# Data Integrity: Why Are We Still Having Issues?

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SIDLEY

# Food, Drug and Medical Device Compliance and Enforcement Practice

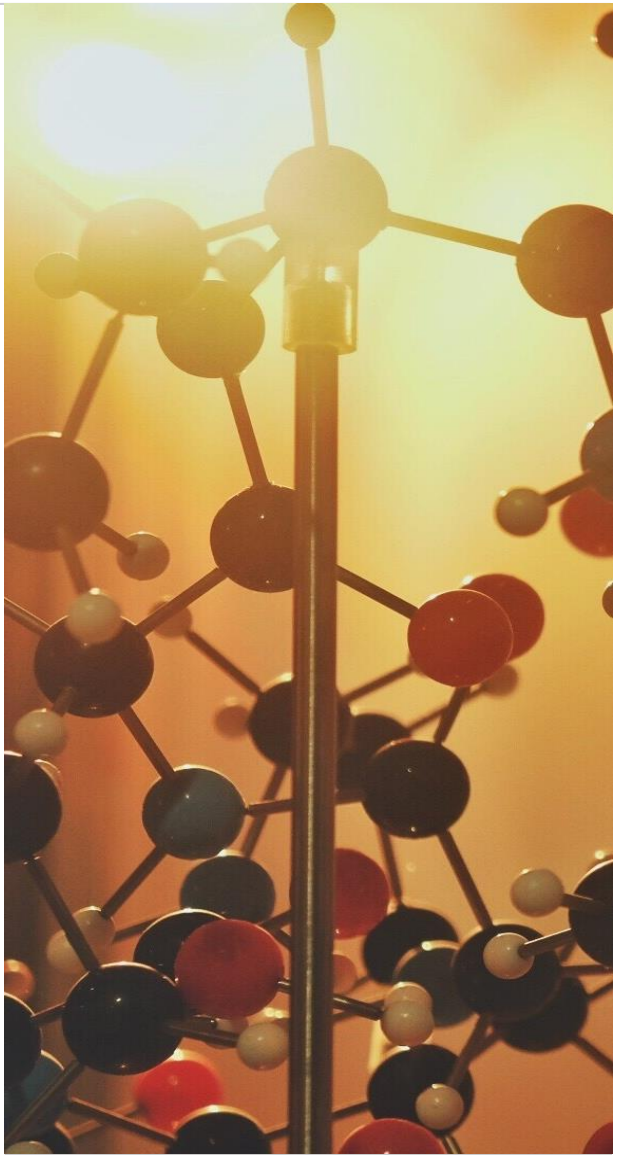
# Regulatory Insight

As many of our lawyers have advanced scientific degrees, we have the capabilities to handle complex scientific and clinical issues.

We also understand the inner workings of government. Our team includes former senior officials from:

- The White House
- U.S. Food and Drug Administration
- U.S. Department of Justice
- Department of Health & Human Services
- Centers for Medicare & Medicaid Services
- Key U.S. Congressional committees
- European Commission
- Swissmedic
- State Council of the People's Republic of China (P.R.C.)
- Ministry of Foreign Affairs, P.R.C.
- Ministry of Commerce of P.R.C.

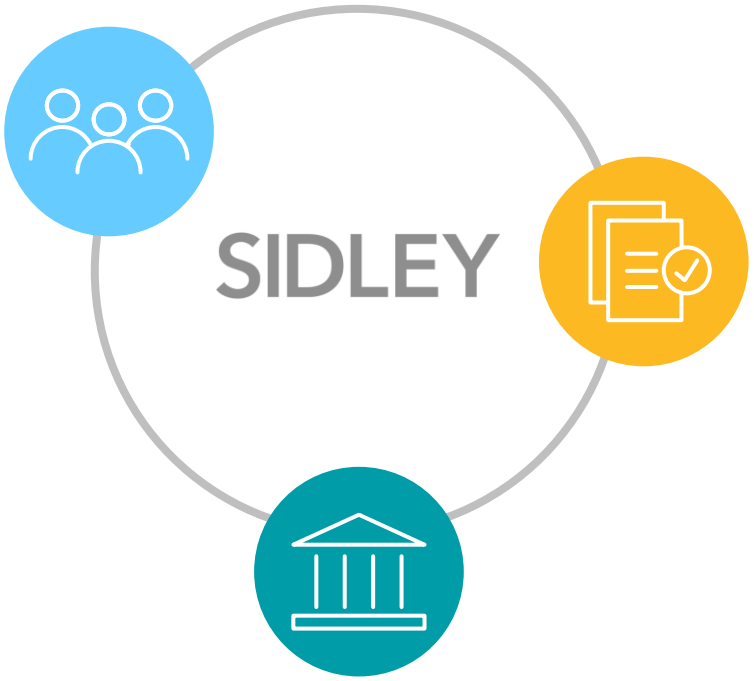
**100+** lawyers from regulatory agencies



