Data Integrity Case Studies

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Disclaimer

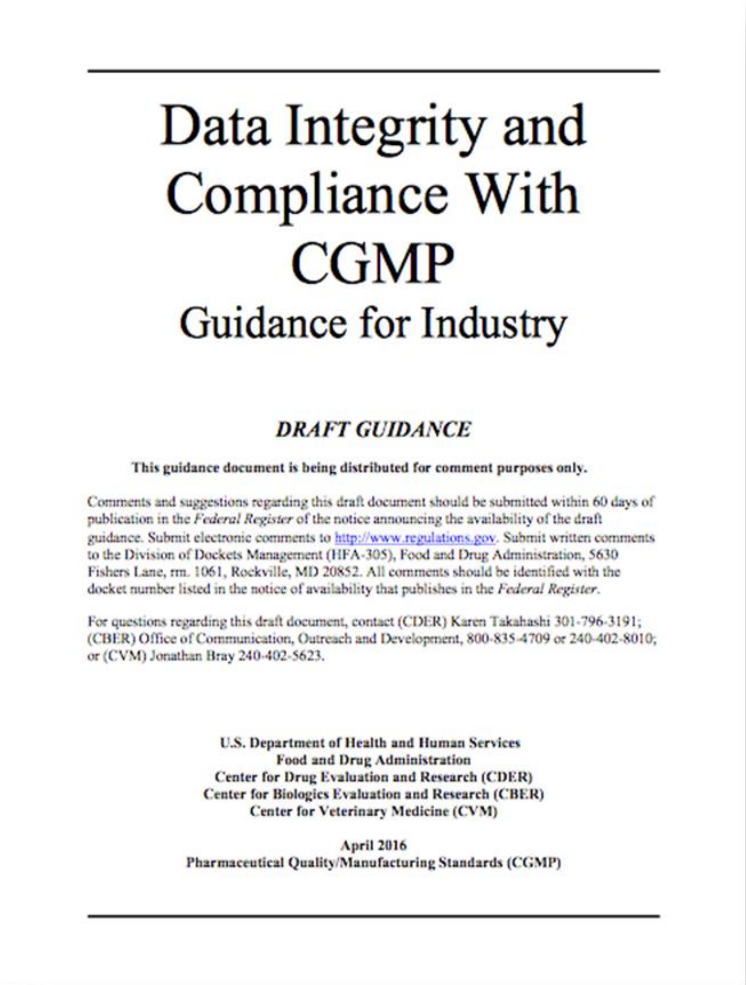
- All the material included in this presentation was obtained from publicly available sources.

Agenda

- Data Integrity (DI) Definition
- FDA Draft Guidance
- ALCOA Definition
- 2015-2016 DI FDA 483's and Warning Letters Summary
- Case Studies Discussion
- Consequences of Non-Compliance
- Data Integrity and Culture
- Data Integrity and QRM
- Questions

Data Integrity is defined by the FDA new "Draft Data Integrity and Compliance Guidance for Industry" as:

"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)".



Data Integrity and Compliance With CGMP

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Karen Takahashi 301-796-3191; (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010; or (CVM) Jonathan Bray 240-402-5623.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Veterinary Medicine (CVM)

April 2016
Pharmaceutical Quality/Manufacturing Standards (CGMP)

- FDA published a draft guidance on data integrity on April 2016.

- It states *"In recent years, FDA has increasingly observed CGMP violations involving data integrity during CGMP inspections. This is troubling because ensuring data integrity is an important component of industry's responsibility to ensure the safety, efficacy, and quality of drugs, and of FDA's ability to protect the public health"*

