 2015*

• Failure to control access to data systems. *January 2015*
Responding to Data Integrity Failures

If you receive an FDA Warning Letter with data integrity citations, respond with 3 key pieces:

• Comprehensive Evaluation
• Risk Assessment
• Remediation and Management Strategy
Comprehensive Evaluation 1

“...a comprehensive evaluation of the extent of the inaccuracy of the reported data . . . .

recent FDA warning letter
Comprehensive Evaluation 2

Examine organizational structure and personnel responsibilities:

- nature of management involvement
- SOPs (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.
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 – examine those 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
Risk Assessment

Assess 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 impact on patients?
• Even if no OOS drugs were shipped, it is important to maintain appropriate preventative controls.
Remediation & Management Strategy

“...A management strategy that includes the details of your global corrective action and preventive 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
Corrective Action and Preventive Action Plan (CAPA)

“As part of your corrective action and preventive 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 CAPA

• analysis of findings
• consultant’s recommendations
• corrective actions taken
• time table
• identification of responsible persons
• procedures for monitoring the plan
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
Goal of successful remediation

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

We want certainty there is no data:

• falsification
• omission
• hiding
• substitution
Data Integrity

Applications for FDA approval of new and generic drugs

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

Last step: re-inspection

• Investigators 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
- Determine the scope
- Commit to voluntary remediation

FDA is much more willing to work with firms that voluntarily disclose and commit to fixing problems.
The Alcoa Example

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

~ Paul O’Neil, former Alcoa CEO

Alcoa’s focus on reducing workplace injuries made facilities more efficient.
Create a Data Integrity Culture

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**
Closing Thoughts

- Data integrity is in everyone’s interests
- Interests of patients and firms are aligned
- Interrupted drug supply is difficult for:
  - firms
  - patients
  - regulators
CGMP Q&As on Data Integrity

Are shared login accounts OK for computer systems?

Are electronic signatures OK for master production and control records?

Can we use actual samples to perform system suitability testing?

Detailed discussion online: [http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm124787.htm](http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm124787.htm)

2015 CDER Guidance Agenda includes CGMP Data Integrity Questions and Answers