# Our Approach

## Full Service

- Develop quality and regulatory reporting systems
- Audit GMP and QSR system compliance
- Coordinate global quality solutions
- Assist clients with complex data integrity and product impact investigations
- Provide training on cGMP and QSR best practices, inspection readiness and adverse event reporting
- Develop strategies for responses to agency actions, including FDA 483 Reports, Warning Letters and Consent Decrees
- Handle enforcement litigation



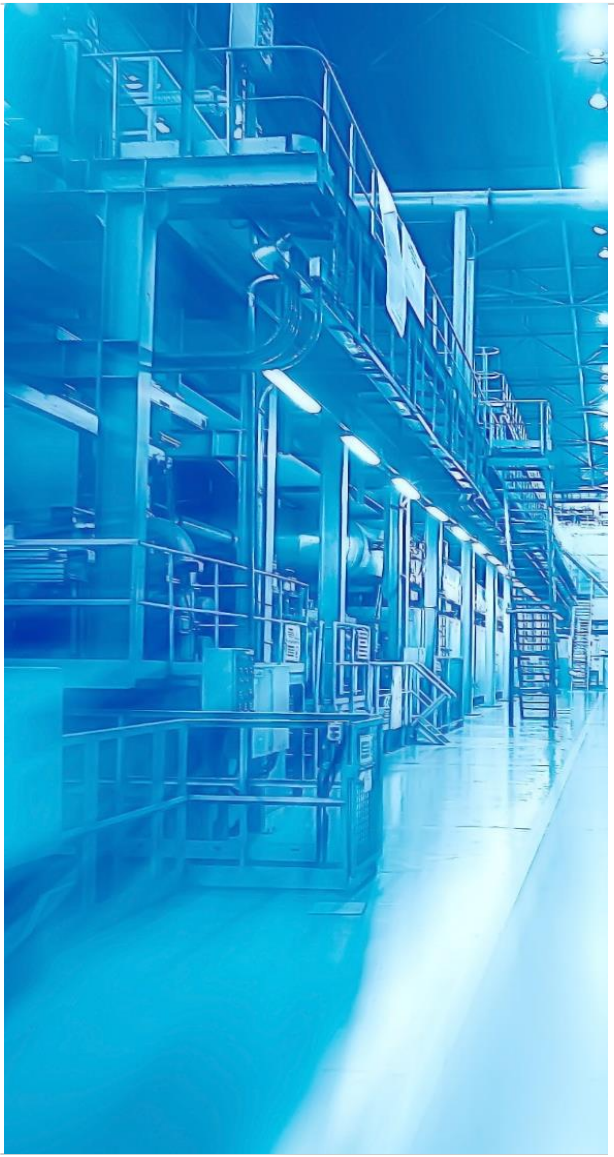

## Cross-Border Coordination

- Europe
- Asia Pacific
- United States
- United Kingdom

## International Agency Insight

- UK Medicines and Healthcare Products Regulatory Agency (MHRA)
- Swissmedic
- Therapeutic Goods Administration (TGA)
- International Conference on Harmonisation Guidelines (ICH)
- China FDA (NMPA)

# Good Manufacturing Practice



- Our team can promptly respond to government inspections and enforcement activities involving manufacturing sites around the world, as well as coordinate action plans and communications with regulators and the media.
- We also advise clients on compliance with a variety of international regulatory bodies. Many of our lawyers have held senior positions at government agencies, including the U.S. Food and Drug Administration.

