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Short Communication

HANDLING THE OUT OF SPECIFICATION (OOS) RESULTS IN PHARMACEUTICAL/ BIOPHARMACEUTICAL INDUSTRIES FOR COMPLIANCE – A HOLISTIC REVIEW

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ABSTRACT

Following the written and operational procedures are mandatory in pharma/ biopharma industries in view of cGMP and to carry out activities for compliance. OOS handling is critical in quality perspective, as invalid OOS is a point of concern by different regulatory authorities. To investigate the OOS result, an operating procedure should be in place. If any result found out of specification, that should be investigated through this procedure. The source of the OOS result should be identified either as an aberration of the measurement process, i.e., laboratory error or an aberration of the manufacturing process. Phase I investigation (laboratory investigation) aims at ruling out any laboratory/ equipment error (which may occur due to instrument, reagent, reference standard, environment condition, test method, analyst and calculation). Phase II investigation (full-scale OOS investigation) consists of a production department for process review. Additional laboratory investigation shall be carried out by production including the cross functional teams if any, if required. The procedure also provide guidance on the number of retests/ resamples permitted. After impact assessment of OOS on product, appropriate corrective action and preventive action (CAPA) shall be proposed to avoid the occurrence in future. This is the first review reported and ideal form of handling the OOS results in any pharmaceutical/ biopharmaceutical industries across the world.

Keywords: Out of specification, quality assurance (QA), laboratory investigation, full-length investigation, root cause, impact assessment, corrective and preventive action, closure.

INTRODUCTION

Some organizations aiming at harmonizing the inspection procedures worldwide by developing common standards in the field of medicinal products and by providing training opportunities to inspectors for human and animal welfare. Most of the pharmaceutical/ biopharmaceutical industries produce and commercialize several drugs as medications to patients to cure their symptoms or diseases. If any noncompliance identified during any stage of the manufacturing (production) or allied stages of manufacturing (Quality Control analysis) with respect to Safety, Identity, Strength, Purity, and Quality (SISPQ) that should be routed through quality element, OOS [1]. Test results that fall beyond the acceptance criteria of predefined specification limit established in drug dossiers, drug master files (DMFs), official pharmacopoeias or by the manufacturer specification of Finished products (FP), InProcess (IP) samples, stability samples (SS), semi-finished products (SF), Excipient (ET), Raw Materials (RM), Intermediates (IS) and Packing Materials (PM) is considered as OOS. Ideally it describes the procedure for investigating the OOS test result(s). In view of patient safety, acceptance criteria to be mentioned for various parameters when or where required [2]. It must be decided by cross-functional teams like Research and development; Pharmacovigilance, Quality control, Manufacturing sciences and Quality assurance based on type of noncompliance like impurities, extractable, leachable, residual solvents, degraded compounds, unsafe product and non-quality products. All these types of products will harm the patients; hence, all nonconformities shall be investigated before the product released into the market.

OOS is a non-classified quality element, as it is critical type. Content of phase I shall be common for all types of process OOS, but content for phase II investigation shall be unique for raw materials, packing materials, bacterial endotoxin test (BET), medical devices, sterility, bioburden (BB) test, total viable aerobic count (TVAC)/ total bacterial count (TBC). In any of the confirmed OOS, failure of the investigation should be routed through fishbone analysis diagram (Ishikawa fishbone diagram). If OOS results are invalid based on reanalysis or retesting results, head QA shall take a decision to release the batch/product/material for further. Some organizations having collaborations with other organizations, in this case, OOS intimation details to be communicated to partners/others. Phase I and Phase II draft investigations report shall be shared with those partners to avoid gaps in investigation. If partners/others having any concerns that should be duly justified before closure of investigation. Contents of the annexure for the phase I, phase II and rejection note to be defined as per requirements of the industrial practice. All the investigative parameters in phase I and II shall be duly justifying throughout the investigation [3, 4].

IDENTIFICATION OF OOS

During the analysis of samples, if result found to be in OOS range shall be notified to the QA department. There are no immediate corrective actions for any type of OOS. Immediate corrective actions/corrections are applicable to another quality element, deviation to nullify or avoid the impact on product quality. In case of OOS identified, simultaneously user department shall discuss with cross-functional teams if required. OOS is not required for in-process tests of process monitoring, or adjustment of the operations being performed to achieve the target result. After identification, carrying out specification, investigation includes the phase Ia investigation, phase Ib investigation, Phase II investigation and phase III investigation [5].

