PDA Manufacturing Science Workshop 2016
P1 Inspecting for Data Integrity: From Manufacturing Floor to Quality Control Laboratories

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Data Integrity & the 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

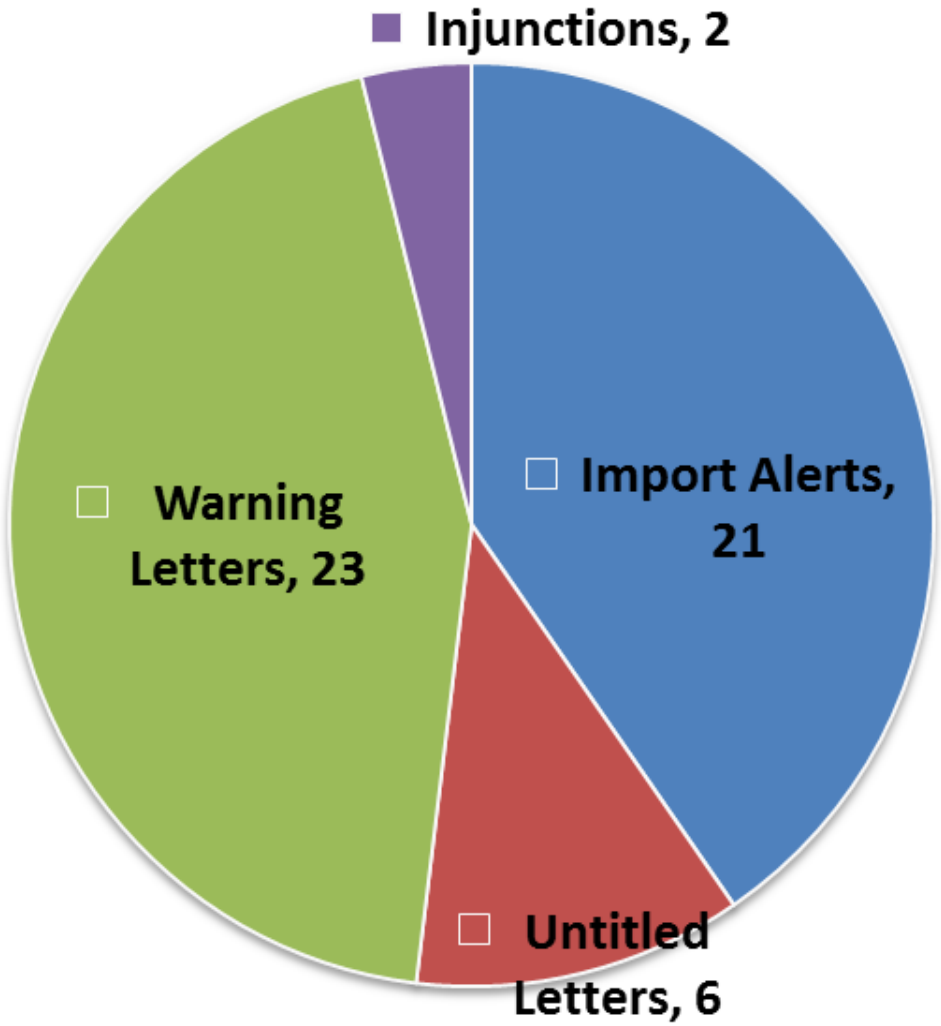
- Are we there yet?
  - Efficient, Agile, Flexible?
  - Reliable Quality?
  - *WITHOUT EXTENSIVE OVERSIGHT?*

Total Compliance/OMQ Actions

Jan. 2015 to Jan. 2016

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

DI WL: 14+



A Tale of Two Firms

Firm 1: DI event transpires (bonus: reported through company hotline!)**.** Investigation, CAPA, and assessment of effects on product quality/risks to patients are well defined and understood. Self-audit and CAPA. FDA learns about the events and CAPAs during a scheduled inspection.