**30+** lawyers
focused on GMP matters

# Data Integrity is Corporate Integrity

*"In God We Trust; All Others Bring Data."*

-W. Edwards Deming

**Data integrity ensures the value, usability, accuracy, and consistency of an organization's data – and decision making based on them – from its creation or acquisition through its analysis, archival, and destruction**

# Misconduct Scale

| Innocent Ignorance | Surprising Sloppiness | Intentional Manipulation |
|---|---|---|
| Misconduct of *uninformed* kind | Misconduct of *lazy* kind | Misconduct of *Intentional* kind |
| • Act is unintentional<br>• Non-compliance is likely unintentional | • Act may or may not be unintentional<br>• Non-compliance is likely unintentional | • Act is intentional<br>• Non-compliance is likely intentional |

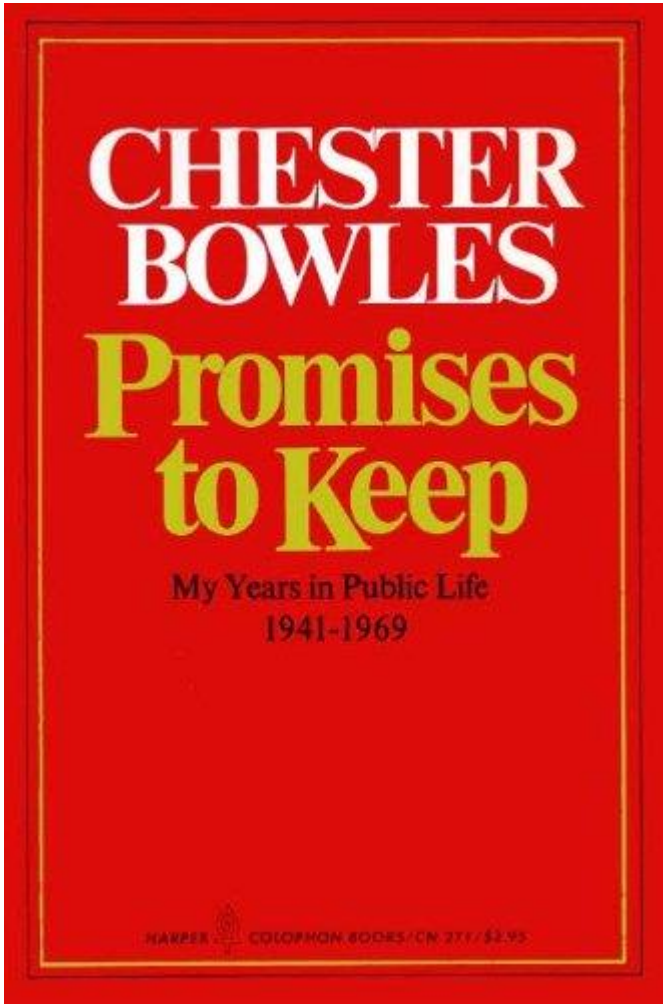
*Adapted from "Misconduct in Research – Innocent Ignorance or Malicious Malfeasance" – S. W. Woollen*

