



Preventing, Detecting, and Responding to Data Integrity Events

Background, Recent Findings, and Agency Expectations

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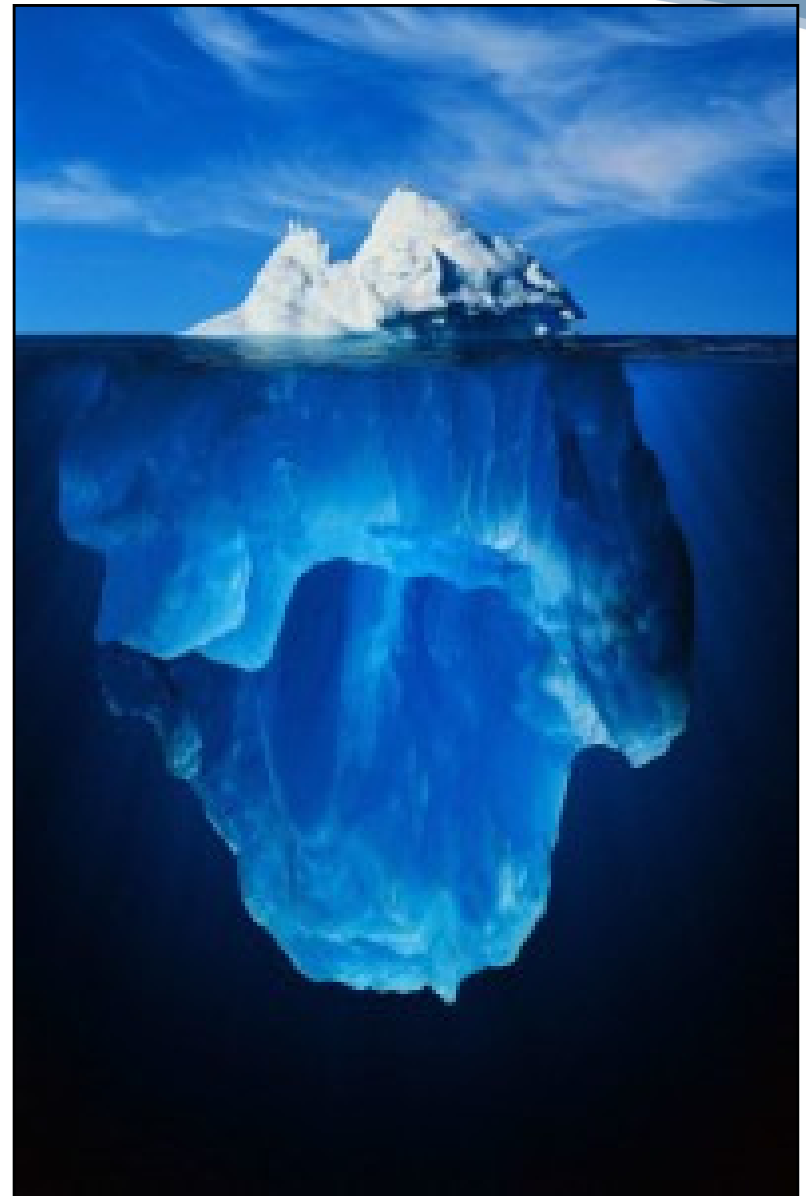
Data Integrity

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?

Other Important Concepts:

-  Metadata
-  Audit Trail
-  Static vs. dynamic records
-  Backup datasets
-  System validation



Nothing New Here

- § 211.68 requires that backup data are exact and complete, and secure from alteration, inadvertent erasures, or loss
- § 212.110(b) requires that data be stored to prevent deterioration or loss
- §§ 211.100 and 211.160 require that certain activities be documented at the time of performance and that laboratory controls be scientifically sound
- § 211.180 requires true copies or other accurate reproductions of the original records; and
- §§ 211.188, 211.194, and 212.60(g) require complete information, complete data derived from all tests, complete record of all data, and complete records of all tests performed.
- **ALL REQUIRED, WHETHER PAPER OR ELECTRONIC!**



APIs - ICH Q7

Computerized Systems (5.4)

- Validation of GMP-related computerized systems; depth and scope depends on diversity, complexity, and criticality of computerized application
- Is the software and hardware suitable to perform the task?
- Record and investigate incidents related to computerized systems that could affect the quality of intermediates or APIs or the reliability of records or test results



