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Review Article……!!!

‘‘HANDLING OUT-OF-SPECIFICATION DURING LABORATORY INCIDENCE”

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ABSTRACT

In quality control laboratories, it is not uncommon to encounter test results on known samples that fall outside the expected range of values. This can pose a dilemma when communicating pass/fail verdicts. To address this issue, a detailed procedure for investigating out-of-specification (OOS) test results has been developed, outlining the responsibilities of both quality control and quality assurance. This procedure provides guidance on conducting a thorough laboratory investigation, including retesting and resampling, as well as manufacturing investigation and interpretation of investigation results. By following these steps, the laboratory can ensure accurate and reliable results, and take appropriate actions to maintain product quality.

INTRODUCTION:

When a product being tested during manufacturing or as a finished product falls outside of the specified limits outlined in official compendia, drug master files, or drug applications, it is referred to as an Out-Of-Specification (OOS) result. Quality assurance and quality control departments are responsible for handling these cases. OOS results can be classified as either assignable or non-assignable causes, and designated personnel will make this determination.

Once the cause of the OOS result is identified, the investigation should be closed out promptly, especially if a lab error has been detected and the batch needs to be released. However, the identified reason for the OOS result may not necessarily be the root cause, and it is essential to fully investigate all possible causes to prevent recurrence.

The purpose of this guidance is to outline a standard procedure for handling Out-Of-Specification (OOS) test results in a quality control laboratory. OOS results can occur in a variety of samples, including finished products, intermediates, raw materials, packaging materials, stability samples, water samples, working samples, working standard qualification, recovered solvents, recovered materials, microbiology analysis, and vendor samples. This procedure aims to provide a clear and consistent approach for managing OOS results in all sample types to ensure accurate and reliable results.

This guidance is not only applicable to handling Out-Of-Specification (OOS) test results in a quality control laboratory but also to the in-house testing of drug product components that are purchased. The principles outlined in this guidance are designed to be universally applicable to all sample types and testing procedures. While this guidance focuses primarily on contract firms responsible for production and laboratory testing, it can be adapted and applied to all relevant situations. The goal is to ensure a consistent approach to managing OOS results across all testing environments, whether in-house or contracted out.

This guidance does not applicable for the following samples:

- In-process samples analysed for the purpose of adjusting process requirement.
- OOS results obtained during analyst qualification.
- Method transfers activity.
- Pre-shipment samples

Regulations on OOS **-**

According to US cGMP 21 CFR 211.192

- "Any unexplained discrepancy of the failure of a batch or any of its contents to meet any of its specifications shall be thoroughly investigated, whether or not the batch has already been distributed.".

- "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."

EU GMP's Chapter 6: Quality Control[2]

To effectively manage Out-Of-Specification (OOS) and Out-Of-Trend (OOT) results, laboratory documentation should include a well-defined procedure for investigating these occurrences. Furthermore, it is important that certain types of data, such as test results, yields, and environmental controls, be recorded in a manner that allows for trend evaluation. If any data falls outside of the expected trend or specification limits, it should be thoroughly investigated to identify the root cause of the deviation. This investigation should be conducted promptly and in accordance with established procedures to ensure accurate and reliable results.

MHRA-

Out-of-Specification (OOS)

– Test result that does not comply with the predetermined acceptance criteria, for example:

- Filed applications, drug master files, approved marketing submissions,
- Official compendia
- Internal acceptance criteria

Few things to consider in OOS process:

Out of specification test results:

A test value that falls outside the established specification or acceptance errors.

Assignable cause:

A scientifically justified explanation of the reason for an out-of-specification result noticed and documented during the investigation.

Analyst error:

An error that is attributable to the person performing the test that resulted in an out-of-specification.

Laboratory error:

An error associated with the performance of attest procedure or due to laboratory equipment malfunction or failure.

Hypothesis testing:

To confirm or rule out a potential root cause of an OOS or OOT result, the investigation may include an examination of sample filtration, sonication, and equipment functionality to identify any possible issues.

Resample:

It is defined as the process of sampling a material/product for investigation from an already sampled batch or consignment.

Retest:

In the context of OOS investigation retest is defined as the reception of analysis on the original sample or resample.

Obvious error:

Any observable cause leads to error.