# Guess the Misconduct…Uninformed, Lazy, or Intentional?

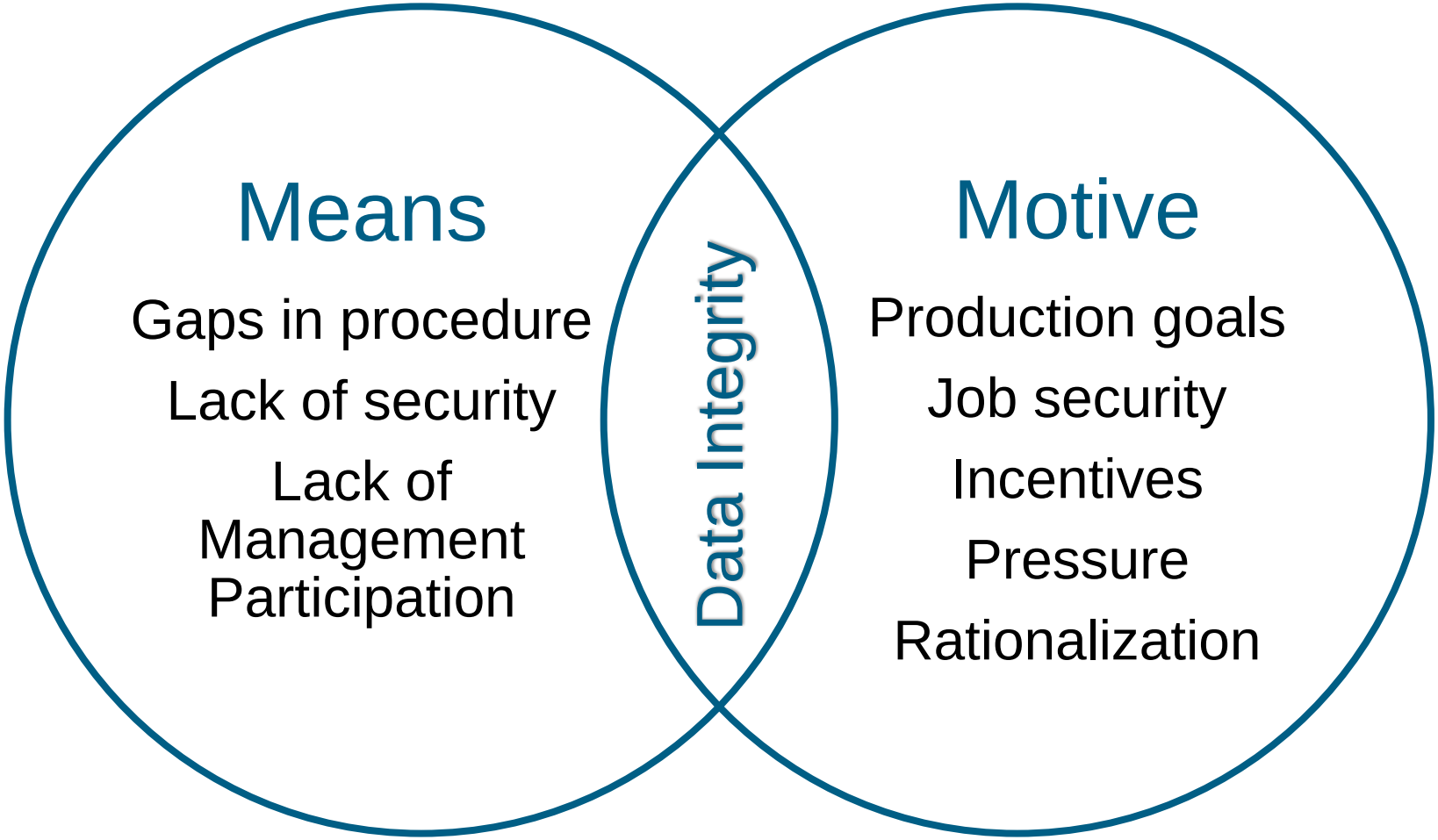
- Discarding original records
- Discarding original records…after accurate transcription
- Prefilling date and time in the batch record
- Prefilling date and time in the batch record… but I documented values when I observed!
- Filling batch record after the process was completed…we are confident on our process!
- Reinjection
- Reinjection…but we reported the original result!
- Backdating
- Backdating… I just “forgot” but it is accurate and it did happen!
- Inaccurate colony count
- Inaccurate colony count…but they were morphed, so could not count accurately!
- On break but still recording activities in the batch record… process doesn’t go on break!
- Improper integration of peaks
- Improper integration of peaks… they were not important peaks, would not have changed the result!
- Manipulating system date and time

