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Ensuring Quality in Pharma: Exploring Pharmaceutical Deviations and Out-of-Specifications, Streamlining CAPA Processes for Compliance and Quality

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This review provide an overview of the various documentation of quality management system, which includes deviations, OOS and CAPA. A detailed case study of deviations, out-of-Specification and CAPA generation is beneficial for improving pharmaceutical capabilities and understanding the documentation associated with a quality management system. It is essential for understanding deviations and out-of-spec in the pharmaceutical industry. The quality of medicines means that they meet the required specifications. The quality management system in the pharmaceutical industry is essential because the drugs or pharmaceutical products are delivered directly to the customer's body. Therefore, identity, purity, safety, and the quality of the products are critical. A Deviation can define as "a deviation from an approved instruction or established standard" The deviation process helps identify potential risks to product quality and patient safety and establish the root cause. Once the root cause identifies, appropriate corrective and preventive actions take to prevent reoccurrence. OOS defines as "A result that is outside the specifications or acceptance criteria established by the manufacturer or laboratory" As the industry moves to newer and more complicated products, quality control procedures must be in place to ensure consistent product quality. "CAPA defined by corrections.

Keywords: Deviation; Out-Of-Specification (OOS); Corrective and Preventive Action (CAPA).

1. Introduction

A set of procedures known as a pharmaceutical quality management system helps 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 systems 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 subsystems 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 final product meets the customer's requirements and the regulatory requirements that the manufacturer obligate to comply with. It uses monitoring methods such as quality assurance to prevent quality deviations and emphasizes quality system documentation to record any problems and their solutions.[1,3]

Fig.1 QMS System

DEVIATION

A deviation is a surprise event that takes place during ongoing operations, activity, records, inputs, manufacturing, analysis, distribution of drugs, raw materials, and packing materials. Deviations reported as soon as they occur and must be investigated to assess the impact. A deviation is defined as a "Departure from an approved instruction or established standard" according to ICH Q7 Good Manufacturing Practice for Active Pharmaceutical Ingredients. Deviations are measure differences between the observed value and the expected value for a process or product condition or a departure from an approved procedure or established standard or specification. Deviations occur almost daily in the pharmaceutical industry. Dealing with deviations and minimizing their reoccurrence are very critical considerations in the pharmaceutical industry's quality management system of the pharmaceutical industry. A deviation could arise during manufacturing, testing and sampling of final goods and raw materials. This article introduces the process of deviation management involves, how to effectively collect and analyze data and identify improvement actions related to deviations. [4]

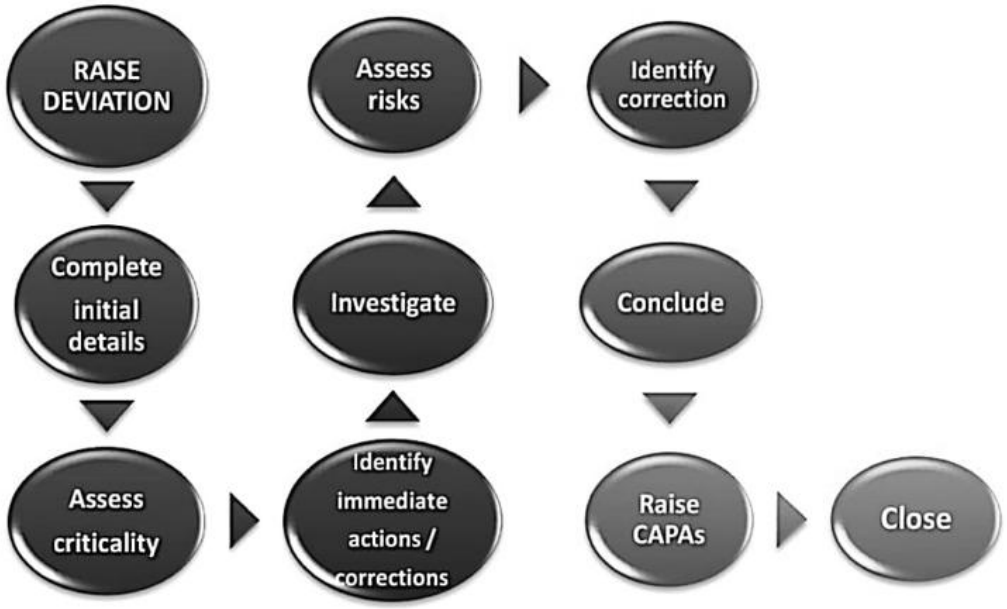

Fig.2 Key Process for Deviation

Types of deviation

1. Planned deviations:

Detailed and pre-approved from the current operating document or system that cover a certain time frame or number of batches. A planned deviations approved before its execution.

A Planned deviation designed in a way that does not impair the safety and efficacy of the product. Examples of planned deviation in the pharmaceutical industry:

- Change in batch size brought on by decreased raw material availability.
- Change in batch size for a certain number of batches.
- Change in the excipients supplier.

2. Unplanned deviation:

The event is another name for the unexpected deviation. It refers to an unplanned or uncontrolled incident that occurs when planned systems or procedures are deviated from during any stage of the production, packing, testing, storage, or holding of a drug product as a result of a system failure, an equipment malfunction, or a human error.

- Accident brought on by human error

- Interruption of supply services.

There are four deviation classification categories including:

1. Critical: A deviation that could have a significant impact on product quality or the GMP system, these are some examples of critical deviation but not limited

A product's cross-contamination or product mix-up.

- Skipping a step in the production process.
- Apply obsolete batch instructions or test procedures.

2. Major: Deviations that may have a moderate to significant impact on the GMP system or the product quality. These are some examples of substantial variations, but they are not entirely complete:

- Equipment failure during processing
- Combinations of cartons of the same product in various strengths.

3. Minor: Deviations are usually unlikely to have a measurable effect on the GMP system or product quality. These are some examples but not all included:

- Minor errors in documents that don't compromise the data integrity.
- Material spillage during dispensing.

4. Incident: Incidents are variations that don't directly impact the products' quality. But they are against cGMP.

- Spilled material in the clean room
- Unauthorized personnel in the production area.[4,5]