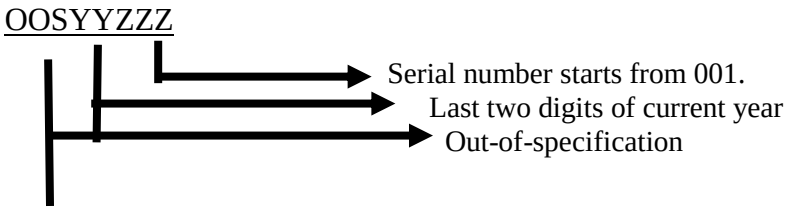
Manufacturing investigation:

Conducting a detailed investigation of the manufacturing process requires a thorough review of various factors, such as the quality and quantity of raw materials and intermediates used, the equipment used for manufacturing, the batch manufacturing record, analytical reports, any deviations or abnormalities, and personal evaluations and training records. By carefully examining these aspects of the manufacturing process, it is possible to identify any potential issues and ensure that the resulting product is of high quality and meets all necessary specifications.

INVESTIGATION PROCESS

If an Out-Of-Specification (OOS) test result is obtained, it is important for the analyst to retain all of the original standard and sample solutions, along with their dilutions, as well as any samples or reagents that were used, and the instrument settings that were employed for the analysis. This documentation must be retained until the results have been fully reviewed and investigated. In the event of an OOS result, it is the responsibility of the analyst to inform the appropriate section in-charge and the head or designee of quality immediately to ensure timely resolution of the issue[9].

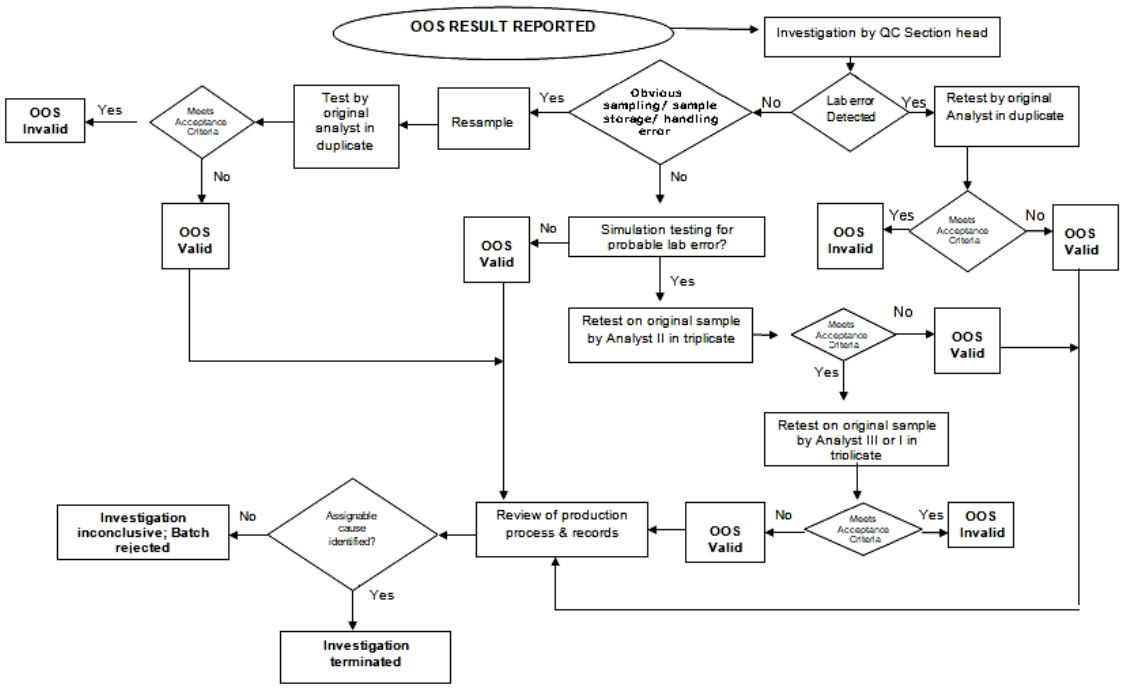
QA shall enter the obtained details in the standard format and assign the OOs report numbers as follows.



Example: OOS19001 represents the first OOs in the year 2019

The Out of specification investigation consists of two phases of investigation.

- Phase I investigation; it's a preliminary investigation phase, which allows elimination of obvious errors and focuses on the laboratory.
- Phase II investigation: it is more in-depth investigation phase under QA oversight, which consists of a more detailed laboratory investigation and includes manufacturing investigation.



Laboratory investigation of OOS results (Phase-I investigation)

A laboratory assessment of the OOS test results shall be performed by filling the format **'laboratory investigation of OOS results'** to find out whether any laboratory errors were made during analysis. And the analyst in charge shall conduct the laboratory investigation to determine the assignable cause for the unexpected result. This assessment may include but is not limited to the following[10].