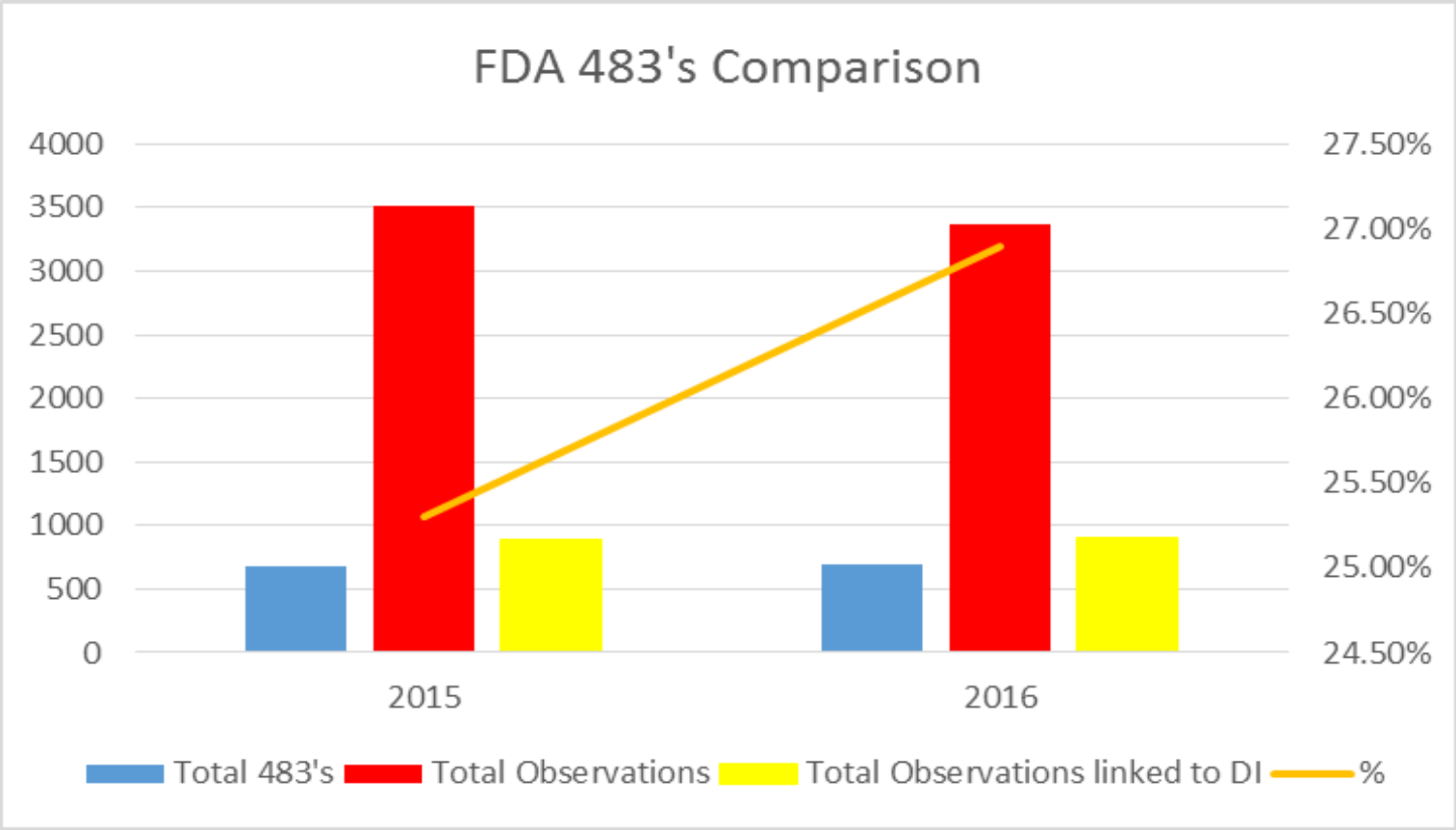
The acronym ALCOA has been widely associated with Data Integrity by FDA

ALCOA	Meaning	Explanation	Comments
A	**Attributable**	Who performed an action and when? If a record is changed, who did it and why?	Who did it? Source Data
L	**Legible**	Data must be recorded in a permanent durable medium and be readable	Can you read it? Needs to be permanent
C	**Contemporaneous**	Data must be recorded when it was performed followed by date and time.	Was it done in real time?
O	**Original**	Is the information the original data or a certified true copy of the original data?	Is it original or true copy?
A	**Accurate**	No errors or editing performed without documented amendments	Is it accurate?

