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A REVIEW ON OUT-OF-SPECIFICATION (OOS) RESULTS AND CORRECTIVE ACTION AND PREVENTIVE ACTION (CAPA)

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ABSTRACT

Out-of-specification results represent a significant challenge in pharmaceutical industries, requiring through investigation to ensure product quality, regulatory compliance, and patient safety. An out-of-specification result occurs when a product or raw material test result falls outside the predefined acceptance criteria. The investigation of such results in crucial for identifying root causes, preventing recurrence, and ensuring the consistency of the manufacturing process. However, challenges such as complex root cause analysis, stringent timelines, cross-functional coordination, and maintaining data integrity makes these investigations difficult. Regulatory bodies like the food and drug administrative have established guidelines for handling out of specification results, emphasizing systematic laboratory and manufacturing process investigations. Effective out of specification management involves detailed documentation, cross-departmental collaborations, staff training, and proactive corrective actions to enhance product quality and compliance. This paper explores the critical nature of out of specification investigations and the approaches necessary to address the associated challenges in the pharmaceutical sector. Corrective action and preventive action is a system of quality practices necessary to remove the root causes of a current nonconformity to prevent the recurrence of nonconformity products, process, and other quality issues.

KEYWORDS: Out of specification, Corrective and Preventive action, Root cause analysis, Regulatory bodies, Investigation.

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-Specifications (OOS). This definition covers crucial characteristics including the substance's identification, potency, and purity. This is handled by quality assurance and quality control department. The reasons for OOS can be classified as non-assignable and assignable. Once the reason for the OOS result has been found, the summons is to close out the investigation as possible, particularly when a lab error has been recognized and the batch being tested now needs to be released. However, the reason for 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.[1]

A set of procedures known as pharmaceutical quality management system helps to ensure the quality of the final product. The degree to which a medication ingredient or product satisfies its intended use and maintains its inherent characteristics is referred to as quality in the pharmaceutical industry. This definition covers crucial characteristics including the substance's identification potency, and purity. A pharmaceutical quality management system (QMS) develops and ensures quality procedures at various stages of the product's life cycle, such as manufacturing and product testing. QMS system are usually repeatable and measurable and based on continuous improvement. Quality unit (QU) plays a critical role in ensuring the identity, strength, quality, purity, and stability of drugs and biological products. The QMS begins with understanding our customer's needs, identifying the subsystem for the project delivery process, and ends with a successful project that satisfies our customers. It encompasses all critical phases of drug manufacturing, including formulation, method development, facilities, supply system and equipment. It ensures that the manufacturer obligate to comply with. It uses monitoring methods such as quality assurance to prevent quality deviations and emphasizes quality system

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documentation to record any problems and their solution.[2,3]

CAPA is a fundamental management tool that should be used in every quality system. This program provides a simple step by step process for completing and documenting corrective or preventive actions. The result will be a complete, well documented investigation and solution that will satisfy regulatory requirements and from the basis for an effective continuous improvement plan for any company. Properly documented actions provide important historical data for a continuous quality improvement plan and are essential for any product that must meet regulatory requirements demanded by FDA and ISO and other quality systems.[4]

OOS (OUT-OF-SPECIFICATION) INVESTIGATION

Pharmaceutical firms utilize the out-of-spec inquiry process when a medication does not adhere to the manufacturer's specifications. It can be the result of improper manufacturing or mislabeling of the drugs. The main goals of the investigation are to determine the root cause of an existing or potential problem.[5,6]

Phase Ⅰ investigation (Laboratory investigation): The Quality control department is involved in the laboratory investigation, which also involves rechecking documents with the same analyst and re-testing with different analysts with the original sample.

❖ **Phase Ⅰa investigations (Primary investigation):** During this stage of the investigation, errors that are obviously made, such as calculations or power failures, as well as fault made during testing, such as spills or errors in setting of equipment parameter. Checklist to recognize the obvious laboratory errors.

