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HANDLING OUT-OF-SPECIFICATION DURING LABORATORY INCIDENCE

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ABSTRACT

Out of specification can be observed test results which fall outside specifications or acceptance criteria established by the product manufacturer or the laboratory. The purpose of the investigation is to determine the cause of the OOS result. The root of the OOS result should be identified either as a laboratory error or manufacturing error. This article explains the detailed procedure to investigate Out of Specification (OOS) test results, including the responsibilities of The Quality control and quality assurance and provide assistance in conducting laboratory investigation. It also explains retesting, re-sampling, manufacturing investigation, interpretation of investigation results.

INTRODUCTION

The OOS (out of specification), if a in process or finished product testing, is falling out of specified limits, that are mentioned in official compendia, drug master file, or drug application can be termed as Out-Of-Specification (OOS). This is handled by quality assurance and quality control department. The reasons for OOS can be classified as non-assignable and assignable. The designated personnel will classify the OOS aseither or non-assignable or assignable cause.Once the reason for the OOS result has been found, the summons is to close out the investigation as fast as possible, particularly when a lab error has been recognized and the batch being tested now needs to be released. However, the reason for the OOS result is not the same as the underlying root cause, and often there is more than one root cause that needs to be fully investigated if reoccurrence is to be prevented. This article describes a procedure for handling of Out-Of-Specification (OOS) test results mainly in quality control Laboratory. The OOS results includes finished products, intermediates, raw materials, packaging materials, stability samples, water samples, working samples, working standard qualification, recovered solvents, recovered materials, microbiology analysis, vendor samples, it is also applicable to testing of drug product components that are purchased. This articles not applicable for the following samples:

- In-process samples analysed for the purpose of adjusting process requirement.
- OOS results obtained during analyst qualification.
- Method transfer 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 will

be thoroughly investigated, whether or not the batch has already been distributed."

- "The investigation will 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 will be made and will include the conclusions and follow-up[1]"

1. EU GMP's Chapter 6: Quality Control

- Laboratory Documentation should include: A procedure for the investigation of Out of Specification and Out of Trend results.
- 6.9 Some kinds of data (e.g. tests results, yields, environmental controls) should be recorded in a manner permitting trend evaluation. Any out of trend or out of specification data should be addressed and subject to investigation.

2. 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

Terms 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 help, confirm or discount a possible root cause it may include regarding sample filtration, sonication, potential equipment failures.

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: It is detail investigation of manufacturing process it includes review of quality and quantity of input raw materials/intermediates, equipment used for manufacturing, review of batch manufacturing record, review of analytical report, deviation/abnormalities if any, personal evaluation/training record review etc [2].

INVESTIGATION PROCESS: When an Out-Of-Specification test result is obtained, the analyst will retain the entire original standard and sample solutions and their dilutions, samples or reagents used and the instrument settings used for analysis, until results have been reviewed and investigated complete. Then inform the OOS result to the section in-charge and head of quality immediately.QA will enter the obtained details in the standard format and assign the OOS report numbers as follows

OOSYYZZZ

1. Serial number starts from 001
2. Last two digits of current yea
3. Out-of-specification

Example; OOS19001 represents the first OOs in the year 2019

The Out of specification investigation consists two phases of investigation.

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

detailed laboratory investigation and also includes manufacturing investigation.

Figure 1: Out of Specification investigation process [8]

Laboratory investigation of OOS results (Phase-I investigation): A laboratory assessment of the OOS test results will be performed by filling the formatto find out whether any laboratory errors were made during the course of analysis. And the analyst in charge will conduct the laboratory investigation to determine the assignable cause for the unexpected result. This assessment may include, but is not limited to the following [3].

- 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

Confirmatory testing: This testing will 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 will bejustified.

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 concered analyst, will be evaluated. The original result will 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 will 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 [4].

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

Hypothesis testing: If an error assignable to the testing laboratory cannot be identified, the QC personnel will refer the matter to the QA for initial assessment and a full scale OOS investigation will 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 will be approved by QA prior to initializing investigational testing [5].

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 in order to identify the root cause or probable cause, but each testing will 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. Hypothesis testing results will not be used to replace the original suspect analytical results.itwill be used to confirm or discount a probable cause. If there is no hypothesis, justification will be provided.

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 will be for assessing the variability.
C. The confidence interval (Cl) is calculated from the below formula:

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

t: value obtained from table
n: sample size

Retesting: A protocol for retesting will be prepared in the format which willcontain, number of retests, acceptance criteria.