CFR Regulations Linked to Data Integrity

1. **21CFR211 Current Good Manufacturing Practices for Finished Pharmaceuticals**
   - a) Sub Part D Equipment
     - i. 211.68 Automatic, Mechanical and electronic equipment
   - b) Sub Part F Production and Process Controls
     - i. 211.100 Written Procedures; Deviations
   - c) Sub Part I Laboratory Controls
     - i. 211.160 General Requirements
   - d) Sub Part J Records and Reports
     - i. 211.180 General Requirements
     - ii. 211.188 Batch Production and Control Records
     - iii. 211.194 Laboratory Records

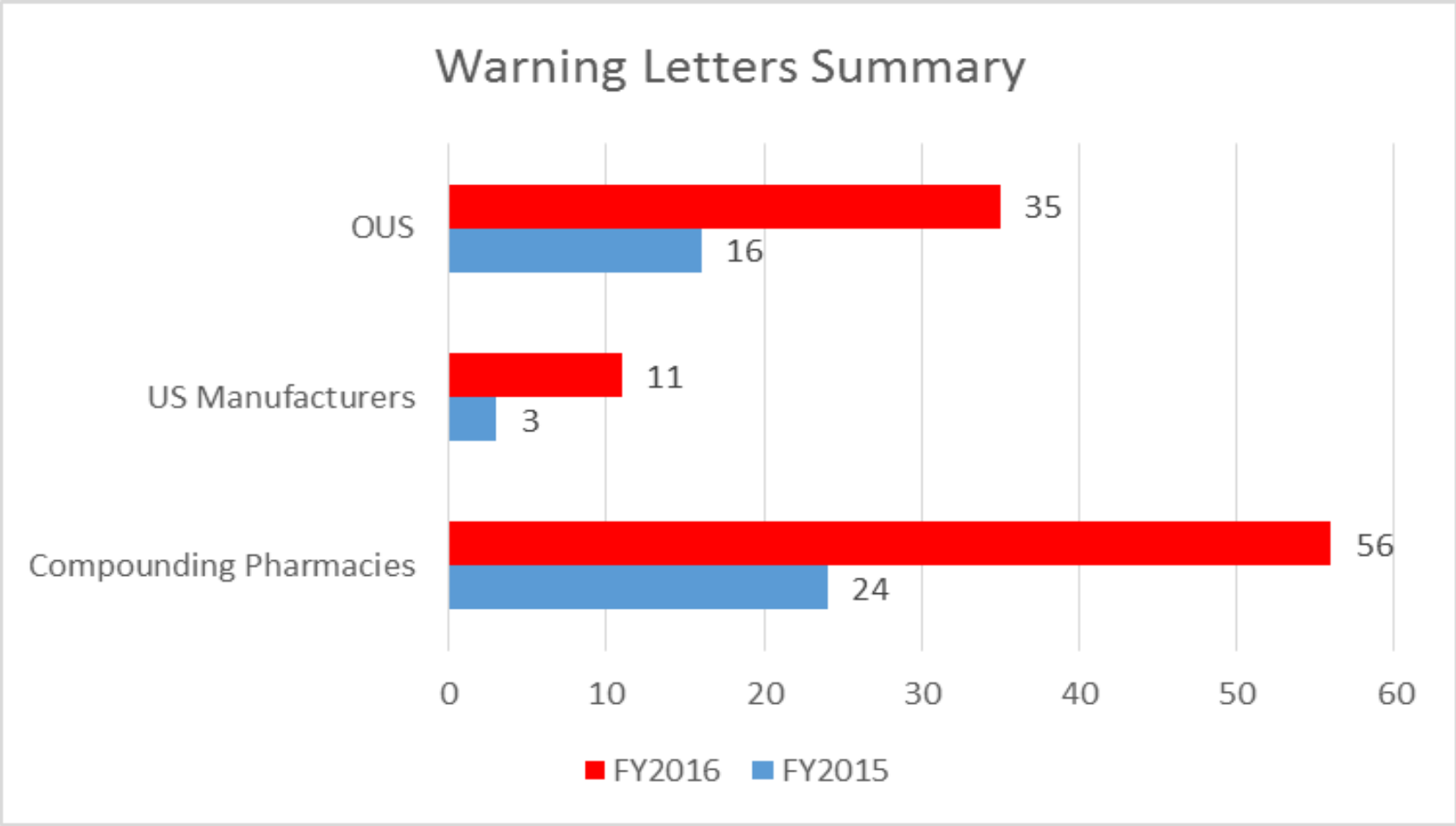
Fiscal Year October 1st – September 30th



