Overcome the Top Challenges of Handling OOS Results by Knowing FDA Observations

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Who decided you should come to this conference?

On the topic of OOS

- What is your biggest concern?
- What is your managers biggest concern?
- What is your company’s biggest concern?
Does it concern you, or your company, to know that soon the FDA will be monitoring your OOS activities.
When the laboratory gets an OOS test result, What should the laboratory do?
Inspectional Guidance

For each element, the firm should have:

• written and procedures.
• documentation from actions defined in the procedure(s).
• Adherence to the written procedures.

Adherence to an adequate Out of Specification (OOS) procedure which includes timely completion of the investigation.
483 Observation

The firm’s procedures for review of out-of-specification results is inadequate, and the firm does not follow their SOP for Failure Investigations.
Expectations

• Procedure
• Follow the procedure
• Records
• Timely conclusion
When do you know you have a problem?
Dear Sirs:

Your firm failed to thoroughly investigate unexplained discrepancies or failures of a batch or its components to meet its specification, whether or not the batch has already been distributed (21 CFR §211.192).
Any unexplained discrepancy (including a percentage of theoretical yield exceeding the maximum or minimum percentages established in master production and control records) or the failure of a batch or any of its components to meet any of its specifications shall be thoroughly investigated, whether or not the batch has already been distributed.
As a contract laboratory, you must comply with the CGMP regulations that apply to the operations you perform, including but not limited to, those that address the operations of your quality control unit, laboratory, investigation systems, documentation systems, and other facets of your operation. As set forth in FDA’s guidance for industry, Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production (available at http://www.fda.gov/downloads/Drugs/.../Guidance\_s/ucm070287.pdf),
Expectations
for any organization working in the pharmaceutical industry

• Procedure
• Follow the procedure
• Records
• Timely conclusion
Guidance for Industry

Investigating Out of Specification (OOS) Test Results for Pharmaceutical Production

1997- Draft

2006 – Final version
Expectations
for any organization working on the pharmaceutical industry

- Investigate all OOS observations
- An OOS procedure
- Follow the procedure
- An OOS log
- Records
- Timely results
Out-of-specification

_all_ test results that fall outside the specifications or acceptance criteria established in drug applications, drug master files (DMFs), official compendia, or by the manufacturer. The term also applies to all in-process laboratory tests that are outside of established specifications.

OOS Guidance – 10-06
Unexpected

Although the subject of this document is OOS results, much of the guidance may be useful for examining results that are out of trend.
Deviation

Deviations and **borderline conformances** are evaluated in accordance with a written procedure. The decision and rationale are documented. Where appropriate, batch deviations are subject to trend analysis.
Unexpected

“Wow, I have never seen a result like that before”
Expectations
for any organization working in the pharmaceutical industry

- Investigate all OOS and unexpected observations
- Trending
- An OOS procedure
- Follow the procedure
- An OOS log
- Records
- Timely results
The FDA investigator observed that your written procedures do not adequately address the need to investigate anomalies, unexpected events, or out-of-trend results. For example, on February 3, 2014, an analyst noticed an anomaly with the CHNOS analysis of sample (b)(4). The analyst repeated the analysis for sample (b)(4) as well as for samples (b)(4) and (b)(4).

There was no documentation that the event was reviewed by your laboratory or reported to your client manufacturing firm.
Analyst

• The primary responsibility for accurate testing lies with the analyst.

• Analyst should be aware of potential problems.

• Analyst should watch for problems that might cause inaccurate results.
Management should

• Provide and maintain an environment that is supportive of compliance.

• Provide appropriate training.

• Provide properly maintained and calibrated equipment and instruments
Analyst should

• Be trained on all applicable procedures.
• Understand the procedures and test methods.
• Use controlled chemicals and reagents.
• Use properly qualified, maintained and calibrated equipment and instruments.

OOS Guidance
Expectations
for any organization working in the pharmaceutical industry

- Investigate all OOS and unexpected results
- Analysts who are trained and alert
- An OOS procedure
- Follow the procedure
- An OOS log
- Records
- Timely results
OOS Observation

Laboratory Investigation

Additional Laboratory Testing

Review of Production
• For example, on multiple occasions, you failed to perform failure investigations for rejected batches or implement any preventive actions.