A. The number of retests will be performed as per retesting control format. if any deviation from retesting control it should be justified.
B. Out of specification results will not be averaged with results which are complying with the specification.additional retesting will not be carried out beyond the number specified in the protocol. the protocol will be on the basis of scientific considerations and the variability of the particular method Ex: In-process history or trend data.
C. The sample for retesting will be used from the same retained portion of the original homogenous sample that was originally collected from the batch tested, and yield the OOS results.
D. For new test portion analysis, all reagents will be prepared freshly.
E. If the hypothesis proves the probable reason as the assignable cause, then the retesting will be carried out as per retesting control format by the same or different analyst after omitting the cause of error using the same aliquots or stock solutions, if these are within the validity of solution stability. If solution stability not available carry out the analysis using fresh preparations of original sample with the QA approval using protocol for full scale investigation format. if any failure observed during retesting further path forward will be decided by QA.
F. If hypothesis not proven the retesting will be done by the first analyst and second analyst as per retesting control format. The second analyst will be at least as qualified and experienced in the method as the original analyst. this entire activity of retesting will be monitored by the section in charge.
G. If any of the individual retest results obtained by either or both first and second analyst are not within the specification, original OOS results stands valid and manufacturing investigation will be initiated.
H. If the retesting results are individually within specification and meet the acceptance criteria as defined in the protocol.it should be as follows,
   A. All individual test results are within the specification.
   B. The average results must be within the specification.
J. Reporting of results for cause not identified: in case assignable cause could not be identified and batch will 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.

K. Record all findings, interpretation, conclusion and CAPA

L. If the OOS result is confirmed, an investigation to evaluate the sampling procedure and integrity of the original sample will be initiated.

Re-sampling: Re-sampling will be done only under the following conditions, if justified.

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

Re-sampling and retest will be done in accordance with a protocol. If any sampling discrepancy is observed during the investigation and any of the above-mentioned conditions exist, then re-sampling will be performed. Re-samplingwill be done by the same method used for the initial sample. If the investigation shows that the initial sampling method was inherently inadequate, anew accurate and valid method will be developed, documented and approved for use. Retesting on re-sampled portion will 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 will 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 will recommend for manufacturing investigation. If required a detailed investigation report can be prepared referring to laboratory investigation of OOS results [6].

Manufacturing investigation: A production batch fails to meet the standards of quality as confirmed by the quality control analysis; detailed investigation will be carried out. A detailed investigation will be carried out by a technical team comprising of representatives from production, quality control, R&D, engineering and Quality assurance to investigate the reason for 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. Get any additional testing done on the product, where necessary carryout experiments in R&D. for OOS observed for any materials sent for outside testing laboratory, the contract laboratory will convey its data, findings and supporting documentation to the site will be reviewed the data same will be investigated and documented.

Interpretation of investigation results: The interpretation of the findings of the full scale investigation along with retest will 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 will be considered as valid and a manufacturing investigation will be initiated. Based on the findings in the investigations QA will perform the final assessment and recommend for material disposition.