# Compliance Theory According to Chester Bowles

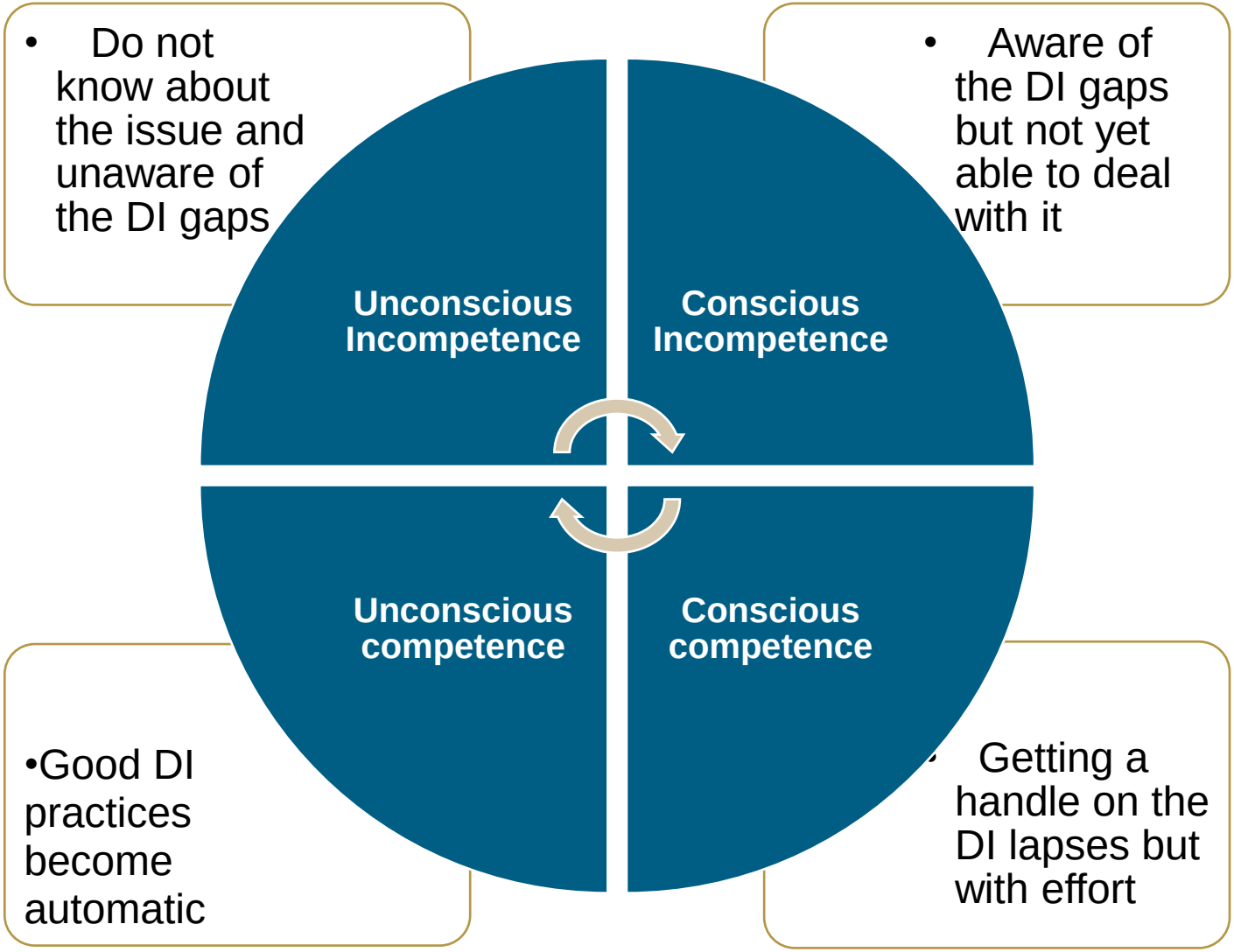
- 20% of the regulated population will automatically comply with any regulation
  - Good guys and message bearers
- 5% will attempt to evade it
  - Rebels
- 75% will comply as long as they think the 5% will be caught and punished
  - In the middle



# Means and Motive



# Corporate Consciousness – Data Integrity



# Why are we still having Data Integrity Issues?

## Quality of Investigations…

- Investigation and corrective actions that do not address DI lapses in a systemic way
  - Investigations should include the evaluation what may have contributed to the problem
  - Identify links to associated systems and procedures
  - Lacks depth

# All We Need is a CAPA…

- "Deluge" of CAPAs
- CAPAs open for extended periods of time without any documented follow-up
  - Is this a resources issue?
  - How does the delay in completing CAPAs affect related systems and product quality?
- Failure to properly evaluate effectiveness of corrective actions
- Ineffective corrective actions

# Human Error is Frequently Cited as a Root Cause…

- Re-training is too often the corrective action for DI lapses deemed to be caused by human error

- The effectiveness of training as a preventive or corrective action will depend on the type of human error that it is intended to prevent or correct

## Lack of Management Involvement…

"Meaningful and effective strategies should consider the design, operation, and monitoring of systems and controls based on risk to patient, process, and product. Management's involvement in and influence on these strategies is essential in preventing and correcting conditions that can lead to data integrity problems. It is the role of management with executive responsibility to create a quality culture where employees understand that data integrity is an organizational core value and employees are encouraged to identify and promptly report data integrity issues. In the absence of management support of a quality culture, quality systems can break down and lead to CGMP noncompliance."

