

# Regulatory Perspective Data Integrity (2017)



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# OMQ focus: quality, risk



## Is a drug adulterated?

FD&C Act

Finished drugs:  
21 CFR 210, 211

API: ICH Q7

## Is patient safety at risk?

High risk → Quick action

Identity?

Contamination?

Sterility concerns?

Sub- or super-potent?

# Data Integrity (DI) Again?

- DI has been a hot topic for the past 5 years.
- The constant discussion has lead to more questions than answers about what is a breach in the integrity of data and what's not a DI issue.
- All DI breaches may be CGMP violations, but not all CGMP violations represent a DI issue.

# Basic Principles

- Regulatory authorities largely rely on trusting industry and people to routinely do the right thing (i.e., when the regulator is not there watching).
- A breach in the integrity of the data is a fundamental failure of the Quality System.

Accurate and reliable test results, essential in assuring the purity, potency (safety and effectiveness) of a drug



"WE'RE PRETTY SURE HE FALSIFIES THE RESULTS, BUT HE DOES IT BEAUTIFULLY."

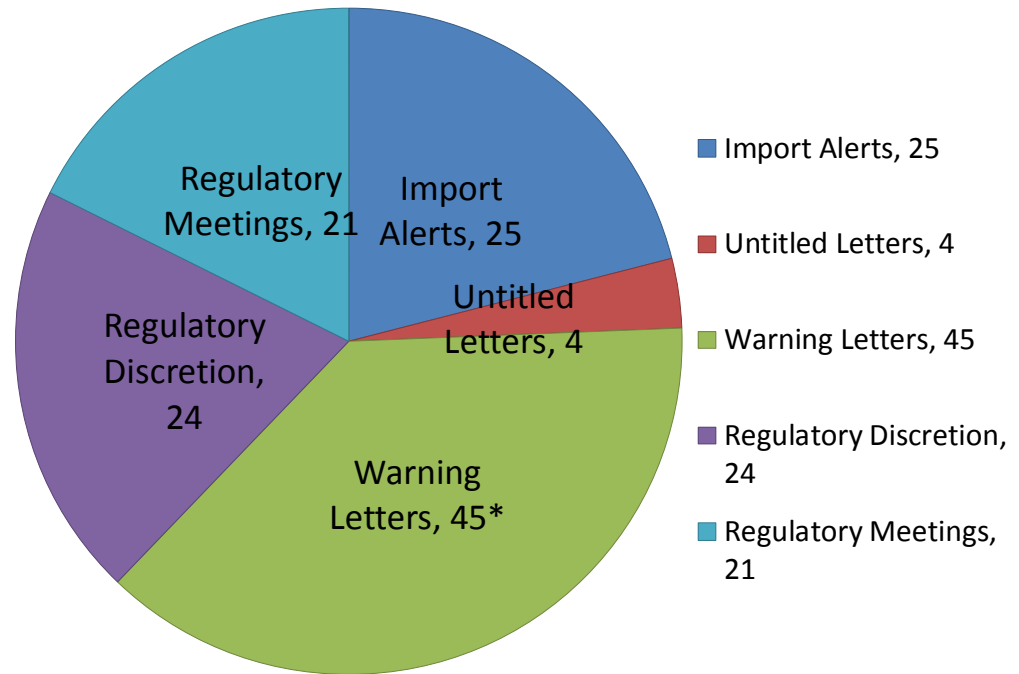
# Problem Statement

“Testing into compliance,” data manipulation, data deletion/record destruction, misreporting, disregarding failing and/or questionable results, all leading to possible breaches in the integrity of critical data, has become one of the most important and relevant topics currently discussed by industry and regulators from around the world.

# Enforcement and Advisory Tools

Regulatory Meetings	Injunctions
Consent Decrees	Import Alerts
Seizures	Warning Letters
Untitled Letters	Others