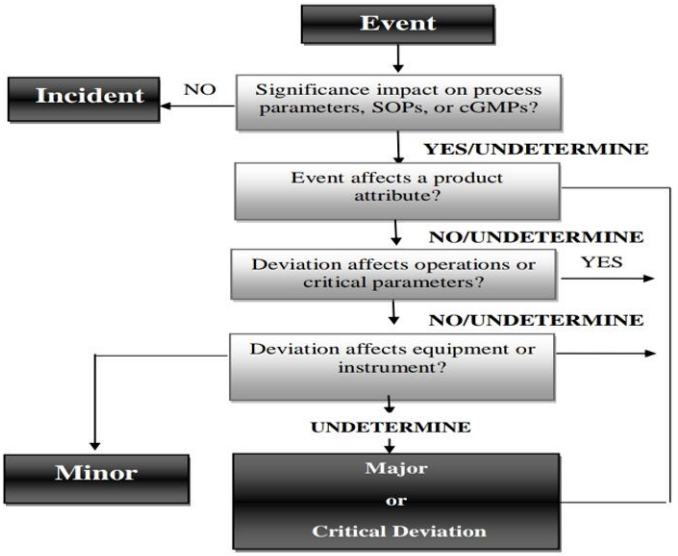

Fig. 3 Deviation classification process

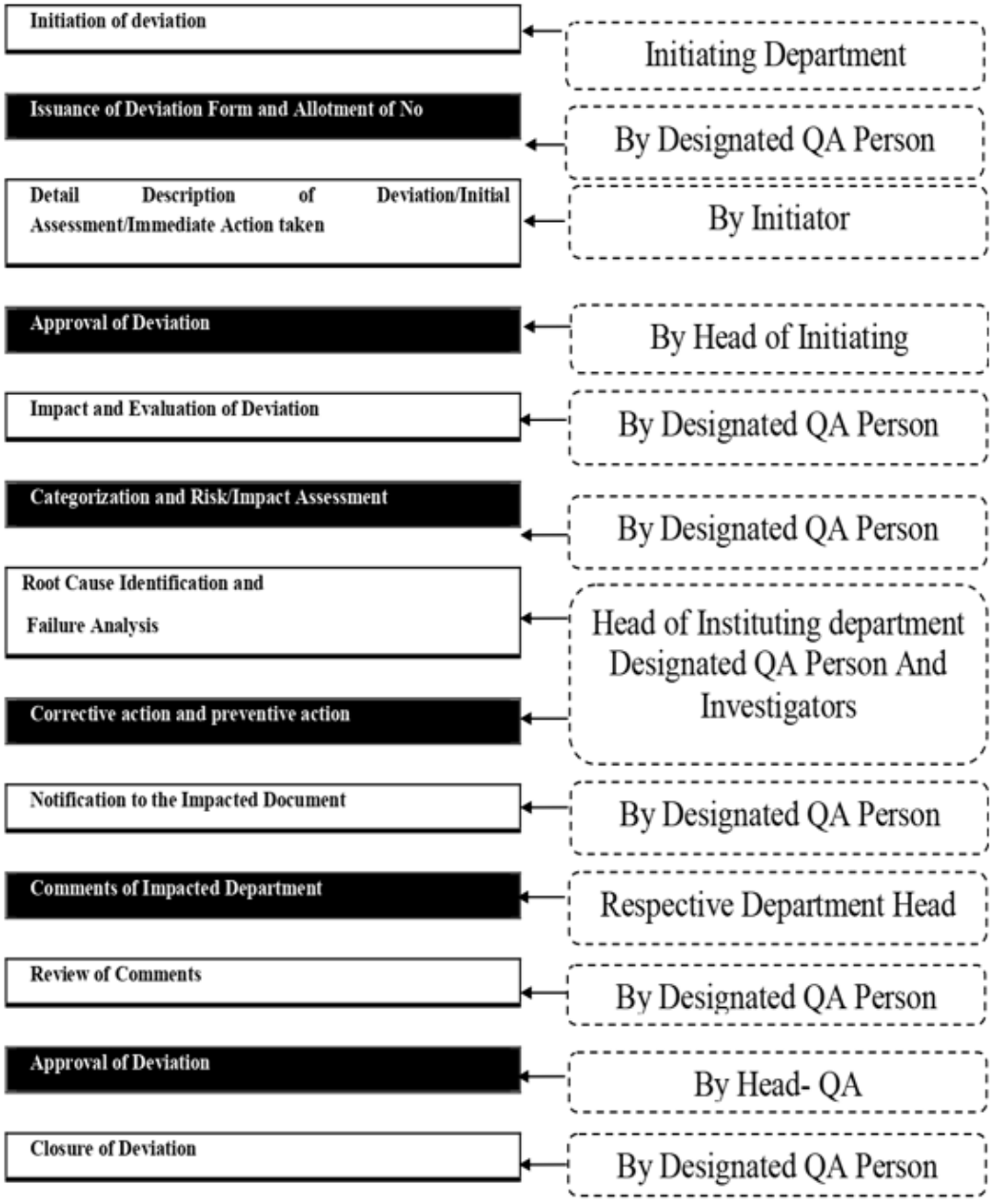

Fig. 4 Flow chart for deviation handling

OUT OF SPECIFICATION

A result that deviates from the preset specifications or established acceptance criteria established by the manufacturer or the laboratory referred to as OOS. Simply, the outcome of a stability test performed by a Quality Analyst (QA) must always correspond to the standards or criteria that were previously defined. If the test result does not meet the specified test result

requirements, the Quality Control (QC) declares the result to be OOS. The analytical result(s) of a batch or material is falling outside of the established specifications ranges called as Out of Specification. All unclear test outcomes that deviate from the established Specification are referred to as OOS test results. All outcomes of tests that don't meet the requirements or standards outlined in drug applications, drug master files, or by the manufacturer are considered OOS results.

Two Major Issues: There are two issues that is important for any OOS, including

What observed results? What specifications?

An out of specification investigation is a process that pharmaceutical companies use when a drug does not meet the specification set by the manufacturer. This can be because the drug was made incorrectly or there was an error in the labeling.[7,8]

Causes of OOS:

Two categories can be used to separate the potential causes of the out of specification. The first is an analysis error, where the product has no error but has a problem in the analysis, and the second is a manufacturing defect of the product, where the analysis is correct however the product actually has a problem. The following are possible reasons why the results did not meet expectations.

1. Test analysis errors in the QC lab: when examining the OOS, this should be investigated first as it is the most likely reason. There are numerous places where errors can happen. There may be a mistake in handling the sample or standard during product analysis. There may be a weighing or dilution problem with the material. In addition, chromatography, titration and even calculations are subject to error.

2. Laboratory equipment malfunction: due to this problem, analysis is also unaware of the occurrence of this error. Equipment or instruments not calibrated on time for their due date can display incorrect results and show product results deviate from the limits.

3. Production Equipment Malfunctioning: the malfunctioning of production equipment causes the actual defect in the manufactured product. Manufacturing equipment malfunction that leads to the production of a defective product is generally observed by out-of-specification.[9,10]

OOS investigation:

Pharmaceutical firms utilize the out-of-spec inquiry process when a medicine 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.

For establishing how to handle OOS products, materials, and batches, several guidelines available:

A. MHRA guideline for OOS

B. CDER guideline for OOS

A. MHRA guidelines

MHRA is Medicines and Healthcare products Regulatory Agency. This organization based in the UK. This organization is in charge of conducting MHRA audits globally. In August 2013, the MHRA released the first industry guidelines on how to perform Out Of Specification (OOS) investigations.[11,12]

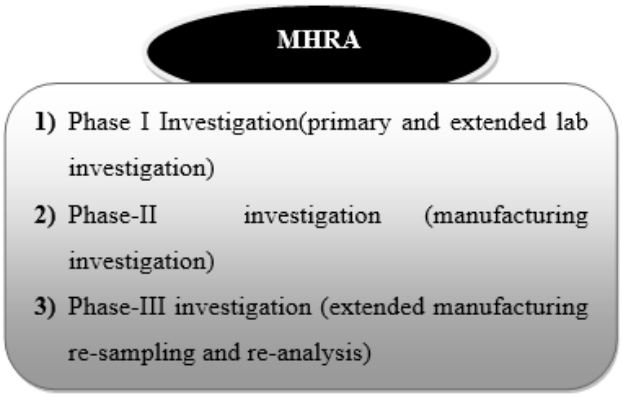

Fig. 5 Investigation as per MHRA guideline

1) 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.

a) 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 faults made during testing, such as spills or errors in setting of equipment parameter. checklist to recognize the obvious laboratory error.