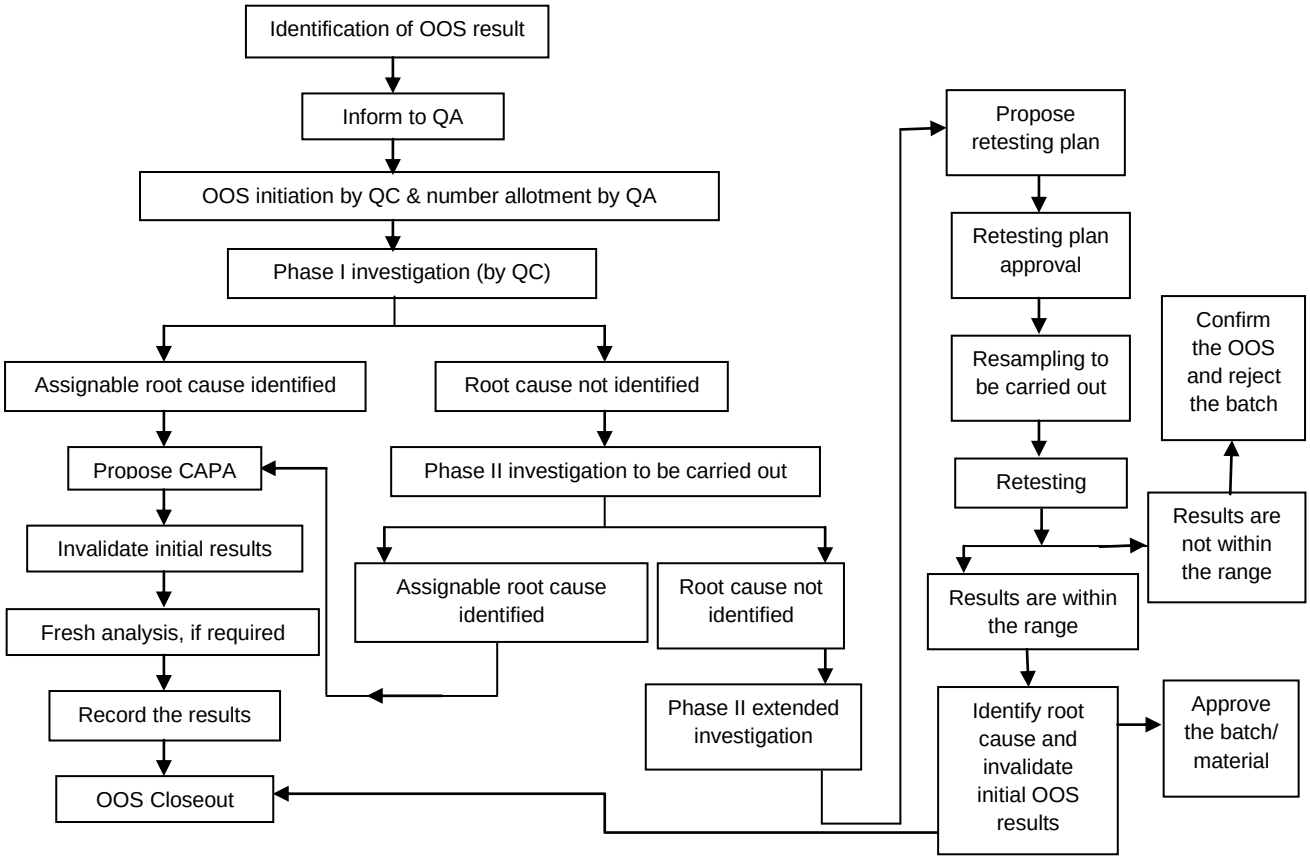

Figure-1: Flow chart of handling the OOS test result

REPORTING TO QA

If OOS result is identified, same should be reported to QA on the same day/ in worse case on next working day/ on case to case basis defined as per predefined operational procedure. Because some of the sample needs to analyze immediately by considering the ongoing process activities. In such situations, decision will be taken by user department head in accordance with head QA in view of compliance. During reporting to QA, raw data shall be attached with notification form or wherever applicable. Before allotting the number, QA personnel review the last one year data of similar or same type of events.