- Verification of raw data / electronic data
- Verification of glassware
- Verification of instrument
- Verification of sample/sampling
- Verification of method
- Analyst training and qualification
- Verification of chemicals/reagents/standards

- Verification of analysis
- Text execution

Based on the laboratory checklist verification and conclusion shall be drawn

Confirmatory testing:

This testing shall be carried out to confirm the error which is known, and to prove or disprove the hypothesis, when error is not clear and suspect.

Examples includes,

- Instrument performance that effecting testing results.
- Wrong volume flask/pipette used for dilution.
- Sample vial contaminated.
- Analyst skipped one step during the analysis.
- Insufficient sonication of sample and standard

1. If the confirmatory testing is not carried out, then it shall be justified.

Example:

- Sample is directly used for analysis.
- Test method does not include dilution.

2. If the cause of the error is detected from phase I investigation and the analyst has understood the cause, record the assignable cause under phase-I conclusion.
3. If the assignable cause is analyst error, then impact on previous sample testing results using the same analytical test method, impact on other samples in the sequence carried out by the concerned analyst, shall be evaluated. The original result shall not be invalidated until thorough investigation is completed and assignable cause confirmed.
4. If the reanalysis result meets the specification, the original result will not be considered for reporting and the reanalysis results to be reported.
5. If the result of retesting does not meet the specification, further OOS process to be initiated.
6. The laboratory investigation shall be completed and forward to QA for assessment and further recommendation.
7. If an assignable cause has not been determined after phase-I investigation, phase II investigation can be carried out.

Laboratory investigation of OOS results (Phase-II investigation):

Hypothesis testing:

If an error assignable to the testing laboratory cannot be identified, the QC personnel shall refer the matter to the QA for initial assessment and a full-scale OOS investigation shall be initiated to investigate the possibilities of probable causes.

In phase-II investigation, a hypothesis using fresh preparations to be performed to help and or discount a possible root cause, what might have happened during initial testing. description of the same shall be approved by QA prior to initializing investigational testing.

The description must contain the following.

- The hypothesis to test the root cause being investigated.
- What samples to be tested?
- The exact execution of the testing
- How the data will be evaluated.

Multiple hypothesis testing can be performed to identify the root cause or probable cause. but each testing shall be carried out with prior approval. Multiple hypothesis testing can be followed with prior approval using request for additional hypothesis testing format and all the hypothesis testing can be performed with normal level of replication as per STP by the same or different analyst. Then Record all findings, interpretation and final conclusion[1].

Hypothesis testing results shall not be used to replace the original suspect analytical results.it shall be used to confirm or discount a probable cause. If there is no hypothesis, justification shall be provided[8].

A. Averaging cannot be used in cases when testing is intended to measure variability within the product, such as powder processing blend uniformity.
B. While averaging assay consideration of using 95% confidence limits ($Cl_{95\%}$) of mean shall be for assessing the variability.
C. The confidence interval (Cl) is calculated from the below formula:

$$Cl = \text{Sample mean} \pm t_{95\%} \frac{\text{sample standard deviation}}{\sqrt{n}}$$

t: value obtained from table.

n:sample size

Retesting:

- A protocol for retesting shall be prepared in the format which shall contain, number of retests, acceptance criteria.
- The number of retests shall be performed as per retesting control format. if any deviation from retesting control it should be justified.
- Out-of-specification results must not be combined or averaged with results that meet the specification. Retesting beyond the number specified in the protocol is not allowed. The

protocol should be based on scientific considerations and the variability of the specific method, such as in-process history or trend data.

- The retesting sample must be obtained from the same homogenous sample that was previously collected from the tested batch and resulted in the out-of-specification (OOS) results.
- For new test portion analysis, all reagents shall be prepared freshly.
- If the hypothesis testing identifies an assignable cause as the likely reason for the OOS result, then retesting must be conducted in accordance with the retesting control format by either the same analyst or a different analyst. The cause of the error must be eliminated, and the same aliquots or stock solutions may be used for the retesting, if they are still within the validity of solution stability. If solution stability information is not available, fresh preparations of the original sample may be used, subject to approval by the Quality Assurance (QA) team and in accordance with the full-scale investigation protocol. If any issues are observed during the retesting process, the path forward will be determined by the QA team.
- If the hypothesis is not proven, the retesting must be conducted by both the first and second analysts individually according to the Retesting Control Format, with the approval of QA and using the protocol for the Full-Scale Investigation Format. The second analyst must be at least as qualified and experienced in the method as the original analyst. The entire retesting process must be monitored by the section in charge[3].
- If any of the individual retest results obtained by either or both first and second analyst are not within the specification, original OOS results stand valid and manufacturing investigation shall be initiated.
- If the retesting results are individually within specification and meet the acceptance criteria as defined in the protocol.it should be as follows,
- All individual test results are within the specification.
- The average results must be within the specification.
- Reporting of results for cause not identified: in case assignable cause could not be identified and batch shall be released based on passing retest results and evaluation, follow procedure as specified below for evaluation:
- Calculate the average of all the retest determination and report average results. Do not consider initial OOS test results for averaging.
- Record all findings, interpretation, conclusion and CAPA.