Year	Total 483's	Total Observations	Total Observations linked to DI	%
2015	678	3506	887	25.30%
2016	691	3361	903	26.90%

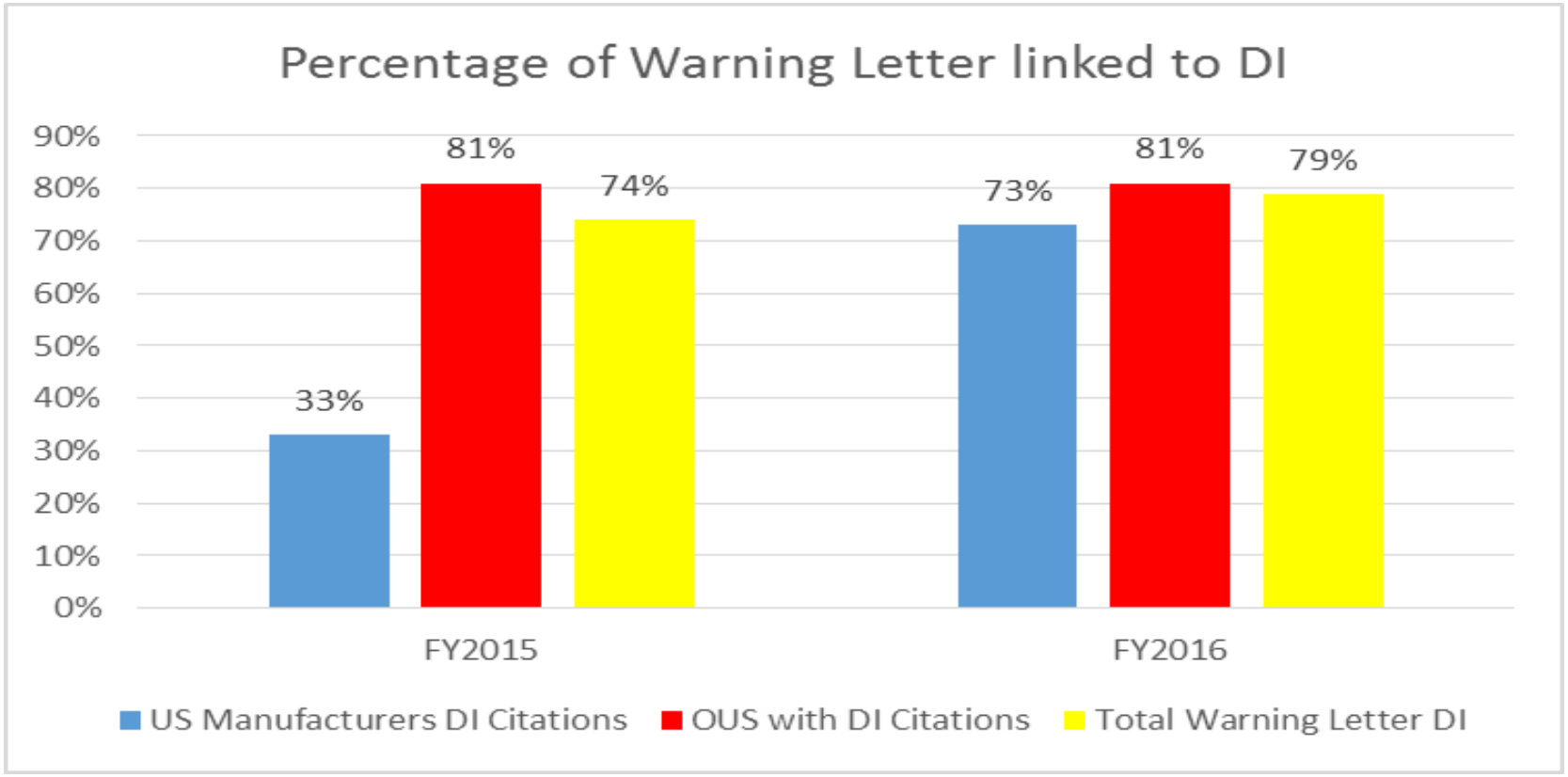
Source:
https://www.fda.gov/ICECI/EnforcementActions/ucm531890.htm#Drugs

Warning Letters Summary



Source: https://www.pharmaceuticalonline.com/doc/an-analysis-of-fda-fy-drug-gmp-warning-letters-0001

Summary of WL linked to DI



- Total excludes Compounding Pharmacies
- Warning Letters listed included references to data management and data integrity citations
- Data Integrity continues to be a focus of enforcement actions by FDA
- FDA has refined its stated requirements for remediation of data integrity deficiencies and in many instances are including such requirements in the Warning Letters.