➢ Qualification and training for the targeted task of analysts.
➢ The performance or calibration of an instrument.
➢ Prepare the dilutions and test solutions.
➢ Reagent and standard validity.
➢ Performance of system suitability.
➢ Correctness of calculation etc.

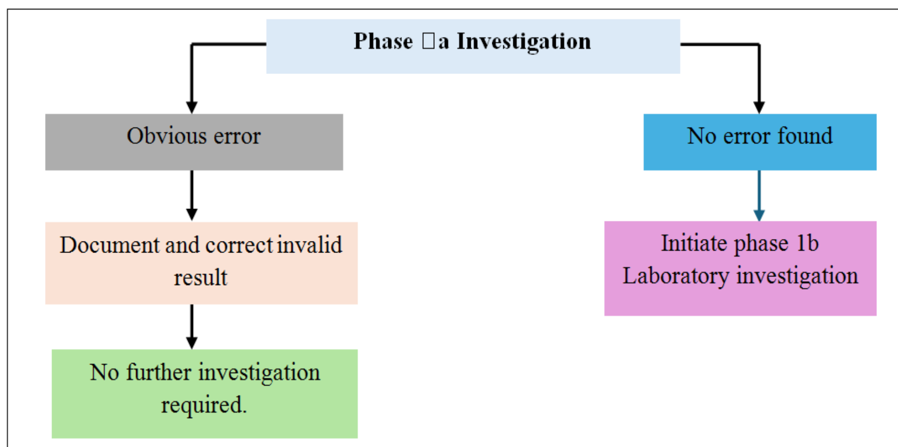

Figure 1: Phase Ia Investigation.

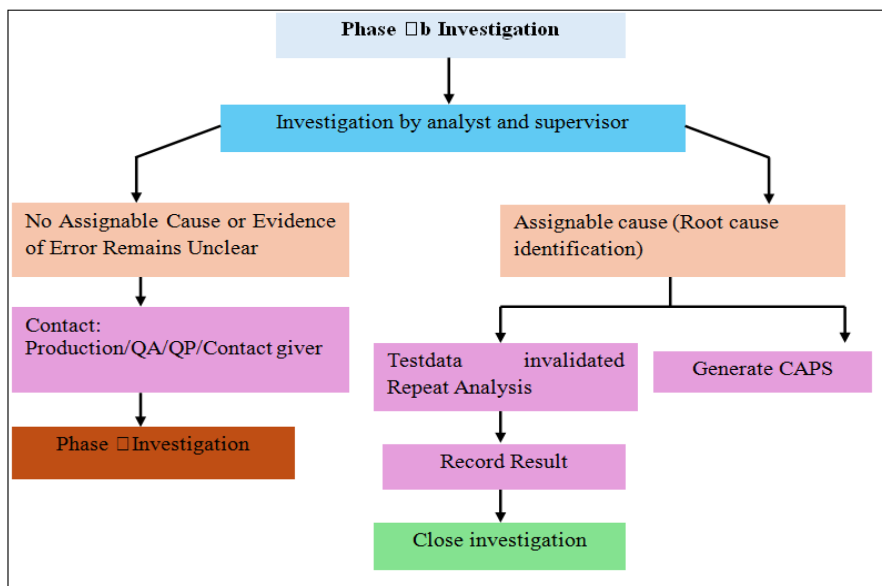

Figure 2: Phase Ib Investigation.

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- **Phase Ⅰb Investigations (sometimes referred as extended lab investigations):** Are preliminary investigations carried out by the analyst supervisor using the laboratory investigation checklist covering the pertinent areas for investigation. On completion of the analyst and supervisor investigation, re-measurement can start once the hypothesis plan is documented and is only to support the investigation testing.[6]

Phase Ⅱ Investigation (Full-scale investigation): When the initial assessment does not find that laboratory error caused the OOS result and testing findings seems to be correct, a full-scale OOS investigation approaches is carried out. Identify the root cause of the OOS outcome and taking the proper corrective and preventive action are usually the objectives of such an investigation. A full-scale investigation includes a review of production and sampling procedures and additional laboratory testing.