- 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 and etc

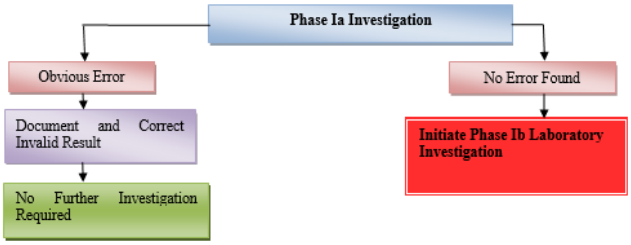

Fig. 6 Phase Ia Investigation

b) Phase Ib investigations (sometimes referred to as extended lab investigations) are preliminary investigations carried out by the analyst and 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.[12]

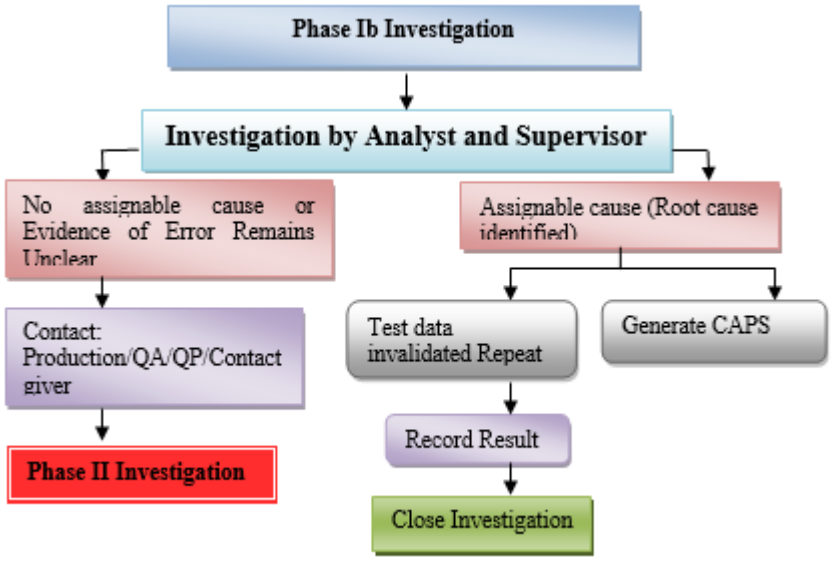

Fig. 7 Phase Ib Investigation

2) Phase-II Investigation: when phase I investigations fail to identify an identifiable laboratory error, phase II investigations are conducted. Written and accepted instructions against the hypothesis guide in phase II investigation. Phase II investigation, includes information about re-sampling, retesting, and averaging.

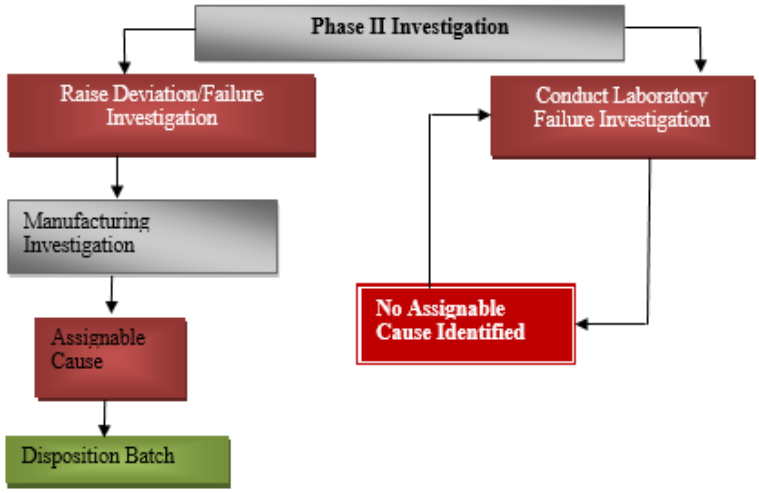

Fig. 8(A) Phase II Investigation

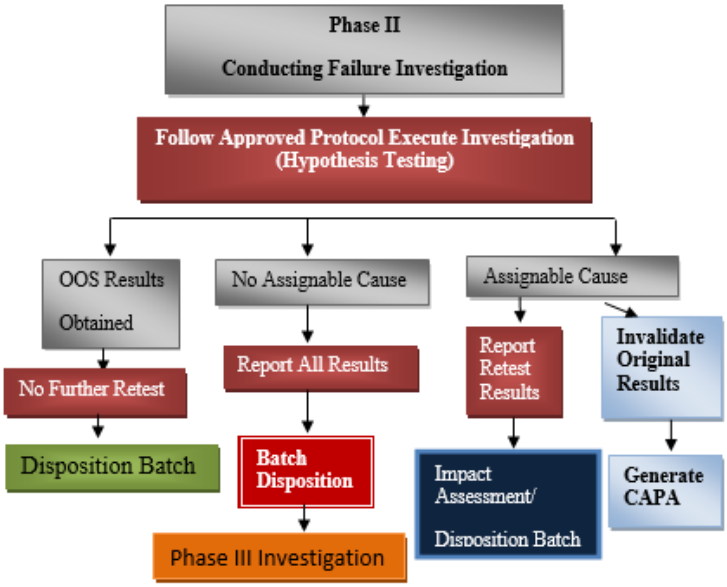

Fig. 8(b) Phase II Investigation

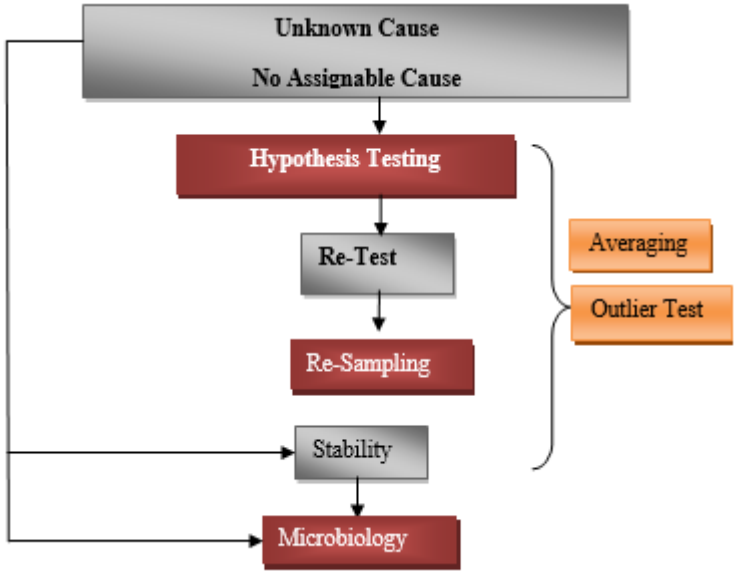

Fig. 8(c). Phase II Investigation

3. 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.[11,12,13]

A. CDER guideline

The Center for Drug Evaluation and Research (CDER) ensure that safe and efficient pharmaceuticals are available to improve people's health in the United States. To analyze out-of-spec test findings, the FDA issued guidelines for "Investigating Out-of-Specification (OOS) test results for pharmaceutical production" in 2006. Guidelines for Out-of-Specification modified in May 2022. The May 2022 revision includes a few minor editing and content changes. The standard also provides further information on averaging findings from the same final sample preparation and clarifies concepts related to outlier results. The term "quality unit" is used instead of "quality control unit." [14]

Fig. 9 Investigation as per CDER guideline

1) Phase I Investigation (Initial Laboratory Investigation): A investigation should be complete, quick, objective, well-documented, and scientifically sound. An initial evaluation of the accuracy of the laboratory's data should be a part of the investigation's initial phase. Whenever possible, it has done before test preparations are discarded. In this manner, the same test preparations can utilize to test hypotheses relating to laboratory error or instrument malfunction. A full-scale OOS investigation should carry out if this preliminary evaluation indicates no defect that could have caused the data to be incorrect.