Source: https://www.pharmaceuticalonline.com/doc/an-analysis-of-fda-fy-drug-gmp-warning-letters-0001

Case Studies

- The following case studies were taken directly from FDA Warning Letter Reading Room. Although information is public, we will not reveal details about company name or locations.
- Both companies received FDA 483's which cited many observations linked to Data Integrity issues among others.
- Both companies responded but received Warning Letters as the agency determined that their responses to the FDA 483 "lacked sufficient corrective actions"

1. Failure to investigate and document out-of-specification results obtained for **(b)(4)**, API.

- For example, on Month/day/year **(b)(4)** lot #**(b)(4)** failed the assay test with an average out-of-specification (OOS) of **(b)(4)**% (specification is **(b)(4)**%). **However, the firm released the batch using a passing retest result without conducting an investigation.**
- In your response you state that the OOS could not be related to the quality of the product because of the individual values obtained (**(b)(4)**% and **(b)(4)**%). Your response is inadequate in that you provided no scientific justification to support your conclusion.

All out-of-specification results must be investigated and documented. We are concerned that you released this batch based on a passing retest result without conducting an investigation.

- The FDA asked for a retrospective review of all batches that yielded OOS results including:
  - Lot number
  - All test values reported (including OOS original result)
  - For each OOS investigation, provide evaluation and conclusion along with established CAPA's.

2. Failure to ensure that approved test procedures for **(b)(4)** and **(b)(4)** HPLC are followed.

- For example, the inspection found **no scientific justification for the current sequence of chromatographic injections performed, which is different to the sequence included in the approved analytical method.** Your analytical method requires that **(b)(4)** and then by the injection of the samples to be tested. The inspection found that a different sample and standard sequence was used for the assay analysis of **(b)(4)** lots **(b)(4)** through **(b)(4)**. Although your response to the inspectional observations state that analysts have been retrained, we remain concerned about current laboratory practices, in that **not all injection results are being reported. For example, the assay test for lots # failed to include all the injection results performed as part of the chromatographic run. Your response provides no explanation regarding why analytical results are selectively reported.**

- The FDA asked for a copy of the investigation concerning the 18 lots of **(b)(4)**, for which they did not follow the HPLC procedure including all individual and average assay results obtained during the assay re-test or re-calculation.

3. Failure to have complete and reliable laboratory control records derived from all tests conducted to ensure compliance with established specifications and standards.

- For example, the inspection revealed that your firm **lacks raw data of the sample and standard weights used for the HPLC assay of (b)(4) and (b)(4). The only record available was an Excel spreadsheet with values entered to calculate the final assay results. In addition, some of the HPLC chromatographs of the lots tested were not included in the batch record.**
- In your response you acknowledged missing raw data, and stated that **all raw data is now required to be maintained and included as part of the batch record.**

- FDA stated that although Company X acknowledged missing raw data, and stated that all raw data is now required to be maintained and included as part of the batch record, they made no commitment to evaluate the extent of the problem and review all previous batches where critical data may be missing.

4. Failure of your quality unit to review and approve all appropriate quality related documents.

- For example, the inspection revealed that the production batch records do not include weigh tickets or printouts of the raw materials, in-process materials, or finished APIs. **The batch records also lack the dates, amounts, and identity of the person weighing the material. We are concerned that your quality unit is not exercising its responsibility during the review of the production batch records to ensure the required information is available, prior to releasing your products.**

- Provide detail of global improvements Company X is making to the production and quality systems to address these issues. Include a copy of the master batch records for **(b)(4)** and **(b)(4)** products.

1. Firm failed to establish an adequate quality control unit with the responsibility and authority to approve or reject all components, drug product containers, closures, in-process materials, packaging material, labeling, and drug products (21 CFR 211.22(a)).