PHASE Ⅱ IVESTIGATION INVOLVES

Review of Production: Another departments that might be affected in this investigation undertaken by the QU are also included, including manufacturing, process development, maintenance, and engineering. If manufacturing occurs off site, the investigation should cover all sites that could be involved. The manufacturing process records and documents should review in detail to identify the possible cause of the OOS results. A quick, accurate, and well-reported assessment should be a part of a comprehensive OOS investigation.

Additional Laboratory Testing: In addition to the testing done in phase Ⅰ, a full-scale OOS investigation may involve additional laboratory testing.

Re-testing: A portion of the investigation may involve retesting the original sample. The sample that used for the retesting was taken from the same homogenous material.

Re-sampling: While retesting refers as analysis of the original, homogenous sample material, re-sampling involves analysing a specimen from any additional units collected as part of the sampling procedure or from a new sample collected from the batch, should that be required.

Reporting Test Results: Averaging and outliner tests are two techniques for reporting and interpreting tests results.

Averaging: When conducting initial testing and OOS inquiry, there are both appropriate and inappropriate reasons used for averaging test data.

Appropriate uses: Averaging data may be an effective technique, but it depends on the sample and the purpose of the analysis.

Inappropriate applications: The drawback of relying on average is that it hides the variations of individual outcomes from tests. For this reason, all individual test results should report as separate values.

Outliners tests: A statistical technique for identifying extreme data in a collection.[5,7,8]

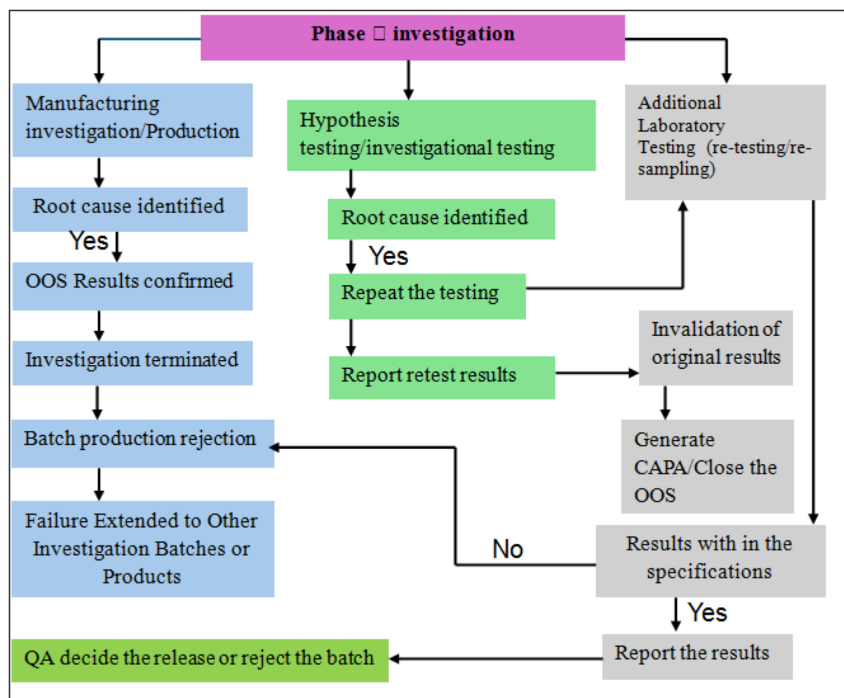

Figure 3: Phase II investigation.