FDA Data Integrity Guidance

## Handling DI Lapses…

The PERSON Approach

- "Coaching" that appeals to people's sense of fear
- Writing another procedure, or adding to the existing one
- Retraining
- Disciplinary measures

# Handling DI Lapses…

The SYSTEM Approach

- Takes into consideration that humans are fallible and errors are to be expected
- CAPAs to change the conditions under which DI lapses occurred
- Develop system with barriers, safeguards and redundant operations

# Recent Examples

# Basic Controls?

Your firm did not have adequate system security and access control for the **(b)(4)** system. For example, unique user accounts and privilege levels were not assigned to individual users for **(b)(4)** software, and the Windows operating system. The analysts had access to delete and overwrite data. Our investigators found approximately 36 deleted data files or folders in the recycle bin.

In addition, your analysts used individualized non-validated **(b)(4)** spreadsheets to calculate assay, impurity, content uniformity, and dissolution test results for a variety of drug products.

https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/missouri-analytical-laboratories-inc-615319-09302021 Accessed September 30, 2022

# Quality Unit Oversight?

**5. Failure to have a quality unit that is independent of production and fulfills quality assurance (QA) and quality control (QC) duties.**

Your quality unit (QU) lacked adequate responsibilities and authorities to assure reliable operations. Your QU failed to ensure good documentation practices in your facility as evidenced by:

- A Batch Manufacturing Production logbook was found with pages torn out

- Numerous signed and partially completed batch records which lacked the "Controlled Copy" stamp were found in the unofficial R&D laboratory

- Destruction of **(b)(4)** API batch record for batch **(b)(4)** that contained manufacturing and analysis records, despite this batch remaining in U.S. distribution. You also destroyed the batch retain sample.

You are responsible for establishing and following appropriate record retention procedures for your API that remains within retest period.

https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/indiana-chem-port-618173-02022022 Accessed September 30, 2022

# Procedural Gaps and Oversight?

B. Your investigation into data integrity breaches, reported to the agency in a **(b)(4)**, was insufficient to determine the scope of the problems at your facility.

Your firm identified recurring instances of the following:

- Operators failed to consistently ensure that personnel monitoring plates contacted gowning surfaces before leaving the ISO 7 area (Grade B).
- Operators failed to consistently ensure that environmental monitoring plates contacted equipment surfaces located in ISO 5 (Grade A) and ISO 7 (Grade B) areas.
- When surfaces were monitored, operators wiped equipment surfaces with **(b)(4)** before sampling the equipment surface.
- Nonviable particle data for ISO 5 (Grade A) was reported as ISO 7 (Grade B) when particles results were higher than alert levels.
- Operators failed to report ISO 5 (Grade A) airborne particulates values using a portable particulate counter, instead they repeated the monitoring of airborne particulates.

https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/toyobo-co-ltd-614177-08192021 Accessed October 3, 2022

# All Manufacturing Data or Only Disposition Data?

Your quality unit (QU) lacked adequate responsibilities and authorities to assure reliable operations. For example:

A. You failed to ensure the audit trail feature was enabled on your Inductively Coupled Plasma - Optical Emission Spectrometry (lCP-OES) instrument to track creation, modification, or deletion of data. This instrument was used to obtain assay results for your drug products.

B. You stored your master batch records as unlocked Excel files which were open to alteration, duplication, and deletion by unauthorized personnel.

C. Your analysts used open Excel files for documenting sample preparation information and final calculations. These records were not retained. For example, your personnel admitted during the inspection that records and data, such as volume of test solution, sample weight, and final calculations, are not retained.

Manufacturing data must be retained to support CGMP activities including but not limited to your batch disposition decisions, stability studies, and investigations.

https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/chemland-co-ltd-593158-02112020 Accessed September 30, 2022

## How Do We Ensure Integrity of Our Data?

- Look beyond documentation – What is going on “behind the scenes”
  - Trust but verify
- Employee empowerment
  - Promote open dialog
  - Critical thinking
- House of Integrity
  - Governance and Validation are your permits
  - Culture and Processes are your foundations
  - People and Training are your walls
  - Management Participation and Internal audit is your roof

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