In case of multiple nonconformances in a batch (during analysis) was identified, should be routed through single notification form. In case of identical parameters in multiple batches of same product is identified, should be routed through single notification form. In case of non-identical parameters in multiple batches of same product, should be routed through individual notification forms for each OOS parameter for thorough and timely investigation.

Numbering format of OOS should be like AAA-OOS-B-CC-YY-XXX. Where, organization name in three letters (AAA), Quality element or noncompliance element in three letters (OOS), Type of OOS in one letter (B) [Either Analytical (A)/ Microbial (M)], Stage of the process in two letters (CC) [Either Raw materials (RM), in process materials (IP), intermediates (IS), packing materials (PM) and finished products (FP)], Last two digits of the financial year or calendar year (YY) and sequential number of the OOS (XXX) or numbering as per predefined organizational procedure. Post allotting the OOS number by a QA personnel, on the same OOS intimation note, phase I investigation target date (7 working days from the date of event happened) shall be mentioned by a QA personnel. The QA personnel shall write a comment as phase I and II investigations shall be carried out parallelly on case to case basis if required. Ideal industry practice about OOS investigation includes, phase II investigation and extended phase II investigation (if required) should be closed within 45 working days for compliance. If any delay in closure shall be justified by user department head with delay justification [2, 6]. OOS result information shall be communicated to cross-functional teams by a QC personnel through OOS intimation report along with supporting data if required.

Investigations of OOS i.e., Phase I (laboratory investigation or hypothesis investigation) and Phase II to be carried out parallelly on case to case basis. If both investigations are initiated parallelly, if root cause identified in phase I investigation, the same to be concluded in Phase I investigation closure by the QA and QA will conclude the phase II investigation as “root cause is identified in Phase I investigation, therefore phase II investigation is aborted”. If root cause is identified in Phase II investigation, same to be concluded in phase II investigation closure by the QA. Later QA will conclude the Phase I investigation with same result and conclude like, Phase I investigation is not required.

LABORATORY INVESTIGATION (QC)

Also called phase I investigation, involves the preliminary laboratory investigation for any obvious errors/ other errors. Investigation to be conducted whenever an OOS result is identified [7]. Upon reviewing the OOS result by laboratory supervisor, laboratory supervisor shall have a discussion with an analyst regarding the failure result. Laboratory investigation may occur because of the instrument, reagent, reference standard, environment condition, test method, analyst and calculation followed in the laboratory. The laboratory supervisor will verify the last one year data with the help of QA personnel. Phase I investigation is conclusive, then appropriate CAPA shall be proposed by the QC, then invalidated the initial results. Record the reanalysis results (if performed) or correct the error (Clerical error, power failure, calibration failure, spillage of the sample, wrong instruments, incorrect of instrument parameters, errors in

dilution/ usage of appropriate and valid standard/ method followed/ sample stored appropriately/ status of balance/ homogeneity of the sampling procedure/ status of instruments, sample preparation method followed/ sample taken is representative/ sampling plan followed/ sampling equipment's status) and close the OOS. If root cause not identified in phase I, then phase II investigation shall be carried out.

In Phase I investigation, if any error is suspected by the QC department, based on the same, hypothesis plan shall be proposed by the QC and that should be duly approved by the QA department. Based on the hypothesis plan, reanalysis shall be carried out and verify the result for compliance. If the results are in specification range, then propose appropriate CAPA. Record the reanalysis results followed by invalidating the initial OOS results. Post initiating the CAPA/ change control, OOS can be closed. If results of Phase I results were not meeting the specification criteria after the hypothesis testing, phase II investigation shall be carried out (Figure-1).

In case of raw material or packing material or any other incoming materials (critical or noncritical) not meeting the specification criteria mentioned as per in-house specification, the QC personnel should initiate a non-conformance report with necessary details (which are not meeting as per pharmacopeia standard) and that shall be duly approved by the QA. Copy of the same document should be produced to warehouse/ supply chain management team. They will revert to the vendor about rejection of lot/batch. Then the vendor shall be informed with rejection note through in-house procedure. Rejection of raw materials, packing materials (primary and secondary) and consumables will be done through a separate annexure. A comparison of current test results with CoA (Wheresoever applicable) will be carried out based on requirements before rejection of materials.