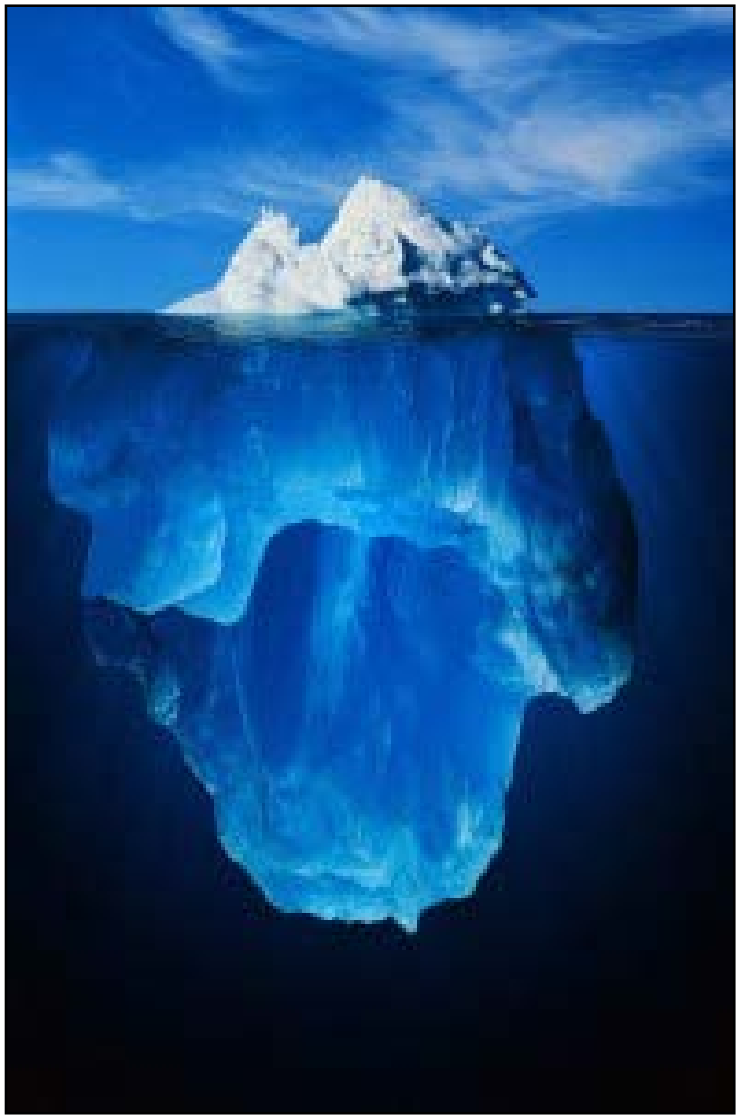
Firm 2: Adverse event triggers FDA inspection. During inspection of the lab, we observe:

- Results have been deleted or replaced; some results not recorded or reported as part of complete records.
- Many analyses were performed without use of audit trails; many analysts shared passwords and permissions.
- 483 Response: This is an isolated event! We will retest the relevant lots and fire the people responsible!

Data Integrity

- CGMP = minimum requirements (FDCA, 210/211/600s, Q7 & other guidance)
- Data integrity underpins CGMP
- Lapses obscure other problems

Tip of iceberg



Data Integrity: Nothing New Here!

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

Esp. Computerized Systems (5.4)

- Validation of GMP-related computerized systems
  - Depth and scope of validation depends on the diversity, complexity, and criticality of the computerized application.
- Investigation of incidents related to computerized systems that could affect the quality of intermediates or APIs or the reliability of records or test results
- Change control for computerized systems
- Records to demonstrate that the system is maintained in a validated state

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 about suitability testing: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm124787.htm

2015 CDER Guidance Agenda includes CGMP Data Integrity Questions and Answers (also 2016)

Warning Letters Jan 15-Jan 16

Why would firms tolerate this behavior?

- 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*
- 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*

Recent Warning Letters (page 1)

- 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*
- Fabricated impurity data, *June 2015*
- Failure to maintain backup chromatograms that would provide “dynamic” data, *May 2015*
- Failure to maintain access controls, *May 2015*

Recent Warning Letters (page 2)

- 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*
- 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 (page 3)

- 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*
- 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 GC, UV/VIS, and moisture analyses, *January 2015*
- Failure to control access to data systems, *January 2015*

Responding to DI WL

3 key pieces:

1. Comprehensive Evaluation
2. Risk Assessment
3. Remediation and Management Strategy

Comprehensive Evaluation (page 1)

What is FDA looking for in a comprehensive evaluation?

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

Comprehensive Evaluation (page 2)

Scope of Evaluation

- People – interviews conducted by consultant
  - Determine specific actions, behaviors, and incentives
  - What remains in place?
- 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

Potential effect on drug product quality

- How did these deficiencies affect the quality of drugs released for distribution?
- Related, if relevant: how were batches produced for pending applications affected?

Management Strategy

"…A **management strategy** that includes the details of your global **corrective action and preventive action plan**."

This CAPA should include:

- 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 Remediation

Last step: Re-inspection

- Investigators review and verify CAPA
- Failure to implement as promised may:
  - Prevent FDA from lifting an import alert
  - Create uncertainty about applications

A Tale of Two Firms, Part II

If you find a DI problem:

- Determine scope, severity, and risks
- Disclose *
- Commit to voluntary remediation

* FDA is much more willing to work with firms that voluntarily disclose and commit to fixing and preventing problems.

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- How will we get there?