- Re-injection of the same solution to rule out any instrument malfunction-related errors.
- Re-dilution or re-pipetting of the same solution to rule out dilution or pipetting errors

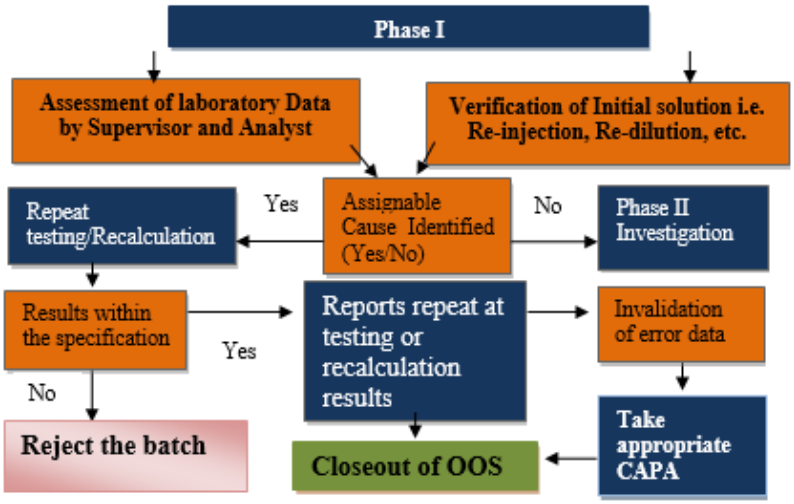

Fig.10. Phase I Investigation

2) Phase II Investigation (Full-scale investigation): When the initial assessment does not find that laboratory error caused the OOS result and the testing findings seem 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 preventative 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 Investigation involves:-

a) Review of Production

b) Additional Laboratory Testing

i. Re-Testing

ii. Re-Sampling

c) Reporting Testing Results

i. Averaging

ii. Outlier Testing

a) Review of Production: All other 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 reviewed in detail to identify the possible causes of the OOS results. A quick, accurate, and well-reported assessment should be a part of a comprehensive OOS investigation.

The following details include in the reviewer's written record.

- A clear justification for the study.
- A list of the variables of the manufacturing procedure that potentially caused the problem.
- The conclusions of the documentation review, including assessment of the actual or probable cause.
- To find out the outcomes of a review if the issue has occurred previously.

b) Additional Laboratory Testing: In addition to the testing done in Phase I, a full-scale OOS investigation may involve additional laboratory testing. These include (i) re-sampling and (ii) retesting a portion of the original sample.

i. Retesting: a portion of the investigation may involve retesting the original sample. The sample that used for the retesting was taken from the same homogeneous material.

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

c) Reporting test results: Averaging and outlier tests are two techniques for reporting and

interpreting test results.

i. Averaging: When conducting initial testing and an 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

iii. outliers tests: A statistical technique for identifying extreme data in a collection.[11,14,1

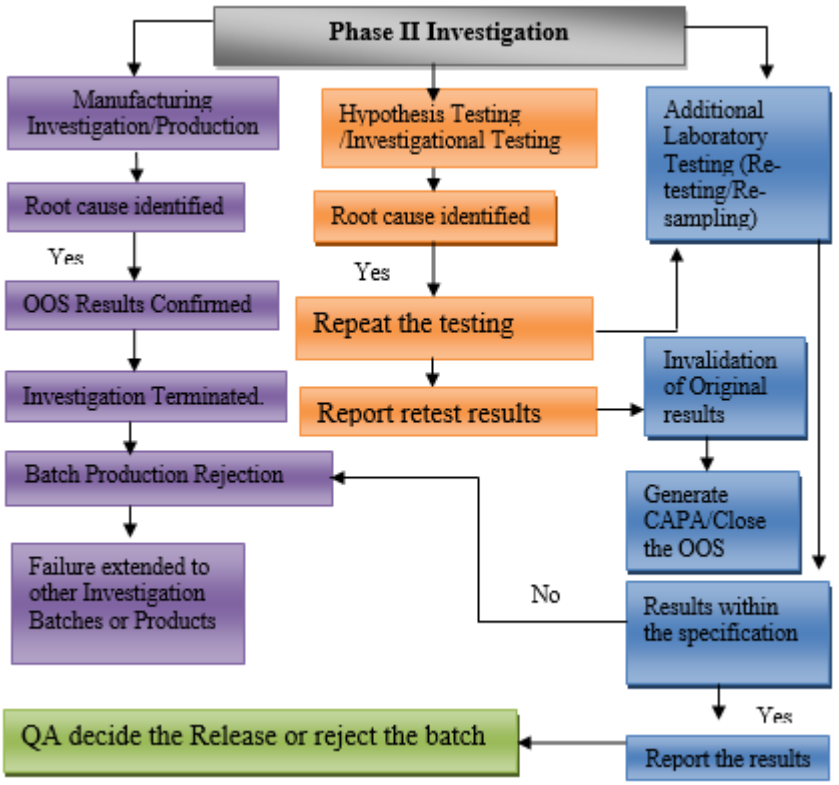

Fig. 11 Phase II Investigation (Full scale Investigation)

A typical OOS investigation process covers the following:

Fig.12 Investigation Process

Tools for OOS investigation & Related corrective and preventive action:

A. 6M Method for Cause and Effect Analysis:

Table 1. 6M Method

"M"	Description	Insights
Manpower	The operational and/or functional labor of people engaged in delivery a product and/or service.	This is an exceedingly rare "cause". Lean posits that "all labor is righteous labor". If "manpower" is identified as a cause resulting in an undesirable effect, it's more likely to be a factor of another of the 6M.
Method	Production processes and their applicable/contributing service delivery processes.	There are frequently processes found to have too many steps, too many signoffs, and integral activities that don't create value and for which a customer wouldn't pay known to be included.
Machine	systems, tools, and facilities used in production	Machines, tools and facilities with their underlying support systems are frequently mismanaged to achieve excellence or, due to technical misalignment, are simply incapable of delivering the intended output.
Material	Raw materials, components and consumables used to satisfy production and/or service delivery.	Materials, components, and consumables are frequently miss specified, mislabeled, improperly kept to preserve physical qualities, outdated, or in any other way that may be better organized and handled..
Measurement	Inspection and other physical measurements (distance, volume, temperature, pressure)	Sometimes, measurement" can be inconsistent or incapable.

