FDA Inspection Trends and Observations

Personal Care Products Council: QA Workshop

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Outline

• 483 Observation Trends
  – Top 10 Observations
  – Investigations and Data Integrity

• Things to consider when utilizing a contract manufacturer
483 Observation Trends – Top 10 11

Top 10 11 483 Observation between 9/1/2015 and 9/1/2016:
483 Observation Trends – Top 10

Top 10 483 Observation between 9/1/2014 and 9/1/2015:
483 Observation Trends - Comments

• There were fewer observations in the 2015-2016 vs 2014-2015 table due to switch from Turbo to eNSpect
• Top six observations for both years are the same
• 211.192, failure to thoroughly investigate unexplained discrepancy is top citation
• Increasing focus on data integrity, 211.68(b), appropriate control over computer systems. This citation has more than doubled between 9/1/2015-2016 (72) versus 9/1/2013-2014 (33).
483 Observation Trends - Investigations

• Why are investigations covered so frequently?
  – Good indicator of quality culture at firm and provide a quick snapshot of what is going on throughout a firm
    • They can be difficult and painful for a firm to do
  – Investigations are part of the Quality System which is required to be covered during every inspection
    • Typically one of the first areas covered during an inspection
483 Observation Trends - Investigations

• Common mistakes with investigations:
  – Did not include all affected products and/or lots
  – Lack of justification for root cause
  – Ineffective corrective and/or preventive actions
  – Fail to include prior occurrences
  – Quality Unit was unaware of discrepancy
  – Not conducted in a timely manner
Specifically, the investigation conducted was not extended to include all commercially released batches of X Tablets labeled with an incorrect expiry period. The investigation was initiated when X Tablets batch 1234 was found during final QA record review to have an incorrect expiry period. The investigation found that Change Request 456, which had been created X, was not closed until six months later.

However, four additional batches of X Tablets were found to have been packaged on-site between the date that Change Request 456 had been initiated and the date it was closed. A Field Alert Report was submitted during the inspection and included a commitment to recall the four lots.
Specifically, corrective actions undertaken as a result of an investigation into human hair contamination did not include all affected drug products. During the packaging of X Tablets batch 1234, a human hair was found in one bottle. At the time the human hair was found, # bottles had already been filled. The packaging line was examined and 2 human hairs were found in the filling machine. The line was cleared and underwent a major cleaning. The # bottles that had been filled before the packaging of X Tablets batch 1234 was stopped were not inspected to insure that they had not been contaminated with human hair. # bottles of X Tablets batch 1234 were released.
483 Observation Trends - Investigations

Specifically, your firm failed to perform adequate investigations with scientifically justifiable conclusions to incidents of out-of-specification (OOS) and/or failed to implement appropriate corrective actions for the root cause determination.

Quality event investigation, QE# was initiated to investigate an OOS result obtained for content uniformity of X Capsules lot 1234 during initial release testing. At each stage (Tier 1 and Tier 2), one of the capsules had a potency value of 123% and 129.0% respectively, which exceeds the limit of each unit. Even though the batch was rejected, the investigation did not provide adequate reason why the capsules failed content uniformity and no corrective action was implemented to prevent reoccurrence.
483 Observation Trends - Investigations

There is a failure to thoroughly review the failure of a batch or any of its components to meet any of its specifications whether or not the batch has been thoroughly distributed.

Specifically, a complaint involving mouth irritation with ABC Product was received and assigned complaint # 123456. The complainant sent in a sample and it was tested, resulting in an out-of-specification result for pH. The product has a gel on one side with a pH specification of # - # and a paste on the other side with a pH specification of # - #. The analyst testing the complaint sample reported a result of #. No investigation was conducted into the out-of-specification result, nor was there any explanation into why only one result was listed.
What is Data Integrity?

**Data Integrity** refers to 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).

FDA Guidance for Industry:

Is this a new requirement?

- 211.68 requires backup data are exact and complete, secure from alteration, inadvertent erasures, or loss
- 211.100 and 211.160 require certain activities be documented at the time of performance and that lab controls be scientifically sound
- 211.80 requires true copies or other accurate reproductions of the original records
- 211.188, 211.194, 212.60(g) require complete information, complete data derived from all tests, complete record of all data, and complete records of all tests performed.
- 212.110(b) requires data be stored to prevent deterioration or loss
Why is Data Integrity Important?