FULL-LENGTH INVESTIGATION (PRODUCTION)

If the root cause is not identified in phase I investigation, then phase II investigation shall be carried out. Sometimes, phase I hypothesis and phase II investigation shall be carried out parallelly on case to case basis. During the phase II investigation, production personnel should be castoff, cause and effect diagram (Ishikawa diagram) to find out the root cause. If root cause is identified in phase II investigation, then preliminary OOS results should be invalidated and phase II results shall be considered for further actions. Propose appropriate CAPA/change control. Further initiating the CAPA/change control, the OOS can be closed. Needless to wait for approval of CAPA/change control. Because as it is the mandatory change, once after initiating the QA can close the OOS. If the phase II results are also not meeting the specification criteria, then extended investigation shall be carried out by involving all cross-functional teams, QC/ Warehouse/ Production/ Engineering in investigation.

EXTENDED INVESTIGATION (QC/ WAREHOUSE/ PRODUCTION/ ENGINEERING)

If no root cause is identified in phase I or II investigation, then extended investigation shall be carried out. The QC department will propose the extended investigation plan, regarding retesting of the product/ material/ sample. Post-approval of retesting of plan by QA, further QC supervisor will allot the experienced analyst, who is equal or more competitor to analysts who performed the initial analysis. The number of retests and analyst philosophy should be as per in-house procedure. But the number of retests need to be defined. Once after the analysis, the results from the both analysis and average results of the analysis should be within the range [7]. Then initial OOS results should not be considered and extended investigation results shall be considered for the batch/ product/ samples. If none of the result or any of the result does not comply in the extended investigation, based on the same batch/ product/ samples should be rejected. Rejection of raw materials/ packing materials/ consumables should be tracked through rejection form by QC.

Further identifying the root cause in phase I/ phase II, then appropriate CAPA/ change control to be initiated. Simultaneously, the impact to be assessed by a QA on material/ product/ sample. Then closure of OOS shall be happened by enclosing the reanalysis results/ retesting results.

All annexures and its contents shall be prepared by respective organizations, as per their format and to in-line with regulatory requirements. Annexures will be issued by respective department person(s). Ideal industries will follow the procedure mentioned above. The CAPA is a tracking document. Change control is authentication document of the proposed changes. The QA will be responsible for closure of the document and retrieval of the same. No addendum procedure is intended for OOS. If any gaps identified in phase I/ phase II investigation including extended investigation, then separate deviation shall be initiated instead of amending the OOS [8]. Changes must be made in the form of amendments to data generated from computerized laboratory data acquisition systems [9]. If phase I or II investigation was not closed within prescribed timelines, extension for the same to be initiated with justification on or before the target date [6]. If phase I investigation is not completed within the timelines, extension should be provided by the QA for the same. But extended timelines should not cross the total timelines of OOS (phase II target date). Once after identifying the root cause in extended investigation, propose CAPA, invalidate the initial results and close the OOS.Trending of OOS shall be done once in 6 months with a window period of +3 months, preferably considering the financial year.

CONCLUSION

OOS described in this short communication is a basic structure which helps to bring all industries in one streamline. It helps, how to handle the OOS results, how to overcome the hurdles during testing and analysis activities. Few of the industries follow like once after completion of the phase I investigation, phase II investigation shall be carriedout and once after the phase II investigation, extended phase II investigation shall be carried out. In view of sample hold time or priority on batch release, on case to case basis QA head in accordance with user department head will decide the investigations of phase I, phase II and extended investigation can run sequentially or parallelly. Once after identifying the OOS result, phase I and II investigation shall be proceeded or phase I hypothesis and phase II investigation or Phase II extended investigation shall be carried out parallelly in view of timelines, which was not mentioned in most of the industrial procedures. In case of the procedural lacuna or human error, CAPA should be proposed to avoid occurrence in future. For all batch failures, the investigation is necessary to find out the root cause. For all types of investigations regulatory agencies required conclusion and follow up. The invalid and confirmed OOS ratio is 91.2 & 9.8% in 2017 across different pharma and biopharma industries worldwide.

CONFLICT OF INTEREST

Authors don't have a conflict of interest regarding this publication and cumulatively carried out this review work. 40% authors (Seetha Ram Kotra, PardhasaradhiMathi, Venugopala Rao Puli & Jawahar Babu Peravali) are doctorate holders (Ph.D) and remaining 60% authors (Suresh Chavvakula, Mutyala Rao Chanda, Yathish M Thimmareddy, Deva Malleswaraiah, Sandeep Pathak & Anjali Kumari Chillara) completed Masters, as per affiliation mentioned in this article.

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