B. Root Cause Analysis (RCA): RCA is the process of finding out the root causes of issues to find the best options for resolution

Fig. 13 Root Cause Analysis Process

CORRECTIVE AND PREVENTIVE ACTION (CAPA)

Corrective action and preventative action (CAPA): corrective action and preventative action is a system of quality practices necessary to remove the root causes of a current nonconformity to prevent the recurrence of nonconforming products, processes, 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."

CA involves finding the causes of some specific problem and then putting in place the necessary actions to avoid a reoccurrence. PA for preventing the occurrence of potential problems.

CAPA DEFINITIONS: corrective and preventive action is segregated between three different subjects:

A. Correction or remedial action

B. CA

C. PA.

A. CORRECTION

In the first instance, correction or remedial action focuses on the immediate situation to eliminate an existing non-conformance or undesirable situation. It is important to note that those actions that focus on the immediate situation do not tackle the root cause but "fix" the problem temporarily.

B. CA

The CA is a reaction to a non-conformity or undesirable situation that has already happened. It assumes that a non-conformance or problem exists and has reported by either internal or external sources. The actions initiated are intended to prevent the recurrence, which include the following steps

- Correct the problem

Modify the quality system so that the process that caused it is monitored to prevent the recurrence.

The CA's documentation ensure that issue was identified, corrected, and installed with the appropriate controls.

C. PA

The PA is a proactive approach and process for detecting non-conformances or undesirable situations that have not yet happened and prevents them before occurring.

- The process include,
- Identify potential problems or non-conformances
- Find the cause of the potential problem/non-conformance
- Develop a plan to prevent the occurrence
- Implement the plan
- Review the actions taken and the effectiveness in preventing the problem.

Why Use CAPA (Corrective Action Preventive Action)?

A fundamental principle of any efficient QMS is locating the primary source of failure. When a problem arises, it is frequently merely a sign of the bigger problem. FDA standards outlining Good Manufacturing Practice (GMP) break off if a corrective action preventive action method is not in place. When fully operational, the CAPA system must fulfill requirements to comply with FDA 21 CFR 820.100

Objectives 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 the correct statistical process control (SPC) techniques are applied to identify recurring quality issues.
- Verify that the RCA work done and comply with the level of risk that the issue are recognized.
- Actions tackle the root cause and offer options for prevention.
- Prior to implementation, CAPA process activities are effective and confirmed or validated.[15]

2. MATERIAL AND METHOD

1. MATERIAL Numerous relevant documents, both internal and external, were used. Internal documents include standard operating procedures [SOPs], batch records, standard testing procedures (STPs), certificates of analysis (COAs), calibration records of related instruments, analytical data of related case studies for OOS, deviation, and so on, while external documents include book references, peer-reviewed journals, supplier reports, published papers (review and research papers), and more. In addition, certain standard design guidelines were followed.

2. METHOD To begin work on this project, firstly visited the pharmaceutical industry and reviewed the standard operating procedures and standard guidelines OOS. After that, observed the activities related to the QC department. The challenges that arise during the manufacturing of dosage forms were examined. In addition, reviewed the documentation relevant to the project. Furthermore, a number of case studies involving deviations and out-of-specifications were evaluated. In conclusion, a draft report was prepared for the project.

3. RESULTS:

CASE STUDY 01:

Case Study on Out of Specification (OOS)

During result reporting of dissolution test of aspirin tablets, result found out of specification limit.

1. Detail of OOS: On dated 17/08/2023, In Quality Control department, Stability Section, During analysis of dissolution test for Aspirin tablets, stability condition 25◦C/60%RH 24 month, dissolution result for batch no. :- A23AP022/ST0350823, did not meet's the acceptance criteria. OOS results are below.

Table 2: OOS results of dissolution test

Unit	Unit 1	Unit 2	Unit 3	Unit 4	Unit 5	Unit 6	Min.	Max.	Avg.	Limit
Observed Value	50%	51%	51%	52%	52%	55%	50%	55%	52%	**NLT 80%(Q) in 30 min.**

2. Immediate Action Taken: The sequence was reviewed and found the sequence was created according to the standard testing procedure. The Instrument method was reviewed and found the instrument method was created according to the standard testing procedure. Verified the alliance log message center and found satisfactory Result calculated and OOS has been initiated.

3. Investigation:

Aspirin Tablets samples for analysis were received in the quality control department Sample management team has allocated A.R. No. and hand over to section supervisor for analysis. As per specification following test parameter were applicable for stability samples. Dissolution test of four batches for Aspirin Tablets were planned on dated 16/08/2023.

Dissolution apparatus instrument ID: QCD-590 &QCD-591 and QCD-332 were used for analysis. Instrument QCD-590 8591 is the 8 vessel test apparatus and QCD-332 is 14 vessel apparatus. Analysis for A.R. ST0250823 was planned on Inst ID: QCD-591 and ST0350823 was planned on Inst ID:QCD-590. However analysis for A R No-ST0290823 and ST0300823 was planned on apparatus QCD-332. The analysis was performed on HPLC system QCD-184. Data was processed on dated 17/08/2023 and after data processing, during result capturing it is observed that out of four batches in one batch (AR. No. ST0350823), dissolution result found out of specification limit in all six unit. However results for batch ST0250823 was found atypical and results for rest of batches were found satisfactory and similar of past station. To find out the root cause and impact assessment investigation has been performed as follow:

3.1 Phase-IA Investigation:

Phase-IA investigation started on dated 18/08/2023 Investigation was performed as per OOS checklist (calculation error, power failure, Instrument failure, testing error and incorrect instrument parameter used), and investigation did not reveal any obvious error Hence further proceed phase- IB investigation.

3.2 Phase-IB: Laboratory Investigation:

Phase-IB Investigation started on dated 18/08/2023.

Laboratory investigation performed as per OOS checklist and no reveal any Laboratory error Further Go and See and Analyst Interview assessment done.

During discussion with analyst it is noticed that analyst has weight the tablets in continuation for batches ST0250823, strength-25mg and ST0350823, strength having 50mg and place in single tray which is sufficient for 20 Tablets.

Error might happening during dropping the tablets into dissolution apparatus. 25mg tablets drop in 50mg and vice-versa.

Thereafter At the time of calculation 25mg strength calculated through label claim 50 mg and 50mg strength calculated through 25mg that's why 50mg strength batch showing results approx 50% and 25mg strength showing results approx 200%.

Based on area response re-calculate the results and observed value are as follow:-

Table 3: Results of Re-calculation

Unit No.	**AR. No. ST0350823**		**AR. No. ST0250823**	
	Initial Result	Re-calculated	Initial Result	Re-calculated
Unit 1	50%	100%	196%	98%
Unit 2	51%	102%	194%	97%
Unit 3	51%	102%	200%	100%
Unit 4	52%	104%	194%	97%
Unit 5	52%	104%	206%	103%
Unit 6	55%	110%	202%	101%
Min.	50%	100%	194%	97%
Max.	55%	110%	206%	103%
Avg.	52%	104%	199%	100%
Specification Limit :- NLT 80% (Q) in 30 min.				

Re-calculated results are with in specification limit and indicate laboratory error at the time of analysis.

4. CAPA:

4.1. Corrective Action:

- Initial analysis invalidated
- Retest Results considered as final reporting.

4.2. Preventive Action:

Training imparted to concern person as precautions to be taken during analysis of dissolution

test.

