FDA's Perspective and Current Findings on Data Integrity

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Topics

- What is data integrity?
- Why is data integrity important?
- List of most commonly cited data integrity problems
- Examples of data integrity problems
- What should you do if you have data integrity problems?
- How can you be part of the solution?

What is Data Integrity?

- Data integrity refers to requirements for complete, consistent, and accurate data
- This type of data should be attributable, legible, contemporaneously recorded, original or a true copy, and accurate (ALCOA)
- The concept of data integrity underpins CGMPs and is a requirement for electronic record keeping and the use of electronic signatures

Why is Data Integrity Important?

- We rely on accurate information to ensure drug quality
- Data integrity problems erode confidence
- We rely largely on confidence that the firm will do the right thing when we are not there

Contractors

Data integrity is not only about ensuring your data is accurate and reliable, but also ensuring that your contractors' data is accurate and reliable.

Top Data Integrity Citations

- Reviewed warning letters from April 2013 – April 2015
- Both API and finished dosage data integrity deficiencies are included under GMP concepts as written in 21 CFR 211 for ease of quantifying results
- One citation per firm, but each citation could include numerous examples

7th Most Common Citation

- Your firm failed to document production and process control functions ***at the time of performance*** (21 CFR 211.100(b)).
  - Cited in 2 warning letters
  - Operator recorded the amount of material dispensed before it was dispensed
  - Employees admitted they do not record activities at the time of performance
  - QA employee signed as reviewing and releasing a batch when he did neither

6th Most Common Citation

- Your firm blended out-of-specification API batches with passing batches to meet specification.
  - Cited in 3 warning letters
  - Failing results were often kept in separate folders and the failing data was not considered when making release decisions

5th Most Common Citation

- Your firm did not document laboratory activities ***at the time of performance*** (21 CFR 211.160(a)).
  - Cited in 3 warning letters
  - Pre-dating or backdating laboratory records
  - Occurred for assay, loss on drying, sample weighing, and stability testing

4th Most Common Citation

- Your firm failed to maintain ***complete information*** relating to the production and control of each batch (21 CFR 211.188)).
  - Cited in 5 warning letters
  - Records for 23 batches did not contain batch numbers, manufacturing dates, expiration or retest dates
  - Approximately 75 ripped batch production records (BPRs) were found in the garbage (some with failing results)

4th Most Common Citation

- Ten bags of torn or partially destroyed original records including CAPAs, preventative maintenance forms, and calibration records were found
- Raw data was written on scratch paper and sometimes differed from the data in the BPR
- Correction fluid was used on production records

3rd Most Common Citation

- Your firm failed to thoroughly investigate any unexplained discrepancy or failure of a batch or any of its components to meet any of it specifications, whether or not the batch has already been distributed (21 CFR 211.192)
  - Cited in 9 warning letters

3rd Most Common Citation

- The following discrepancies or failures were not investigated:
  - 4 batches of failing API were used in fifteen finished dosage batches
  - Failing assays were repeated until passing results were obtained (occurred at numerous firms)
  - Environmental monitoring results were recorded as zero but actually had growth

3rd Most Common Citation

- The following discrepancies or failures were not investigated:
  - "Unofficial" visual exam conducted for sterile injectables to remove vials with visible contamination so that the batch would pass the official visual exam (occurred at 2 firms)
  - Used three different analytical methods until obtaining passing results

2nd Most Common Citation

- Your firm failed to exercise appropriate controls over computer or related systems to assure that only authorized personnel institute changes in the master production and control records, or other records (21 CFR 211.68(b)).
  - Cited in 15 warning letters

2nd Most Common Citation

- Cited in numerous warning letters:
  - Audit trails were disabled
  - A shared username and password was used by many analysts
  - Users were able to manipulate, delete, or overwrite electronic raw data
- Firm's laboratory practice is to print chromatograms and delete electronic raw data files

Most Common Citation

- Your firm failed to ensure that laboratory records included ***complete data*** derived from all tests necessary to assure compliance with established specifications and standards (21 CFR 211.194(a)).
  - Cited in 21 warning letters

Most Common Citation

- Cited in numerous warning letters as failure to retain complete data:
  - "trial" sample injection data was not kept as part of the data for a batch
  - Sample weights, sample preparation and sample dilutions were not retained
  - Deleted data detected in audit trails
  - Overwriting data
  - Ripped up data found in the garbage

Most Common Citation

- Microbiological data missing:
  - Not reporting microbiological counts
  - Hundreds of environmental monitoring samples were not collected
  - Some microbiological sample plates/tubes were missing from the incubator
  - No microbiological testing was conducted; however, microbiological test results were reported on the certificate of analysis (COA)

Most Common Citation

- Certificates of analysis missing data:
  - Data on the COA sent with the batches was different than the COA the firm retained on file
  - COA retest date was changed to an expiration date and listed as eleven months later
- No raw data in support of results reported on COA
- Samples with no identification were discarded during the inspection

Most Common Citation

- Firm deleted all electronic raw data supporting HPLC release testing
- Standards were injected and used as sample results
- Duplicate logbooks were kept
- Complete raw data to support test method validation was not retained
- Integration parameters for HPLC analysis were not retained

What Can Data Integrity Problems Mean for Your Firm?

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

Rebuilding Confidence

- 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

How Can You Be Part of the Solution

- Look for gaps in how you control your records
- Ensure employees have appropriate user privileges
- Audit your data in a risk-based manner
- Verify the authenticity of your contractors' data

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