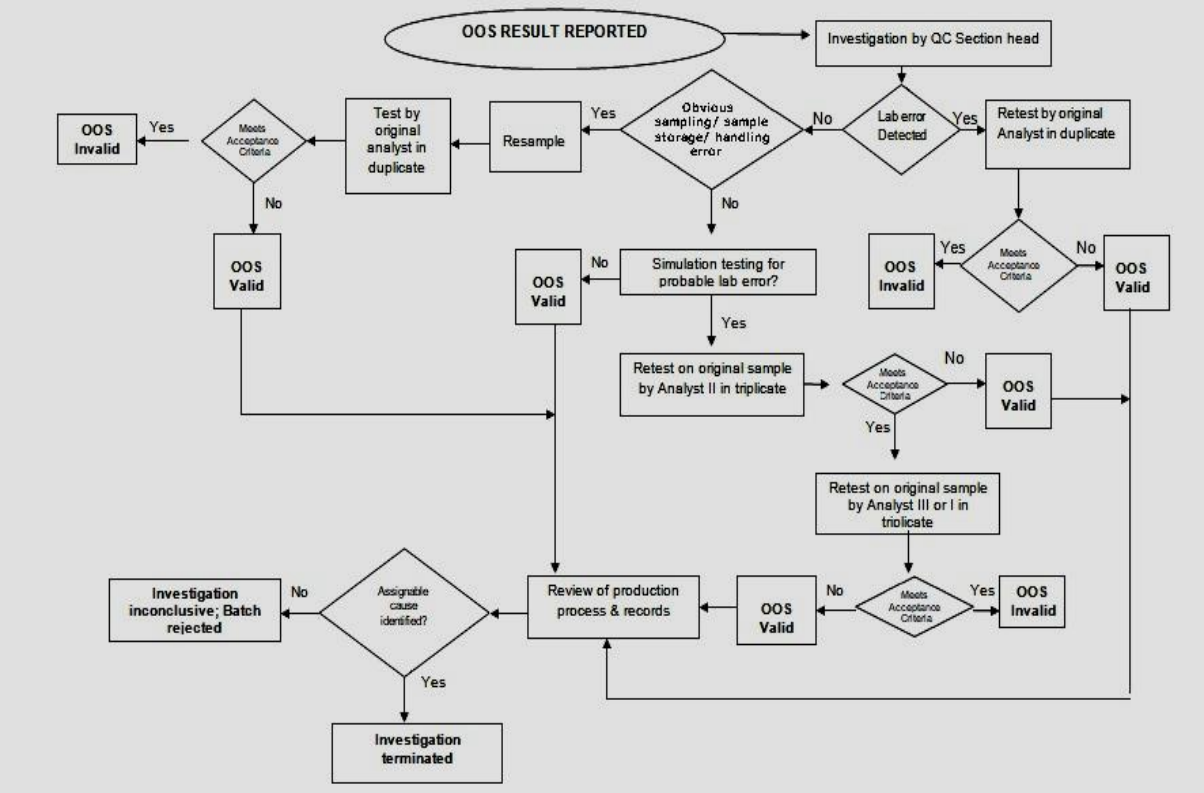

Figure 1: Out of Specification investigation process

Image source: Ankur Choudhary, OOS investigation flow chart, pharmaceutical guideline [Cited 15 may 2019]

The final disposition of the material will be followed as per the procedure. OOS test results will be included in the Annual product Review. The out of specification should be completed within 30 working days from the date of OOS result. if this cannot be completed within the time period, take approval from QA for investigation time extension with justification. All out of specification will be trended every year, verify the repeated failures and implementation of Corrective and Preventive action and its effectiveness [7].

SUMMARY:

OOS incidents may lead to batch rejection, each incidence needs to be adequately investigated hence a detailed procedure for handling of out of specification was discussed and their issues are addressed. Based on the study OOS must be there as a full investigation with a CAPA system.OOS results and investigations should be reviewed at regular intervals. Trending of OOS investigations should be in place to determine if an issue is isolated or widespread.OOS entries should be investigated and closed in a timely manner. Investigating OOS incidents thoroughly is an essential part of Good Manufacturing Practice. The frequent occurrence of OOS results indicates that the manufacturing and analytical procedures not in control.

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Conflict Of Interest: None

REFERENCES:

1. Ermer J, Miller JH, editors. Method validation in pharmaceutical analysis: A guide to best practice. John Wiley & Sons; 2006 Mar 6.

2. Swartz M, Krull I. Investigating out-of-specification results. LC GC NORTH AMERICA. 2004 Feb 1;22(2):132-7.
3. Kuselman I, Pennecchi F, Burns C, Fajgelj A, de Zorzi P. IUPAC/CITAC Guide: Investigating out-of-specification test results of chemical composition based on metrological concepts (IUPAC Technical Report). Pure and Applied Chemistry. 2012 Jul 9;84(9):1939-71.
4. Hoinowski AM, Motola S, Davis RJ, McArdle JV. Investigation of out-of-specification results. Pharmaceutical technology. 2002 Jan;26(1):40-51.
5. Lee DC, Webb ML, editors. Pharmaceutical analysis. John Wiley & Sons; 2009 Feb 12.
6. Immel BK. A brief history of the GMPs for pharmaceuticals. Pharmaceutical technology. 2001 Jul;25(7):44-53
7. Food and drugs chapter I, code of federal regulation [title 21, volume 4],https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=211.192
8. Ankur Choudhary, OOS investigation flow chart, pharmaceutical guideline [Cited 15 may 2019]https://www.pharmaguideline.com/2017/09/oos-investigation-flow-chart.html