## 2017 Enforcement Actions



Through Sept. 1, 2017  
 Excludes compounding-related actions

\*Domestic and Foreign



# Will FDA Issue an Import Alert?

## CGMP Import Alert issued if:

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



# Myths about data integrity problems



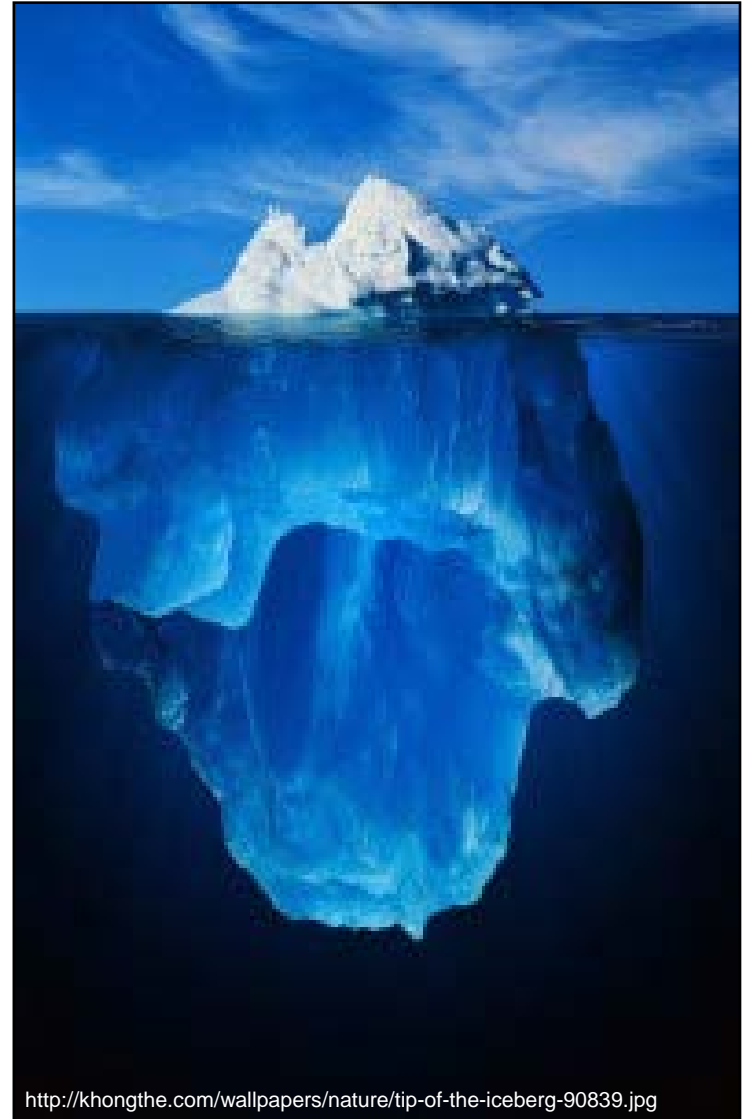
- It's only a QC issue in the laboratory.
- It's only seen in HPLC chromatography or GC equipment.
- It's only the responsibility of a person doing the wrong thing.
- Senior and corporate management are not responsible and could not have known.
- Only one system is affected.
- It's just a matter of improving 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.**

# Data integrity

- CGMP = minimum requirements
- Data integrity underpins CGMP
- Lapses obscure other problems

**Tip of the iceberg**



<http://khongthe.com/wallpapers/nature/tip-of-the-iceberg-90839.jpg>

# DI: Reflection of a Firm's Quality System Maturity



Level 4:

*Routinely* acts preventively as described in level 3. Fully institutionalizes and reinforces (rewards) a vigilant culture that makes lasting manufacturing & system improvements.

Level 3:

More proactive. *Increasingly* detects emerging adverse trends, surfaces major issues, and makes meaningful manufacturing & system improvements.

Level 2:

Nearly always reactive, but there is willingness to change. Patchwork corrections are the norm.

Level 1:

Small problems ultimately snowball into larger ones, and management becomes aware only when there is a crisis.



# Common Terminology When Data Integrity is Found



- Falsification of data
- Alteration of data and events
- Misleading information, statements or facts
- Misrepresentation of what really happened
- Untruthful statements
- Deceit
- Forgery



# Backdating, transcribing, recreating or making up records



# Common Terminology When Data Integrity is Found



- Provide or submit inaccurate information to gain a benefit or intention to deceive
- Breach in the integrity of data
- False information
- Data manipulation
- Misrepresentation of the facts by commission or omission of data or description of events
- Misreporting or selective reporting information

# Falsification of Data or Not Completing Records Contemporaneously is a Serious GMP Violation. Why does it happen ?

- Deficient Procedures
- Poor Quality Unit Oversight
- Immature Quality System
- Deficient training and procedures
- Bad behavior, encouraged by poor quality culture





Is unplugging or interrupting the chromatographic run or acquisition phase a DI issue ?



# More Data Integrity Failure Examples

- Releasing failing product as if they had passed
- Testing into compliance
- Not saving electronic or hard copy data that would confirm the failing results
- Question – *Why would firms tolerate this behavior?*

If you are cited for a DI problem don't  
make it worse



# Also, Do Not Run Away When a Regulator Knocks on the Door



# Don't Make Up Stories



# Dilemma for Regulators



**Case 1:** A firm obtains a failure (OOS), documents a “root cause”, implements a CAPA(s), determines there is no impact on patients and does not submit a Field Alert Report as they believed the problem was contained, defined and understood.

