CDER Compliance Perspective:
Data Integrity Trends

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Office of Manufacturing Quality

- We evaluate compliance with Current Good Manufacturing Practice (CGMP) for human drugs based on inspection reports, evidence gathered by FDA investigators, and other sources.

- We develop and implement compliance policy and take enforcement actions against violative drug manufacturing establishments.

Source: FDA
Enforcement tools

- Regulatory Meetings
- Injunctions
- Consent Decrees
- Import Alerts
- Seizures
- Warning Letters
- Untitled Letters
- And More

2016 Enforcement Actions

- Import Alerts, 47
- Regulatory Meetings, 27
- Regulatory Discretion, 27
- Untitled Letters, 4
- Warning Letters, 54

Excludes compounding-related actions
What is data integrity?

- **Data integrity** – requires that data are **complete**, **consistent**, and **accurate**.
- CGMP = minimum requirements
- Data integrity underpins CGMP
- Lapses obscure other problems

**ALCOA**

- Attributable
- Legible
- Contemporaneous
- Original / true copy
- Accurate
Fraud, Untrue Statements of Material Facts, Bribery, and Illegal Gratuities

• House Subcommittee on Oversight and Investigations investigated generic drugs manufacturers and FDA (1988)
• Four FDA employees found to have accepted illegal gratuities
• Broad patterns and practices of fraud in eleven generic drug companies abbreviated new drug applications.

In response: Application Integrity Policy (AIP)

FR FDA 09/10/91 NOTICE 56 FR 46191
Features of AIP

• Once AIP is invoked, FDA suspends review of the application or applications until the provisions of the AIP are met by the applicant holder.

• Intended to assure the accuracy and reliability of data & information in applications submitted to FDA for scientific review and approval.

• No statute of limitations
Data Integrity Violations

- Testing into compliance
- Cherry-picking data
- Re-using data
- Batch records that don’t match test results
- Audit trails and back-ups going on and off
Why Data Integrity Lapses?

- Business culture?
- Financial pressure?
- Obedience to authority?
- Self-perpetuating system?

Cressey Fraud triangle, https://algaonline.org/
Process failure

Investigate:
Method isn’t capable (AIP?)

Test into compliance

CAPA for the process

Expand scope of investigation

WL/IA

Possible WL/IA for other methods

CAPA(s)

Communicate with FDA

METHOD NOT VALIDATED PROPERLY IN APPLICATION
Case study: Stability samples

This is only a test. If it were an actual sample, it would be reported in the official data package.

• “Trial injections” of “stability samples” saved in the “test” folder.
• Official samples analyzed after “trial injection.”

Warning letter?

Your response indicates that the “Test” folders were used to equilibrate the analytical columns and to determine when the system was ready for analysis. It is your responsibility to follow validated methods that include specific procedures to assess the suitability of your instruments... (March 2015)
Case study: Administrator privileges
“If I could turn back time…”

Warning letter: We observed systemic data manipulation across your facility, including actions taken by multiple analysts and on multiple pieces of testing equipment.

Specifically, your Quality Control (QC) analysts used administrator privileges and passwords to manipulate your high performance liquid chromatography (HPLC) computer clock to alter the recorded chronology of laboratory testing events. (May 2016)
Case Study: Clinical Studies

Inspection uncovered documents that described the substitution and manipulation of subject samples to allow otherwise failing studies to meet bioequivalence and bioavailability endpoint.

Advisory letter:

*FDA found evidence documenting that you engaged in practices and processes that undermined the analytical methods used at your site, which resulted in the submission of invalid study data to the FDA.*
Specific findings:

**Study results were statistically impossible:**

- Pharmacokinetic (PK) profiles were nearly identical for multiple subject pairs
- Facility could not explain how independent subjects (in multiple cases) had identical PK profiles when the PK parameters are variable

*Data substitution and manipulation were systemic where the effect was observed over a large number of subjects, across multiple studies, across multiple years.*
Draft guidance

*Data Integrity and Compliance With CGMP*, draft guidance for industry (April 2016)

- Why? FDA has increasingly observed CGMP violations involving data integrity during CGMP inspections.
- 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 public health.

Responding to Data Integrity Failures

Recent FDA Warning Letters with data integrity citations include data integrity section, requesting firms respond with three key items:

• Comprehensive evaluation
• Risk assessment
• Remediation and management strategy (including corrective action plan)
THANK YOU
QUESTIONS?