• We rely on accurate information to ensure drug quality
• Data integrity problems break trust
• We rely largely on trusting the firm to do the right thing when we are not there
Important Concepts

- Metadata
- Audit Trails
- Static versus dynamic records
- Backup datasets
- System validation
Laboratory records do not include a complete record of all data secured in the course of each test, including all graphs, charts, and spectra from laboratory instrumentation.

1) The firm has no mechanisms for the electronic back-up of data obtained in the course of analytical testing. The original raw data is printed off and the electronic data is erased.

2) The firm’s HPLC, LC and GC instruments have no password protection, user role restrictions, locked time or date stamps, or audit trail to demonstrate the information provided is an accurate representation of the original results.
Warning Letters – Data Integrity

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)).

- Trial HPLC, GC, and UV injections
- Raw data (sample preparation) not maintained
- Discarded data in the trash
Warning Letters – Data Integrity

For related substances analysis, three sample injections of vial 1_8 named “TEST” were run prior to the reported sample injections. The “TEST” injection data was stored in the “Trial” folder located on a personal computer with no audit trail linked to the HPLC.

During the inspection, the calculations you performed using the target sample weight showed the “TEST” injections were OOS as compared to the specification. The “TEST” injections were not reviewed and evaluated when making the batch release decision.
Warning Letters – Data Integrity

Your 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)).

– Lack of basic lab controls to prevent changes to electronically stored data
  • Audit trails turned off
  • No controls to prevent substitution, deletion, or overwriting of data
  • Sharing user names and passwords
Data Integrity - Test

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

2016 CDER Guidance Agenda includes CGMP Data Integrity Questions and Answers
Things to consider with contract manufacturer

• Should have a Quality Agreement
  – Quality Agreement is a comprehensive written agreement that defines and establishes the obligations and responsibilities of the Quality Units of the product Owner and Contracted Facility involved.
  – A Quality Agreement does not exempt contracted facilities from CGMP requirements related to the operations they perform, regardless of whether such CGMP requirements are specifically discussed in the Quality Agreement.
• For example, final approval or rejection of drug product to the market (211.22(a)) cannot be delegated by Owner to contracted facility via a Quality Agreement.
Things to consider with contract manufacturer

• Quality Agreement (continued)
  – Both Owners and Contracted Facilities must work together to establish and maintain quality oversight of contracted operations to assure drug products have the appropriate safety and quality.
  – The most critical elements of a Quality Agreement are the sections delineating the parties’ respective responsibilities and the discussion of change control.
    • How are changes communicated, documented and approved?
    • What risks might the type of change contemplated present to product quality?
Things to consider with contract manufacturer

• Conduct an audit
  – Go on-site to see operations at Contracted Facility
  – Review 483s and FDA inspection reports
  – Any unapproved drugs manufactured there?

• ISO Compliance ≠ CGMP Compliance
Things to consider with contract manufacturer

Warning Letters note when Contracted Facilities and Owners are not working together:

• “...you state that you have informed your clients on the importance of validating the methods, but they have chosen not to validate the methods. In addition, you state that you will inform them again in writing.”

• “...you failed to address the impact of the observed method deficiencies on the test results provided to your customers and to indicate whether you will inform your customers of the result of such evaluation.”

• “Your response, however, is inadequate because it does not include an evaluation of the data already provided to your clients, which were generated using the unqualified reference standards and unstandardized titrant solutions. Furthermore, your response does not indicate whether you will inform your customers of the result of such evaluation as it relates to their drug product(s)”
Things to consider with contract manufacturer

Warning Letters have been issued to both Contracted Facilities and Owners:

• **Contracted Facility**: “As a contract laboratory that tests drugs, your firm is responsible for complying with CGMP. In addition, it is also essential that your firm provide test results for evaluation and consideration by the owner of the product to consider in its final disposition decision.”

• **Owner**: Failure to properly evaluate contract laboratory to ensure CGMP compliance of operations occurring at the contract site. Did not audit the CTL; after FDA inspected, Owner audited and found critical and major deficiencies.
  
  – “Although you have agreements with other firms that may delineate specific responsibilities for each party, you are ultimately responsible for the quality of your products and the reliability of test results. Regardless of who tests your products or the agreements in place, you are required to manufacture these products in accordance with the Act to assure their identity, strength, quality, purity, and safety.”
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Any questions?

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