- Quality unit allowed the use of adulterated **(b)(4)** USP API, dated MM/DD/YR, manufactured at the ABC facility.
- Quality unit approved certificates of analysis (COA) for **(b)(4)** and **(b)(4)** API, as well as finished products, prior to conducting all quality control and release testing. Production manager falsified the documents by signing and dating the "Prepared By" and "Checked By" sections of the COA.
- Quality unit failed to identify data integrity issues in 11 batch production records reviewed during inspection. Production manager admitted that he falsified the signatures of other employees in the "Prepared By," "Reviewed By," "Approved By," and "Authorized By" sections.

2. The firm failed to exercise appropriate controls over computer or related systems to assure that only authorized personnel institute changes in master production and control records, or other records (21 CFR 211.68(b)).

- Computer in quality unit area did not have controls to restrict access and prevent unauthorized changes to data files and folders. All employees had access to your Annual Product Review (APR) spreadsheet. The desktop computer containing the APR was not locked.

- In this case, as part of the Warning Letter, FDA specifically requested aspects under a "Data Integrity Remediation" which included the following major points:
  - A full investigation on DI issues to include:
    - Investigation protocol and methodology; a summary of all laboratories, manufacturing operations, and systems to be covered by the assessment; and a justification for any part of the operation proposed to be excluded.
    - Interviews of current and former employees to identify the nature, scope, and root cause of data inaccuracies. Interviews be conducted by a qualified third party.

- An assessment of the extent of data integrity deficiencies at facility. Identify omissions, alterations, deletions, record destruction, non-contemporaneous record completion, and other deficiencies. Describe all parts of facility's operations in data integrity lapses were discovered.
- A comprehensive retrospective evaluation of the nature of the testing and manufacturing data integrity deficiencies. Qualified third party with specific expertise in the area where potential batches were identified to evaluate all data integrity lapses.

- A management strategy for the firm that includes the details of a global corrective action and preventive action plan. Strategy to include:

  - Detailed corrective action plan that describes how to ensure the reliability and completeness of all of the data generated, including analytical data, manufacturing records, and all data submitted to FDA.

  - Comprehensive description of the root causes of data integrity lapses, including evidence that the scope and depth of the current action plan is commensurate with the findings of the investigation and risk assessment. Indicate whether individuals responsible for data integrity lapses remain able to influence CGMP-related data at the firm.

- Interim measures describing the actions taken or will take to protect patients and to ensure the quality of drugs, such as notifying customers, recalling product, conducting additional testing, adding lots to the stability programs to assure stability, drug application actions, and enhanced complaint monitoring.

- Long-term measures describing any remediation efforts and enhancements to procedures, processes, methods, controls, systems, management oversight, and human resources (e.g., training, staffing improvements) designed to ensure the integrity of the company's data.

- A status report for any of the above activities already underway or completed.

Consequences of Non-Compliance

- FDA-483 Observations
- Warning letters
- Import alerts
- Withheld product approvals
- Cancellation of government contracts
- Product recalls
- Seizure
- Consent decree of permanent injunction
- Civil money penalties
- Suspension or revocation of licenses
- Prosecution (including indictments and temporary or permanent debarment, if found guilty)
- Damage to company's reputation
- Loss of sales
- Loss of jobs
- Loss of Share Value
- Closing or take-over company

- You can fix systems
- You can fix processes
- You can fix procedures

- Can you "fix" people?
  - How do you change behavior?
  - How do you create "Culture"?

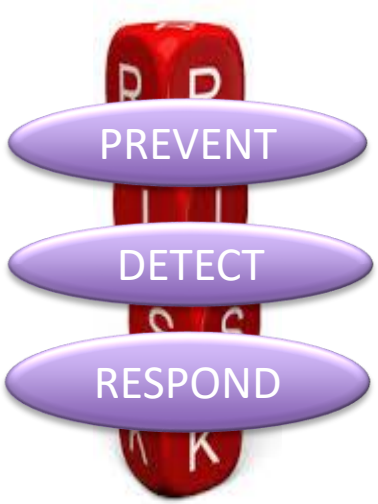
Why DI Issues Happen?