More on ICH Q7

Computerized Systems (5.4)

- Changes to computerized systems made according to change procedure; formally authorized, documented, and tested
- Records of all changes, including modifications and enhancements to hardware, software, and any other critical component
- Show that system is maintained in validated state



Why Data Integrity Matters

- **Patient Safety**
- **Access to Effective Drugs**

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

*~ Dr. Janet Woodcock
21st Century Manufacturing Vision*



Why Data Integrity Matters

- Data integrity provides foundation of pharmaceutical quality.
- Without reliable data, 21st Century vision (manufacturers produce high quality drugs without extensive regulatory oversight) cannot be realized.
- Breaches of data integrity erode confidence of regulator and public.



Why Data Integrity Matters

Data integrity breach: often leads to adulterated drug under U.S. law

Drug is adulterated because data integrity breach is a violation of CGMP.

- Under U.S. law, adulterated drug is subject to detention.
- Generally, significant CGMP issues require re-inspection.
- Firms must fix problems and be re-inspected.



Why Data Integrity Matters

“...the term ‘current good manufacturing practice’ includes the implementation of **oversight** and controls **over the manufacture of drugs to ensure quality**, including **managing** the risk of and establishing the safety of raw materials, materials used in the manufacturing of drugs, and finished drug products.”

Food and Drug Administration Safety and Innovation Act, Sec. 711
Enhancing the Safety and Quality of the Drug Supply



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.



Recent Warning Letters

- 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
- Quality Control Personnel created unauthorized folders on computerized laboratory systems without appropriate oversight – January 2015
- Trial HPLC injections, disregarding test results, and reporting only results from additional tests – January 2015
- 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
- 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



Recent Warning Letters

- 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
- Altered results of identity test results – April 2015
- Failure to maintain backups of chromatograms that would provide “dynamic” data – May 2015
- Failure to maintain access controls – May 2015
- Fabricated impurity data – June 2015
- 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
- Failure to control access to data systems – July 2015



New 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>

[2015 CDER Guidance Agenda](#) includes CGMP Data Integrity Questions and Answers



Responding to Data Integrity

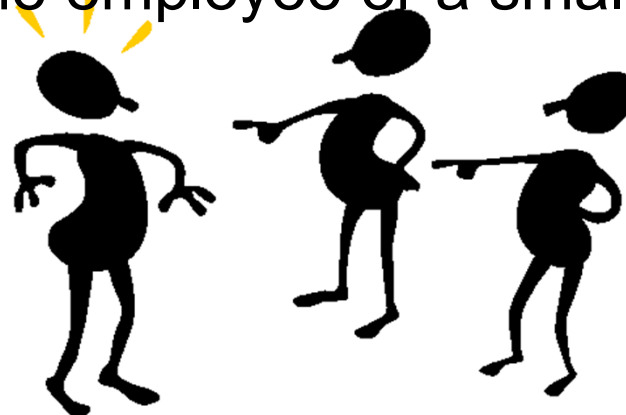
1. Comprehensive Evaluation
2. Risk Assessment—Product Quality
3. Management Strategy
4. (Do it! And keep us posted!)
5. Re-inspection

Comprehensive Evaluation

Conduct a **comprehensive evaluation** of extent of data integrity deficiencies.

- Consultants highly recommended, not required
- **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 to solve it.





Comprehensive Evaluation

What is FDA looking for?

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

Scope

- People – interview people identified by FDA (consultant)
- Systems – involved in data integrity breach ***and other related systems that could have same problems:***
 - ▶ raw materials, components and ingredients
 - ▶ testing records
 - ▶ production and process records
 - ▶ equipment



Risk Assessment

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.



Management Strategy

“...A **management strategy** that includes the details of your global **corrective action and preventative action plan.**”

Key Elements of CAPA:

- analysis of findings
- consultant's recommendations
- corrective actions taken
- timetable
- identification of responsible persons
- procedures for monitoring the plan



Management Strategy

- *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.

Certainty there is no:

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



Re-Inspection

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



Application Data Integrity

- 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.



Find a Data Integrity Problem?

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



Closing Thoughts

Unreliable data

- difficult to achieve efficient, reliable, and robust systems
- risk of regulatory action
- costly for patients and companies (and us)

There is no killing the suspicion that deceit has once begotten.

—George Eliot

But...

Sunlight is the best disinfectant.

—William O. Douglas



Questions?

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