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Phase Ⅲ Investigations: The phase Ⅲ inquiry shall examine the completed production inquiry and joint laboratory investigations into the questionable analytical data, including approved method validations for the possible causes of the results obtained. Once a batch is rejected, there are no restrictions on additional testing to identify the root cause of failure and take corrective action.[5,6,9]

DEVELOPMENT OF CORRECTIVE AND PREVENTIVE ACTION (CAPA)PROGRAM

Corrective action and preventive action is a system of quality practices necessary to remove the root causes of a current nonconformity to prevent the recurrence of nonconformity products, process, and other quality issues.

"CAPA is generally defined by Correction. The CAPA system is an important QMS in the pharmaceutical industry and is a critical tool to achieve sustainable compliance through continuous improvement."[8]

The four key CAPA definitions are

CAPA (Corrective and Preventive Actions): A systematic approach that includes actions needed to correct (correction), avoid recurrence (corrective action) and eliminate the cause of potential nonconforming product and other quality problems (preventive action).

Correction: Action to eliminate a detected nonconformity. Corrections typically are one-time fixes. A correction is an immediate solution such as repair or rework. Corrections are also known as remedial or containment action.

Corrective action: action to eliminate the causes of a detected nonconformity or other undesirable situation. The corrective action should eliminate the recurrence of the issues.

Preventive action: Action to eliminate the cause of a potential nonconformity or other undesirable potential situation. Preventive action should prevent the occurrence of the potential issues.[10,11.12]

Objective of CAPA Implementation

- Verification of a CAPA system procedure(s) that satisfies the standards of the quality system regulation is one of the goals of CAPA implementation. It has to be described and recorded.
- Proof that the correct sources of product and quality issues have been found.
- Identification of negative trends that has tracked.
- Verify that correct statistical process (SPC) techniques are applied to identify recurring quality issues.
- Verify that the RCA work done and comply with the level of risk that issue are recognized.
- Actions tackle the root cause and offer options for prevention.
- Prior to implementation, CAPA process activates are effective and confirmed or validation.[8]

Benefits of Un-unified CAPA System

1. Financial

- Influence technologies.
- Opportunities for prevention.
- Simplification through elimination of manual steps.
- Lowers cost through centralized function.

2. Consistency

- Uniform processing.
- Common language.

3. Compliance

- Readily retrievable information.
- Faster proactive analysis.
- Connects the dots to identify systemic issues.
- Visibility for cross-site issues (e.g., inspections and supplier problems).

4. Management Control

- Early alert system that facilitates prevention.
- Instantaneous, real-time view of company-wide issues.
- Improved communication and teamwork.
- Facilitates integrated trending for large volume of data.
- Linkage among sites for products that are sold as a system.[13]

Common CAPA Violations

- No established procedures for implementing.
- CAPA no true root-cause analysis, failure investigations inadequate.
- Complaint handling too specific, do not look at overall system.
- Failure to document CAPA action.
- No validation.
- Failure to designate and document executive responsibilities.
- Infrequent quality audits.
- Inadequate procedures for quality audits.
- Inadequate procedures for documenting CAPA.[14,15]

When is CAPA Relevant?

Currently, there are five different types of information sources that can trigger a CAPA.

- Complaints from customers, either direct or indirect users (consumers).
- Process deviations as a result of a manufacturing inconsistency or production failure, or an engineering non-conformity, which causes the defect relative to the production deviation, non-conformance or out-of-specification that may occur.
- Laboratory investigation or analysis.
- Grassroots efforts by employees, e.g., an engineer who notices an oil spill and organizes a corrective action.[16]

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CAPA PROCEDURES

Implementing an corrective or preventive action capable of satisfying quality assurance and regulatory documentation requirements is accomplished in six basic steps:

1. Identification

The initial step in the process is to clearly define the problem. It is important to accurately and completely describe the situation as it exists now. This should include the source of the information, a detailed explanation of the problem, the available evidence that a problem exists.

2. Evaluation

The situation that has been described and documented in the "identification" section should now be evaluated to determine first, the need for action and then the level of action required. The potential impact of the problem and the actual risks to the company and/or customers must be determine. Essentially, the reasons that this problem is a concern must be documented.