• The inspection found that your firm failed to perform an investigation for the failure of (b)(4) Injection (b)(4) mg/ml lot (b)(4) to meet in-process pH requirements. This failing pH result was confirmed by your QC laboratory.
You have failed to maintain adequate documentation to substantiate the invalidation of out of specification (OOS) results that would support the conclusions made during OOS investigations in the stability and quality control laboratories. Between June, 1996 and the dates of the inspection, XXX OOS investigations were conducted. Approximately XXX (70%) of these investigations were directly related to product potency and/or product quality. These investigations involved some type of finished and in process product assay (blend, composite, content uniformity, and dissolution).
Of the investigations which involved finished product samples, only once was the initial OOS analytical result reported as the true value. In all other instances, the initial laboratory OOS result was invalidated predominately due to analytical error. These investigation results raise concerns about how these conclusions were reached by the laboratory and the ability of your laboratory staff to properly conduct the analytical testing required.
Request for Quality Metrics
Guidance for Industry

This guidance document is being distributed for comment purposes only. Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the Federal Register of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the Federal Register. For questions regarding this draft document contact (CDER) Tara Gooen Bizjak at 301-796-3257 or (CBER) Office of Communication, Outreach and Development at 1-800-835-4709 or 240-402-7800.

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
July 2015
Pharmaceutical Quality/CMC
Current Good Manufacturing Practices (CGMPs)
FDA plans to request the following data

• The number of OOS results for the product, including stability testing. 101

• The number of lot release and stability tests conducted for the product. 500

• The number of OOS results for lot release and stability tests for the product which are invalidated due to lab error. 101
Quality Metric #3
Invalidated Out-of-Specification (OOS) Rate

The number of OOS test results for the finished product invalidated by the establishment divided by the number of OOS results divided by the total number of tests performed by the establishment in the same timeframe

\[
\frac{100}{101/500} = 0.002
\]
Quality Metric #3
Invalidated Out-of-Specification (OOS) Rate

Interpretation

- The fraction of invalidated OOS results per test.
- An indicator of the effectiveness of the QC laboratory
- Target – 0
- Acceptable - ???
- Lagging
Quality Metric #3
Invalidated Out-of-Specification (OOS) Rate

As a leading Quality improvement tool

• Calculate and trend each month:
  – Fraction of invalidated OOS results by product
  – Fraction of OOS results by analyst

• Investigate and CAPA for high values.
Warning Letter

For example, your firm failed to determine the cause of the OOS for ***** lot ***** that failed the uniformity of delivered dose test specification with a reported value of (b)(4)% during the 9-month stability interval. This same lot also failed the uniformity of delivered dose attribute during the 12-month stability interval. It was only after the 12-month OOS result that your firm decided to initiate a product recall for this Spiriva lot. We are concerned about the management decision to allow adulterated product to remain in the market between the 9 and 12 month stability stations.

320-15-13
Warning Letter

Your firm failed to thoroughly investigate any unexplained discrepancy or failure of a batch or any of its components to meet any of its specifications, whether or not the batch has already been distributed (21 CFR 211.192).

Your firm failed to conduct an adequate investigation that should have resulted in your implementation of corrective actions to prevent recurrence of the problem and evaluate other potentially affected lots.
Specifically, on April 17, 2012, your (b)(4) site reported that out-of-specification (OOS) endotoxin results were at or above the (b)(4) EU/ml limit in *****. We note that a portion of batch ***** was shipped to a contractor, (b)(4), for distribution to the U.S. market, on January 5, 2012. Your investigation into the (b)(4) ***** failures began on April 17, 2012, and you continued to test and re-test samples from this lot through August 14, 2012. In an attempt to find the root cause of the OOS results, your firm used different endotoxin testing platforms, tested at three different laboratories, wiped external vials with (b)(4), and used (b)(4) to try to mitigate endotoxin failed results. Subsequently, your firm tested nine ****retain samples and six (b)(4)***** samples on multiple dates with several failures. In addition, your firm sent one ***** retention sample and one (b)(4) ***** sample to an external testing laboratory. The extensive repeat testing of (b)(4) ***** samples resulted in inconsistent passing and failing results. At no point did you conduct quantitative endotoxin testing to determine the extent of the endotoxin specification failure.
OOS Guidance boundaries

• Applies to
  – Chemistry-based testing.
  – Testing required by CGMP regulations.
Does retesting that invalidates the original OOS observation identify the cause of the OOS test result?
When the initial assessment does not determine that laboratory error caused the OOS result and testing results appear to be accurate, a full-scale OOS investigation using a predefined procedure should be conducted. This investigation may consist of a production process review and/or additional laboratory work. The objective of such an investigation should be to identify the root cause of the OOS result and take appropriate corrective and preventative action.
Does retesting that confirms the original OOS identify the cause of the OOS??
Please note that § 211.192 requires a thorough investigation of any discrepancy, including documentation of conclusions and follow-up. Implicit in this requirement for investigation is the need to implement corrective and preventative actions.
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