5. RESULTS AND CONCLUSION:

5.1. Ishikawa Diagram (Fishbone Diagram)

To find out the root cause and impact assessment Ishikawa Diagram has been used as a Investigation tool. Upon identifying the issue, reviewed the breakdown results that were within the prescribed limits. Additionally, proposed corrective and preventive actions to avoid such errors in the future.

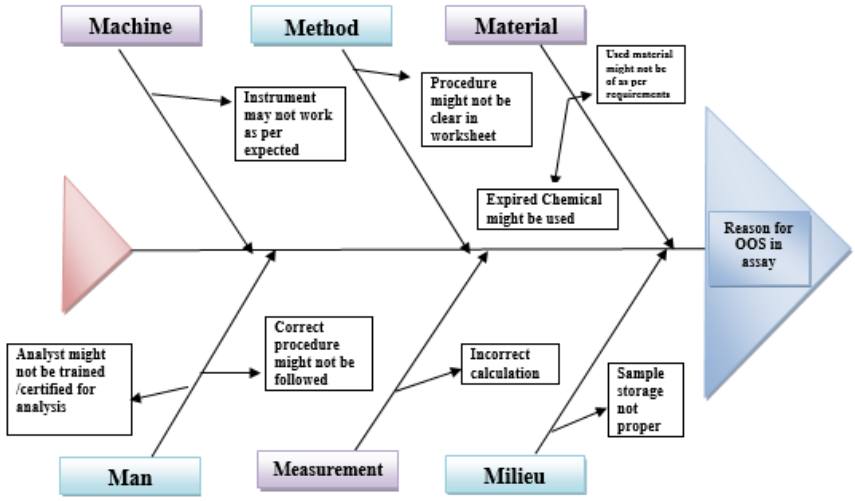

Fig. 14 Ishikawa Diagram

1. Man (People)
2. Machine (Equipment)
3. Material (Raw Material)
4. Method (Process/Procedure)
5. Measurement (Calculations)
6. Milieu (Working/Storage Conditions).

1. Man (People):

- Analyst might not be trained or certified for analysis.

Training record of analysts have been reviewed and it is noted that analysts are trained and certified on related SOP required for analysis. Analysts are trained to perform the testing and have adequate knowledge on the testing method.

Analyst Error: Tablets of different strengths (25 mg and 50 mg) were mixed up, leading to incorrect weight and dissolution.

Lack of Attention to Detail: Analyst might not have properly verified the tablets before placing

them in the dissolution apparatus.

2. Machine (Equipment)

- Instrument/Software may not work as per expected norms.

Calibration record for HPLC instrument (Instrument ID. QCD-184) has been reviewed and it is observed that calibration was performed successfully. During reviewed of data it is observed that instrument and equipment work well within acceptance limit and as per standard norms. HPLC instrument and other instrument were inspected and found that instrument was in calibrated state.

Interpretation:

On the basis of above data it is interpreted that instruments were used in analysis are calibrated and Instrument works as per expected norms and there is no breakdown during analysis of these batches. Hence, this hypothesis related to machine is ruled out.

3. Material (Excipients/Chemicals):

- Used material might not be of as per requirement.

The chemical and reagents used in the analysis is according to the chemical grade written in standard testing procedure, no any error was observed. Results of previous stability sample time point for these batches were reviewed were found satisfactory. Area of standard solution also found comparable to previous analysis. Results of other test i e. Appearance, Related substances, and Assay were reviewed, found within the acceptance criteria.

Interpretation:- On the basis of above observation it is interpreted that analyst had used correct material was as per requirement for analysis hence this hypothesis is ruled out.

- Expired chemical/ standard might be used.

During review of raw data it is observed that Mobile phase was used in the analysis which was prepared on dated 16/08/2023 and dissolution media was used in the analysis which was prepared on dated 16/08/2023. Analyst has used chemical within expiry date.

Interpretation:-

On the basis of above observation it is interpreted that chemicals used in the analysis of Dissolution test are within expiry date. Hence, this is ruled out.

4. Method (Process/Procedure):

- Procedure might not be followed

During review of raw data and discussion with the analyst it is found that all the procedures are followed as per standard testing.

Interpretation:- Based on review of data against standard testing procedure it is observed that analyst has prepared mobile phase, diluent, standard solution as per intended procedure. System suitability parameter were found as per procedure and base line, peak shape also found satisfactory.

- Analysis Method: There might have been some issues with the setup of the dissolution

test process.

- Test Procedure Error: Mixing up the tablets of different strengths during the test procedure, not separating them properly for each analysis.

5. Measurement (Calculations):

- Calculation might not be done correctly

During review it is observed that analysis of Dissolution test was performed on Waters HPLC having (Empower-3) software which was auto calculation done through LES software and found satisfactory.

Verified integration parameter and found inline with standard testing procedure.

Interpretation:-

On the basis of above observation it is interpreted that calculation performed correctly. Hence this hypothesis related to measurement is ruled out.

6. Milieu (Working/Storage Conditions):

- Sample Standard might not be stored as per requirement.

During review of stability condition of sample it is observed that, after withdrawn of sample from stability chamber, sample were stored in quality control laboratory at designated place and in appropriate condition. Verified the log book of "Daily temperature monitoring record, no excursion were observed. Standard and sample solution were injected with in 24Hrs. Interpretation:-

On the basis of above observation it is interpreted that sample are stored as per

require condition. Hence, this hypothesis related to environment is ruled out.

No issue mentioned with the environmental conditions such as temperature and humidity during the test.

5.2. CONCLUSION:

Based on the investigation it is observed that analyst is trained and certified for analysis

Reagent and chemical were used in the analysis are recommended grade.

Mobile phase standard and sample solution were prepared as per procedural recommendation System suitability and instrument performance were found satisfactory.

A. Observations Found From Root Cause Analysis (RCA):

Analyst error where 25mg and 50mg tablets were mixed up, resulting in the wrong calculation during the dissolution test.

- Human Error (Analyst Error) is the root cause, so addressing it through process updates and training is critical. Proper labeling of tablets and verification steps should be introduced to prevent future mix-ups.

- Impact Assessment: Since the error was isolated to one batch, the other batches passed

the stability test, and recalculating the results resolved the issue. However, this error should be flagged, and stricter protocols for handling samples should be established.

5.3. Suggested Corrective Action Implementation

• Corrective Action:

o Reinforce proper training for analysts, emphasizing attention to detail when handling tablets of different strengths.

o Update SOPs (Standard Operating Procedures) to include a step where tablets of different strengths are clearly identified and placed separately.

o Conduct a re-training session for laboratory staff to avoid similar errors in future testing.

• Suggested Preventive Actions:

o Re-evaluate Testing Procedures: Make sure that the dissolution test procedure is clearly outlined with emphasis on handling tablets of different strengths separately. Include checks in place before the dissolution begins.

o Improve Equipment Setup: Recheck and update instrument setups, ensuring they are suitable for different batch analysIs, and cross-check all equipment IDs to avoid errors during batch testing.

• Incorporate Double-Checking System: Before conducting dissolution tests, implement a double-check system by the senior person where a senior verifies the strength and quantity of tablets before placing them in the apparatus.

5.4. Concluding Recommendations:

1. Enhance Staff Training: Make sure analysts are trained to identify and properly handle different strengths of tablets.

2. Standarize Work Procedures: Implement an SOP for handling and testing stability samples with clear guidelines for mixing or separating tablets.