3. Investigation

In this step of the process a procedure is written for conducting an investigation into the problem. A written plan helps assure that the investigation is complete and nothing is missed. The procedure should include: an objective for the actions that will be taken. The procedure to be followed, the personnel that will be responsible, and any other anticipated resources needed.

4. Analysis

The investigation procedure that was created is now used to investigate the cause of the problem. The g0al of this analysis is primarily to determine the root cause of the problem described, but any contributing causes are also identified. This process involves collecting relevant data, investigating all possible causes, and using the information available to determine the cause of the problem. It is very important to distinguish between the observed symptoms of a problem and the fundamental (root) cause of the problem.

5. Action plan

By using the results from the analysis, the optimum method for correcting the situation (or preventing a future occurrence) is determined and an action plan developed. The plan should include, as appropriate: the items to be completed, document changes, any process, procedures, or system changes required, employee training, and any monitors or controls necessary to prevent the problem or a recurrence of the problem. The action plan should also identify the person or persons responsible for completing each task.

6. Follow up

One of the most fundamental steps in the CAPA process is an evaluation of the actions that were taken. Several key questions must be answered:

- Have all of the objectives of this CAPA been met? (Did the actions correct or prevent the problem and are there assurances that the same situation will not happen again)
- Have all recommended changes been completed and verified?
- Has appropriate communications and training been implemented to assure that all relevant employed understand the situation and the changes that have been made?
- Is there any chance that the actions taken may have had any additional adverse effect on the product or service?[17]

Challenges of implementing CAPA

Historically, most organizations have relied upon the wisdom and experience of their internal experts to identify root causes. Experts attempt to solve all problems using their experience of tried and true past solutions. The main pitfall of this strategy, however, is that their solution is completely dependent upon and limited by their expertise. If the root cause happens to lie outside the scope of their expertise levels, they are not likely to find it. Therefore, they must design a series of closely monitored experiments to test their hypotheses and to determine if they are on the right track in locating the root cause. The problem with designing and implementing these experiments is that they are invasive requiring personnel, equipment, laboratory resources, down time and funding. If the experiment is a failure, the internal experts must repeat the same costly process again: brainstorming another portable cause and conducting yet another experiment. This process can be time-consuming and lower the morale of those involve.

The companies are discovering that deductive reasoning and comparative analysis are faster, easier and more cost-effective ways to identify root cause and implement a corrective action. Several proprietary programs use deductive reasoning and comparative analysis. The primary focus of such processes is improving a diagnostic technique through better data collection. Data is collected using a observed and comparative questioning technique. A unique and simple tool is used to synthesize the collected data into information that tells the root cause story.[18]

CONCLUSION

Investigating out of specification (OOS) is a critical process in ensuring product quality, compliance with regulatory requirements and maintaining the integrity of pharmaceutical and manufacturing operations. A thorough and systematic approach to OOS investigations is essential to identify the root cause, implement corrective and preventive actions, and ensure the continued safety and efficacy of the products. Successful OOS investigations require collaboration between various departments, strict adherence to well-documented procedures, and the use of root cause analysis tool to avoid premature conclusions. Moreover, it is essential to differentiate between laboratory errors

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and manufacturing-related issues to avoid costly rejections or unnecessary re-testing. Accurate documentation not only serves as evidence for regulatory bodies but also facilitates internal learning, process improvements, and trend analysis to prevent future occurrences. CAPA ensure it`s easy to record the corrective action request, undertake root cause analysis and take action, identification and assessment recognizing issues and evaluating risk, checking effectiveness and closing CAPAs. The statement describe what happened, when it occurred, how often it occurred, and under what condition. The result will be a complete, well documented investigation and solution that will satisfy regulatory requirements and form the basis for an effective continuous improvement plan for any company.

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