- Time Pressure
- Insufficient education & understanding (WHY)
- Fear for mistakes
- Performance Pressure
- Am told by leader
- Reputation
- Money
- Culture or accepted behavior

How to approach DI Breaches?

Companies need to assess what are the areas of vulnerability within their companies in other words application of QRM

Data Integrity Risk Factors



Personnel

- Not aware; Not trained; Culture

Data Review

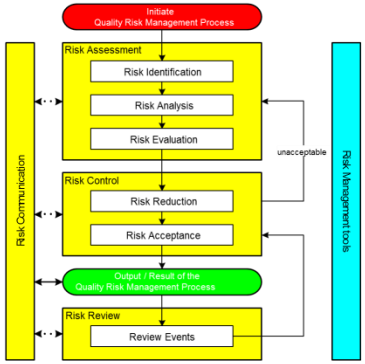
- Insufficient; Not done, Not in SOP

Processes

- Not validating for intended use

Outsourcing

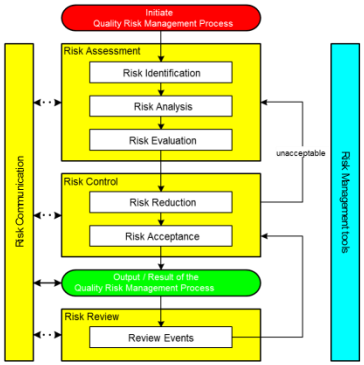
- QC Lab
- Manufacturing



Data Integrity Risk Factors

PREVENT

- Personnel (Internal/External)
- Validation
- Security Controls
- External Sources
- Documentation Control



DETECT

- Audits
- Data Review

RESPOND

- Governance/Findings/Actions

- Personnel (Internal/External)

  - State and enforce high standards of ethics and integrity by:
  - Training employees on proper data handling and reporting
  - Company Values and Code of Conduct
  - Emphasize that everyone in the company is responsible for data

- Validation

  - Computerized systems should be validated for intended use
  - Identify the Risks: What are the controls to Prevent Data Integrity Issues? What are the controls to Detect Data Integrity Issues?
  - Include Data Life Cycle requirements
  - Identify Critical Data and Records
  - Backup and Recovery

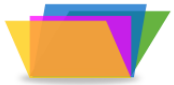
- Security Controls

  - Protect at both the physical level (building/room) and the informational level (network and application)
  - Access Controls: users, password controls, segregation of duties
  - Include Cyber Security (be protected from the outside)

- External Sources

  - Contractors and vendors for variety of GxP services
  - Audits and Inspections should include reviews for data integrity controls
  - Quality Agreements should include data integrity controls.

- Documentation Control



  - Managing the life of the data (initial creation, review, approval, storage, obsolete)
  - Ensure policies and procedures define the requirements for both paper and electronic data and their usage.

- Audits

  - An independent audit program that utilizes auditors who are qualified by education, experience and training to evaluate the quality systems used for collecting, analyzing, reporting and retaining information and data.
  - The audit program will include periodic audits to confirm adherence to established requirements for data integrity.

- Data Review

  - Good Documentation Practices
  - System Audit Trail: Tracks actions of System Administrator, Reviewed periodically based on risk, Defined in Administrators SOPs
  - Data Audit Trail (Tracks actions of users, reviewers, and approvers; Reviewed when the data is reviewed; Defined in User Operational SOPs)

- Governance/Findings/Actions

  - Develop Data Integrity Policy and Procedures to address data ownership throughout the lifecycle
  - Consider the design, operation and monitoring of processes / including control over intentional and unintentional changes to information
  - Investigate/Correct/Prevent
  - If warranted, conduct an in-depth documented investigation of any alleged instance of falsification, fabrication, or other misconduct involving data integrity issues

A Strong Quality Culture is best indicated by what it is done when Nobody is Looking

Culture is the Cornerstone of Quality

References

- www.fda.gov; FDA's Electronic Reading Room – Warning Letters
- https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM495891.pdf - Data Integrity and Compliance with cGMP; Guidance for Industry
- https://www.fda.gov/ICECI/Inspections/ucm481432.htm#Drugs
- https://www.pharmaceuticalonline.com/doc/an-analysis-of-fda-fy-drug-gmp-warning-letters-0001

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