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Warning Letters Demonstrating Data Integrity Problems

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Topics

- Definition
- Why is data integrity important
- Examples of data integrity problems
- Red flags for FDA
- What data integrity problems can mean for your firm
- How to resolve data integrity problems

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Definitions

- Data integrity may mean:
 - accurate and reliable data and information
 - ensuring data trustworthiness and reliability, as related to the security of the information/data
 - See FDA's Guidance to Industry: Part 11, Electronic Records; Electronic Signatures — Scope and Application, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070295.pdf>
 - the degree to which a collection of data is complete, consistent, and accurate.
Syn: data quality
 - IEEE definition
 - See Glossary of Computer Systems Software Development Terminology (8/95), available at <http://www.fda.gov/ICECI/Inspections/InspectionGuides/ucm074875.htm>
 - ALCOA: Attributable, Legible, Contemporaneous, Original, and Accurate
 - Under Good Clinical Principles, FDA may look to see that the process of data creation at the site can be reconstructed and that it matches the information submitted to the agency. If problems are discovered, the integrity of the data are questionable.

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Why is Data Integrity Important?

- Undermines the safety and efficacy and/or assurance of quality of the drugs that consumers will take
- Data integrity problems break trust
- We rely largely on trusting the firm to do the right thing when we are not there

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Data Integrity – What We See

- Not recording activities contemporaneously
- Backdating
- Fabricating data
- Copying existing data as new data
- Re-running samples
- Discarding data

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Data Integrity – What We See

- Releasing failing product
- Testing into compliance
- Not saving electronic or hard copy data

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Data Integrity Example

- Batch production record
 - 7 instances where employees signing as completing manufacturing steps were not on premises at the time the steps were completed
 - 2 employees involved

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Data Integrity Example

- Batch production record
 - Over 30 batch records (80% of those reviewed)
 - Data was removed and new data was added
 - Including: dates, signatures, temperatures, test results, weights, volumes, and times
 - Employee scraped off entries with hand-made tool
 - Management was aware of this for at least 2 years
 - Firm had no CGMP training

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Data Integrity Example

- Stability
 - Testing conducted late but recorded as being tested on time
 - No samples available, however testing data was generated

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Data Integrity Example

- Quality Control Data
 - Test results for one batch were used to release other batches
 - Occurred for at least 3 batches
 - This happened at three unrelated firms

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Data Integrity Example

- Quality Control Data
 - Employee used same sample for identity testing on a regular basis

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Data Integrity Example

- Microbiological testing
 - Growth on microbiological plates was observed and recorded as no growth
 - The plates were double checked by a second employee
 - This happened at three unrelated firms manufacturing sterile finished dosage forms

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Data Integrity Example

- Quality Control Unit
 - Releasing product with known contaminants
 - Repacking failed product without assessing impact of failure
 - Repacked product was released

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Data Integrity Example

- Dissolution Data
 - Evidence did not support the reason to invalidate the test results
 - Dissolution data discarded with no investigation

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Data Integrity Example

- Quality Control Data
 - Data supporting test results was missing

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Data Integrity Example

- No raw data for:
 - Standard preparation
 - Sample weights
 - Sample solution preparation and sample dilutions

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Data Integrity Example

- HPLC integration parameters were changed and re-run until passing results were obtained
- Audit trail function was disabled
- Senior colleague directed the chemist to record false data in the logbook

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Data Integrity Example

- Sample and reagent weights are written on small pieces of paper and transcribed onto analytical worksheets
- Then, small pieces of paper were discarded

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Data Integrity Example

- Unofficial testing of samples with file names like test, trial, or demo
 - Some failed specification
 - All were saved on personal computers instead of a network

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Data Integrity Example

- Out-of-specification or undesirable results were ignored and not investigated
 - Re-testing without justification
 - Product released despite failing sterility testing
 - Failing or suspect HPLC assay results are overwritten

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Data Integrity Example

- There are no controls to prohibit unauthorized changes to electronic data
 - Turning off the audit trail function
 - Altering or deleting analytical result files

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Data Integrity Example

- Quality Control Data
 - Destruction of raw data not meeting specification
 - Missing raw data
 - Re-writing laboratory notebooks
 - Unjustified invalidation of data and re-testing without a laboratory investigation
 - Refused to allow FDA to talk to employees

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Data Integrity Example

- Making up records during an FDA inspection
 - Batch records
 - Training records

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Data Integrity Example

- Delaying, denying, limiting or refusing an inspection
 - Raw data found in the garbage
 - Unlabeled or partially labeled vials dumped down the drain
 - Providing false information during an FDA inspection

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Red Flags for FDA

- Manual processes
- No complaints, deviations or out-of-specification investigations
- No archival data (i.e., microbiological test results, thin layer chromatography, titration)
- First-to-file applications
- Firms with a large volume of applications

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Recent Trends

- The Agency has recently been using consent decrees as a way to address application related data integrity problems
- Criminal plea to charges of submitting false data in drug applications
- Increase in data integrity findings

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What Can Data Integrity Problems Mean for Your Firm?

- Recalls
- Warning or Untitled Letter
- Import Alert
- Injunction
- Seizure
- Application Integrity Policy Invocation

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Data Integrity – Rebuilding Trust

- Hire a third party auditor
- Determine the scope of the problem
- Implement a corrective action plan (global)
- Remove individuals responsible for problems from CGMP positions
- Complete a satisfactory inspection

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