**VS**

**Case 2:** A reported adverse event triggers an FDA inspection. Investigator finds unreliable data:

- Results have been altered, deleted or replaced.
- Some results not recorded.
- Unjustified retest to invalidate the failing results
- Many analyses were performed without audit trails.

# Questions:

1. How should a regulatory agency proceed ?
2. What should a firm found with DI problems do? When should a firm contact the agency?
3. How should such dilemma be resolved?
4. What immediate questions should be may be raised? What Actions should be taken ?
5. How do we determine, impact, scope and extent of the problem, and determine possible trends?
6. How do we determine pattern and practice?



# Consequences of Violation to Federal Laws and Regulations (CGMPs)

1. Regulatory Actions (e.g., Dis problems) may take months/years to resolve (WLs, Uls, Import Alerts, NC Status)
2. Lost of credibility, reputation, trust and confidence from patients, regulators, industry and stockholders, etc.
3. Unnecessary delays in approval of pending and new drug applications
4. Impacts business reputation



# Consequences of Violation to Federal Laws and Regulations (CGMPs)

5. Because of the time it may take to recover (from breaches in DI), companies ability to focus on new technology and enhancement of processes and systems may be affected
6. Financial impact in contractual agreements with consultants and independent parties
7. Products are usually transferred to CMOs or other sites

# Consequences of Serious Violations to Federal Laws and Regulations (CGMPs)



8. May required full organizational changes
9. A company may be subject to criminal investigation that may result in prosecution
10. Companies may be placed under Injunction/Civil/Criminal Action
11. Product deemed adulterated could be seized

# Why is Data Integrity Important?



- Without reliable data, CDER vision (manufacturers produce high quality drugs without extensive regulatory oversight) cannot be realized.

# Why is data integrity important?

- DI is the foundation of pharmaceutical quality
- FDA relies on firms to do the right thing when we are not there.
- Breach in DI (records/electronic) erodes confidence/breaks trust of regulator and public.
- FDA CGMP surveillance inspections are usually focused to determine adherence to CGMPs, not to verify all data. Changing due to recent events.

# 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

“...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

## **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.

# Dilemma: Lack of Reliable Information

**Case 1:** Failure occurs but 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.



# Data Integrity: Not a New Concept



## Principles from the paper-and-ink era still apply:

- § 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.

# Data Integrity Failure Examples

## Common problems:

- 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

# 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

# Where do we draw the line ?

## DI scenario or Egregious CGMP violation?

1. Is backdating a DI situation or CGMP violation that needs immediate attention?
2. Is discarding or not keeping chromatograms, sample preparation information a DI problem or just a bad practice? Why
3. Is it a pattern. error or isolated incident ?
4. Does the intention matter?
5. Commission/ Omission

# Areas to Re-examine

Process  
Knowledge  
Change  
Controls  
Critical  
Parameters

Complaints  
Returned  
Goods

All Systems  
Affected &  
Extent of  
Problem

OOS  
Results-  
electronic  
and raw  
data

Deviations-  
process/lab

Critical  
Parameters, In-  
Process/  
Finished/  
Stability

Training  
Rejections

Feedback  
from "Shop  
Floor"

Current Staff  
Competencies

Raw  
Material  
Data

Results of  
Audits &  
Inspections

Process  
Trending Data  
Retrospective  
Review

# EXAMPLES OF WARNING LETTERS

Will be Discussed During  
Session of Inspection  
Trends

# SUMMARY

## 1. Integrity of Data: An Indication of a Healthy Quality System

- The inability to detect and prevent breaches in data integrity practices raises serious concerns about the reliability and effectiveness of the quality system.
- It is imperative that the data generated and used to make manufacturing and quality decisions is trustworthy and reliable.

# Summary

## 2. Commitment to Quality is Essential

- Significant impacts to the public health worldwide
  - Cost of poor quality
  - Cost to patients – drug shortages, adverse events, etc.
- Industry needs stronger commitment from the top down and bottom up; proactively identify and promptly correct issues; maintain facilities and equipment; implement robust quality management systems
- FDA is doing its part
  - Refocusing how we oversee quality



# Q&As on Data Integrity

## Draft guidance for industry



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>



FDA compliance information online:

[www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm081992.htm](http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm081992.htm)



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Office of Manufacturing Quality/Division of Drug Quality I  
Branch 2