Successfully Dealing with OOS (Out of Specification) Test Results in FDA Regulated Industries

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Dealing with OOS: presentation by Meena Chettiar
Learning Objectives

• In today’s session you will: Understand
• What an OOS Test Result is
• Why is it very important to learn how to deal with the OOS test result in the FDA Regulated Industries?
• Practical Issues in different industries when we encounter OOS test results from our chemical, physical and microbiological testing
Remember: Dealing with OOS Results in the FDA Regulated Industry can follow the Six Sigma Way from the time we encounter an OOS result all the way to product release with supporting evidence that FDA will deem acceptable! It is a lot of testing and documentation + doing it right.
Dealing with OOS: A Big Challenge for Regulated Industries

• In the testing world of the Pharmaceutical, Medical Devices and Food Industry, you cannot keep repeating a failing test until you pass. We will discuss:

• 1. FDA’s guidelines and regulatory expectations when we end up with a test result that does not meet the product specifications, i.e., OOS test result.

• 2. How do we deal with all possible scenarios of OOS results?
FDA has a Guidance Document for Investigating OOS Test Results

• Do we retest, if yes, how many times? What is reported as the final results for product release and can we release the final product when we get OOS test results? When is the product fully rejected when an OOS is obtained for a commercial product? Can apply to DVV Testing after TMV.

• At the end of this session you will have a strong foundation for successfully dealing with test results that end up becoming out of specifications for your pharmaceutical and medical device markets
Examples of FDA 483/Global Warning Letters for OOS Test Results

• Your laboratory failed to conduct investigation for numerous OOS results for CFU, HPLC Assay and Conductivity Test results and the contract lab did not notify the customer.

• Your QCU approved and released 2 batches of antibiotics despite an initial OOS assay result. Your QCU released the batch after retest even though the investigation did not identify any assignable cause for eliminating the original test result.
Key Terminologies related to OOS

**Aberrant Result:** Atypical result based on the specification or historical knowledge.

**Assignable Cause:** Root cause from a well documented identifiable error proven from a thorough investigation of why the test result may have been wrong originally. The root cause may at times not be very specific (specific being wrong dilution, wrong sample tested) such as inadequate training, human error, method not specific enough, method not robust enough for all analysts (technique is not precise for analysts of all levels).

**Confirmatory Testing:** Testing performed to confirm potential sources of laboratory error.
Key Terminologies related to OOS continued

**FDA Guidance Document for OOS:** Recommended practice/ FDA regulatory expectations to deal with OOS test result.

**Identifiable error:** A procedural deviation or calculation error that can be identified with certainty through tangible evidence.

**Invalid Test Result:** A result that can be invalidated during OOS investigation with a clear evidence for laboratory error.

**Laboratory Error:** Error during analytical testing that results in invalid test results that may or may not be OOS.

**OOS Test result:** A final test result that does not meet the specifications laid out for the product. OOS test result must be confirmed through proper scientifically based rational investigation.
**Key Terminologies related to OOS continued**

**Investigation Phase:** Type and time of investigation determines if it is phase 1 (immediately) or Phase 2 (repeated with some evidence of probable root cause)

**Out of Trend Test Result:** Aberrant result typically falling outside historical/expected stability/control charting test range

**Reanalysis:** Re testing from same set of standard or same sample preparation. This helps determine if there is an assignable cause.

**Retest:** Testing a new sample from the original sample by reweighing or re preparing from original stock solution. Retest may involve resampling of the original sample. Nature of retest must be clearly specified during a OOS investigation
Key Terminologies related to OOS continued

**Root Cause:** Basic underlying cause for the failure which when addressed and eliminated will prevent reoccurrence of a problem.

**Suspect Test Result:** Test result that is out of specifications that is considered as suspect test result until accepted/invalidated through lab investigation of the OOS.

**Test Method Validation:** Establishment of documented evidence for a high degree of assurance the test method will produce reproducible and accurate validated test result consistently under pre-established testing conditions.
How does cGMP’s 21 CFR 211.192 define OOS Test Result and what does it require for OOS?