3. Root Cause Prevention: Develop a verification system where two analysts check each step of the process to avoid such errors in the future.

5.5. Final Outcome:

Recalculated dissolution results fall within specification limits, indicating that the root cause was a Human error. Corrective and preventive actions will ensure this does not happen again and improve the accuracy of future testing.

CASE STUDY 02

Out of Specification(OOS) results observed in assay test potentiometer (Autotitrator). Result observed 33.0% on dried basis against the specification limit :- 98.5 to 101.5%(ods).

1. Detail of OOS: On date 09/03/2022, QC department, Raw Material section observed OOS result during analysis of assay test of Acetaminophen Batch No- AMP22363, A.R. No-RM0940322, on Autotitrator instrument QCD-417. Observed result is 33.0% on dried basis

against the specification limit :- 98.5 to 101.5%(ods).

2. Immediate Action Taken: Inform to QA person & Investigation team. Laboratory investigation has been initiated. Review the weight of sample preparation and found as per procedure. Review the calculation and found satisfactory. Verify raw data on worksheet and glassware and found as per procedure.

3. Investigation: Based on investigation analysis performed on potentiometer, after generation of data on software calculation was done and result found OOS. Investigation was done to find out the root cause of this OOS.

3.1. Phase IA

- Laboratory investigation was started on 10/03/2022
- The phase IA investigation was performed as per the OOS checklist.

During online monitoring of analysis it was observed that after dispensing of start volume (1.000 ml) screen of instrument hang and the titrant from the burrette continuosly dispensing into the titration vessel. After 1-2 minute the screen resumes the titration graph and captured the erratic volume. This is identified by analyst and supervisor. This might be the possibility of showing OOS results. Further investigation shall be escalated to Phase 1B to identify the other possible error which could leads to OOS results.:

3.2. Phase IB :Laboratory Investigation:

Started on dated 10/03/2022

3.2.1. Review and evaluation of analytical data:

Review of the analytical data was done and observed that analyst used the correct analytical technique and test procedure as per worksheet and current specification. All the details were verified and found satisfactory. Details mentioned in the worksheet was verified and found complying.

 Interpretation: Analyst used correct procedure mentioned in the analytical worksheet correct method was used for analysis and correct Worksheet was followed for analysis.

 Conclusion: In the investigation it has been noted that analyst has used the correct worksheet and procedure followed is correct.

3.2.2. Analyst competency:

Details of person involved in the analysis are as follows:

Analyst certification record of analyst was verified and found that analyst was certified to perform the analysis.

 Interpretation:- On the basis of their observation it is interpreted that analyst was certified for analysis of Assay test on Autotitrator

Conclusion: In the investigation it was identified that analyst has knowledge about the test.

3.2.3. Recommendation and Hypothesis Plan:

The hypothesis is planned as follows on dated 10/03/2022

Reanalysis shall be performed after dipping the electrode in water with stirring for 10 minutes.

Note:-

- Electrode to be dipped properly in titration vessel
- Ensure the connectivity of the instrument before starting the analysis.

3.2.4. Out come of Hypothesis Study:

Hypothesis study was done on dated 11/03/2022 and observed result of analysis and found out of specification.

Hypothesis Results:- 98.2% (ods) ; 97.9% (asb)

Specification limit:- 98.5% to 101.5% (ods)

3.2.5. Extended Laboratory Investigation:

The matter escalated to vendor and discussion done to find out the root cause for OOS results. Protocol has been prepared to performed the joint analysis with the Vendor (Lab Mumbai and Lab Pithampur). Protocol was executed with vendor analyst on dated 12/04/2022. The analysis performed in presence of Mumbai Analyst and AMV team Pithampur.

During analysis following precautions were taken as suggested by Mumbai Analyst.

Weight of sample taken in mg (Precision of sample upto 2 decimal points)

During sonication magnetic bead was placed in the titration vessel to ensure if sample particle remain undissolved.

- During and after sonication, the titration vessel was not cover with the aluminium foil to inhibit the condensation.
- Cooling of sample done without covering the titration vessel to ensure that the steam of the solution is completely removed. After this titration vessel cover with the foil.
- Further practice has been verified and there was no issue in the procedure followed
- Minutes of meeting prepared.
- Report against the protocol has been prepared
- The result of Protocol Based analysis found with in the specification limit.

Reanalysis was performed in triplicate.

3.2.6. Reanalysis:-

Reanalysis was performed in triplicate. The analysis of sample was done by the same analyst on the Original sample available in QC in triplicate. The analysis was performed on date 14/04/2022. The precautions suggested by vendor analyst was used during final analysis of sample. The Result of analysis are as follows:

Table 4: Results of Reanalysis

S. No.	Activity	Results	Specification Limit
1	SET-I	99.3% (ods)	98.5% to 101.5% (ods)
2	SET-II	99.5% (ods)	
3	SET-III	99.8% (ods)	

Final Conclusion:

Based on the analyst and supervisor online observation and investigation, assay test results found 33.0% in initial analysis due to system was stuck during titration, for that electrode sense the end point inadequately.

- Hypothesis result also found out of specification it may be because of the quantity of the sample to be taken is very low and need to be taken in mg instead of gram upto two decimal place. (as per vendor analyst.)

The result of triplicate analysis was found with in the specification limit.

- The average results of triplicate analysis shall be considered as finaal results.

The precautions suggested by vendor analyst are followed during final analysis in triplicate.

Impact analysis (Major/Minor):

- There is no impact as material is not released for further use
- Reanalysis performed in triplicate and results found well within specification limit.
- Results of vendor were verified and found within limit. The result are 99.1%(ods).
- Based on Impact assessment, AR. No. RM0930322 sample re-analyzed on 15/04/2022 and results found 99.0% however the initial result of this sample is 99.8% hence no impact on impacted sample analysis.
- Further 2 more batches of Acetaminophen were analysed on dated 15/04/2022 and result of analysis found with in the specification limit. The result of analysis are as follows:

Table 5: Results of Acetaminophen

S. No.	Material Name	AR. No.	Result (%)
1	Acetaminophen	RM0950322	99.6 %
2	Acetaminophen	RM0960322	99.2 %

4. Root Cause Analysis:

OOS result that is 33.0% obtained in initial analysis is due to system got hanged during titration by which electrode does not sense the end point correctly which result in out of specification result. Sample quantity is very low and analyst taken the sample weight in gram as per mentioned in analytical worksheet, this can be the probable cause behind the OOS result in hypothesis.

5. CAPA:

5.1. Corrective Action:

Initial Analysis invalidated, Investigation and Hypothesis planned.

5.2. Preventive Action:

Analytical worksheet revised for addition of some precautions.

6. RESULTS AND CONCLUSION:

5 WHY technique and Pareto Chart

To find out the root cause and impact assessment 5 WHY technique and Pareto Chart has been used as a Investigation tool. Upon identifying the issue, reviewed the breakdown results that were within the prescribed limits. Additionally, proposed corrective and preventive actions to avoid such errors in the future.