- If the OOS result is confirmed, an investigation to evaluate the sampling procedure and integrity of the original sample shall be initiated[4].

Resampling:

Resampling shall be done only under the following conditions, if justified.

- The sample was contaminated in the laboratory.
- The sample was spilled, or container was broken.
- Inadequate storage and packing condition.
- When there is wide variation in results from same original composite sample.
- If sample quantity is insufficient for retesting.

A protocol should be followed for resampling and retesting. If there are any sampling discrepancies observed during the investigation and if any of the conditions mentioned earlier exist, resampling should be carried out. The resampling must be performed using the same method as the initial sample. In case the investigation shows that the initial sampling method was intrinsically inadequate, a new valid and accurate method must be developed, documented, and approved for use.

Retesting on resampled portion shall be done by original analyst and a second analyst as per retesting control under the supervision of the section in charge. the number of retests, acceptance criteria and justification for averaging the results, if any shall be followed as per the approved protocol and as per retesting control.

Retesting results are individually within specification and meet the acceptance criteria as defined in the protocol.it should be as follows,

- All individual test results are within the specification.
- The average results must be within the specification.

Record all findings, interpretation, and final conclusion. Based on the laboratory investigation, if the material failed to meet the required specification the QA head shall recommend for manufacturing investigation. If required a detailed investigation report can be prepared referring to laboratory investigation of OOS results[7].

Manufacturing investigation:

If a production batch does not meet the quality standards as confirmed by the quality control analysis, a thorough investigation must be conducted. The investigation should be carried out by a technical team that includes representatives from production, quality control, R&D, engineering, and quality assurance to determine the root cause of the failure.

Review the batch record and other supporting documents as follows, but not limited to,

- Quality and quantity of input raw materials

- Equipment used for manufacturing.
- Review of batch manufacturing record
- Review of analytical report.
- Deviation
- Personal evaluation
- Training record review.

Extend the investigation to other batches to evaluate the impact on one or more batches, if required review the quality trends for the product in-order to determine the extent of deviation from the regular manufactured batch. If necessary, conduct additional testing on the product and perform experiments in the R&D department for any OOS results. For materials that were sent for testing outside of the laboratory, and where an OOS was observed, the contract laboratory should provide its data, findings, and supporting documentation to the site. The data will be reviewed, investigated, and documented accordingly[6].

Interpretation of investigation results:

The interpretation of the findings of the full-scale investigation along with retest shall be done by quality control and quality assurance functions to ensure that, under no circumstance the laboratory invalidates the OOS result based on passing retest results alone. If any of the individual retest results are not complying with the specification the OOS shall be considered as valid, and a manufacturing investigation shall be initiated. based on the findings in the investigations, QA shall perform the final assessment and recommend for material disposition in the format.

The Standard Operating Procedure (SOP) for Non-conforming Material Disposition must be followed for the final disposition of the material. OOS test results must be included in the Annual Product Review. The investigation of any out-of-specification must be concluded within 30 working days starting from the date when the OOS result was obtained. If this cannot be achieved within the stipulated time, approval from QA must be obtained for an extension of the investigation time, along with a justification in the format for Extension of Time Period for OOS Investigation. All out-of-specification cases must be trended annually, and repeated failures must be identified, followed by the implementation of corrective and preventive actions to ensure their effectiveness[5].

Summary:

OOS incidents may lead to batch rejection, each incidence needs to be adequately investigated and the issues are addressed. Moreover, the OOS must be:

In terms of best practice, the following should be in place:

- There is an OOS system.
- With OOS there is full investigation and a CAPA system.
- All results are documented.
- That the documentation is of a high standard.
- OOS results and investigations are reviewed at regular intervals.
- Trending of OOS investigations are in place to determine if an issue is isolated or widespread.
- OOS entries are investigated and closed in a timely manner.

The final disposition of non-conforming material must follow the Standard Operating Procedure (SOP) for Non-conforming Material Disposition. Out-of-Specification (OOS) test results must be included in the Annual Product Review. The investigation of any OOS result must be completed within 30 working days of detection. In case of an extension, approval must be obtained from Quality Assurance (QA), with a justification in the Extension of Time Period for OOS Investigation format. Annual trend analysis of OOS cases is mandatory to identify repeated failures, followed by the implementation of corrective and preventive actions to ensure their effectiveness.

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