• “Any unexplained discrepancy of the failure of a batch or any of its contents to meet any of its specifications. This shall be thoroughly investigated, whether or not the batch has already been distributed.”
CGMP’s 21 CFR 211.192 (Cont’d)

• “The investigation shall extend to other batches of the same drug product and other drug products that may have been associated with the specific failure or discrepancy.

• A written record of the investigation shall be made and shall include the conclusions and follow-up.”
FDA Guidance Document Draft and Final Version

• Draft: 30 September 1998
• 12 October 2006 in the Federal Register under Pharmaceutical cGMP
Key Decision Factors for OOS

- Definition of reportable values?
- Use of averaging? Rounding?
- Number of retests?
- Second analyst?
- Use of outlier testing?
- What specification limits? For which customer?
- Defining testing into compliance?
What Exactly does a OOS Test Result Include? Sources?

The term OOS results includes all test results that fall outside the specification or acceptance criteria established in drug applications, drug master files, official compendia, or by the manufacturer of the medical device or food product that falls under the FDA/Regulatory Jurisdiction.
Key Points to Remember When You Get an OOS Test Result

• Initiate OOS soon after discovery of OOS result per your SOP for OOS. Notify QA/QC heads even if the OOS is from your contract testing lab. All reportable values must be documented.

• Do not average only results with in spec to get an in spec results to release with.

• QA must see all Reportable Test Results.

• Do not ever eliminate any test result without a strong rationale and DO NOT REPEAT TEST UNTIL YOU GET INTO COMPLIANCE!
A lab test result may originate from several sample preparations

![Diagram showing the relationship between sample preparations and reportable values](image)

Figure 2
Batch/Lot Testing may originate from a single test

![Diagram](Figure 1)

- Batch
- Sample
- Preparation
- Inj
- Reportable Value, RV
What Does Phase I Investigation Involve?

• Why is Phase I Investigation important for an OOS?
• The purpose is to find the possible cause of the OOS.
• Is the root cause test measurement or manufacturing?
• “Batch rejection does not negate the need to perform the investigation.” Batch rejection must be supported.
• The first phase should include an assessment of the accuracy and source of failing test results.
Responsibility of the Analysts from Testing Lab (Contract/ On site)

• Analysts should check the data for compliance with test specifications before discarding test preparations or standard preparations.

• After documentation, calculation check the QA Dept. and client (internal/ external) must be notified immediately so the product is not released erroneously/pre maturely.
OOS Assessment by QC/QA Supervision

– Must be objective
– Timely, Unbiased
– No preconceived assumptions
– Prompt thorough assessment of data
– Phase I investigation may likely throw light into the source of the OOS: Laboratory error or product manufacturing error?
On to Phase II Investigations

• Unconfirmed OOS requires a full scale OOS investigation per your predefined procedure/SOP
• Find the root cause document as CAPA
• Review production and sampling procedures
• Investigations must be thorough and based on regulatory expectations to avoid Type I and Type II errors, supporting documentation needed at all levels: Leave no stones unturned!
Review of all possible sources of errors Including Production Errors

- QC/Inspection team conducts the investigation, keeping QA in the loop.
- This is an inter departmental or contract lab/client team effort with inputs from
  1. QC Lab/QA Management
  2. Manufacturing
  3. Process Development
  4. Maintenance
  5. Engineering
Key Rules for Retesting per FDA Guidance Document

• A retest can be from another test of a portion of the original sample or a new sample brought into the lab.
• FDA prefers a second analysts do the retest.
• Don’t “test into compliance.”
• Specify the number of retests in your OOS Documentation.
• Prepare a protocol before retesting and get it approved by QA/Client. Specify what is changing.
• If the original test error is found the retest results can be averaged and original test result eliminated.
Concluding the OOS Investigation

• If a root cause is found, invalidate the initial result and use the retest value(s) in its place, document findings and release product per your SOPs.

• If the OOS is confirmed the batch is rejected.

• If the OOS is inconclusive and the retests are consistently within specification, then QA *may* still be able to justify releasing the batch with solid rationale/process investigation per SOPs.
Final Take-Aways

• Can you now fulfill the requirements for product lot release or rejection through effective OOS Investigation for any test?

• Do you have a bullet proof OOS Investigation system that will not result in FDA 483/Warning letters/ Global non conformances?
Questions?

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