6.1. 5 -WHY Technique:

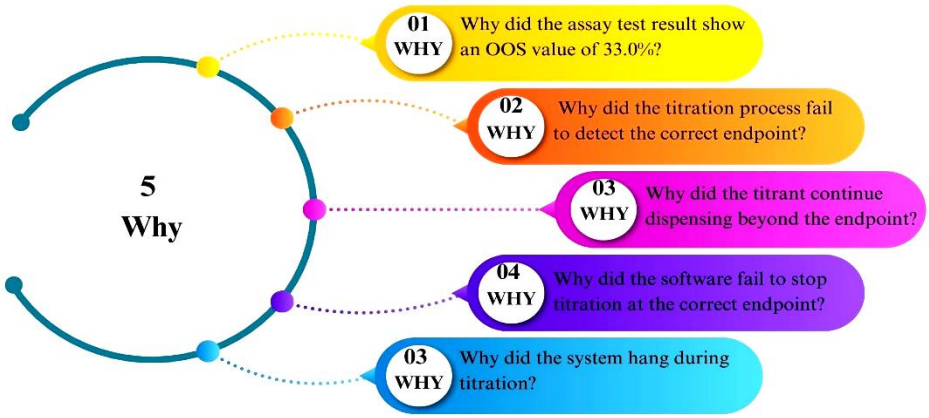

Fig. 15 5-WHY Analysis

- 1st Why: Why did the assay test result show an OOS value of 33.0%?

The titration process did not correctly detect the endpoint, leading to an inaccurate assay result.

- 2nd Why: Why did the titration process fail to detect the correct endpoint?

The titrant continued dispensing into the titration vessel beyond the expected endpoint.

- 3rd Why: Why did the titrant continue dispensing beyond the endpoint?

The software of the Autotitrator (QCD-417) did not stop titration at the correct endpoint.

- 4th Why: Why did the software fail to stop titration at the correct endpoint?

The system froze (hung) during titration, causing a delay in processing and capturing erratic volume.

- 5th Why: Why did the system hang during titration?

The software encountered an unexpected malfunction, possibly due to lack of pre-analysis diagnostic checks or instrument connectivity issues.

6.1.1. Root Cause Analysis:

The OOS occurred due to a software malfunction in the Autotitrator, which caused the system to freeze during titration. This resulted in incorrect endpoint detection and an inaccurate assay result.

6.1.2. Corrective & Preventive Actions (CAPA):

1. Instrument & Software Fixes:

o Implement preventive maintenance and software updates to avoid system hang issues.

o Validate electrode functionality before analysis.

2. SOP Enhancement:

o Include a pre-titration checklist for verifying system stability and connectivity.

o Introduce a step for manual verification of endpoint detection in case of system freeze.

3. Analyst Training & Process Improvement:

o Train analysts on troubleshooting common titration issues.

o Ensure proper sample weighing techniques are followed (mg level, two decimal points precision).

4. Reanalysis & Robustness Study:

o Conduct reanalysis using different titration instruments to confirm results.

o Perform robustness studies to evaluate the impact of instrument conditions on assay outcomes.

5. Long-term Risk Mitigation:

o Implement real-time monitoring and logging to detect software malfunctions before they impact the analysis.

o Conduct periodic audits to ensure compliance with enhanced SOPs.

6.2. Pareto Chart Technique:

The Pareto Chart is a quality control tool based on the Pareto Principle (80/20 Rule), which states that 80% of problems are caused by 20% of factors. This technique helps prioritize the most significant causes of a problem by arranging them in descending order of frequency or impact.

6.2.1. Step 1: Possible Causes

Collect all relevant data that could potentially contribute to the OOS result. This includes:

• Instrumental Issues: Calibration, maintenance, and operation of the Autotitrator (QCD-417).

• Sample Preparation: Errors in the preparation of the sample, including weighing, dissolving, or drying.

- Reagents: Potential issues with the quality, preparation, or expiry of reagents.
- Operator Errors: Mistakes made by the operator during the analysis process.
- Environmental Factors: Conditions such as temperature, humidity, or equipment failure.
- Methodology: Any potential deviations from the standard operating procedure (SOP) or method issues.
- Raw Material Quality: Issues related to the batch of Acetaminophen (e.g., impurities, moisture content, etc.).

6.2.2. Step 2: Quantify the Frequency of Each Cause

Evaluate the frequency or impact of each potential cause

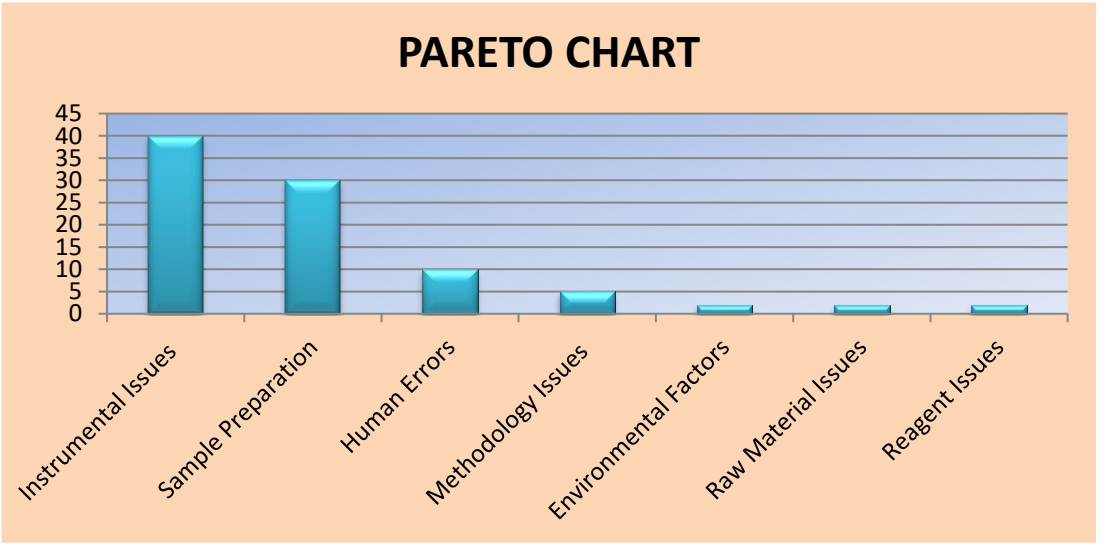

Fig. 16 Pareto Chart.

6.2.3. Step 3: Analyze the Pareto Chart

From the Pareto chart, we observe that three key factors contribute to nearly 80% of the OOS cases:

- Instrument Malfunction (System Hang) – 40%
- Incorrect Sample Preparation (Grams instead of mg) – 30%
- Human Errors for handling of samples- 10%

Instrument Malfunction + Incorrect Sample preparation + Human Errors = 80% of total issues

Other factors contribute to only 20%

Thus, focusing on fixing the top three issues would resolve the majority of OOS cases.

6.2.4. Step 4: Corrective and Preventive

1. Instrument Malfunction Fixes (40%)

- Implement preventive maintenance and real-time system monitoring.
- Conduct system Verification before titration.
- Update software and introduce an auto-restart feature in case of system freeze.

2. Sample Weight Precision Training (25%)

- Mandate sample weighing in mg (precision up to two decimal points).
- Provide training to analysts for accurate sample preparation.
- Introduce automated weight verification before analysis.

3. Human Error(10%)

- Train analysts on troubleshooting common titration issues.
- Verification should be done by 2 analysts and 1 senior.

6.2.5. Final Outcomes:

By addressing the top three factors identified in the Pareto analysis, 80% of OOS cases can be prevented. This structured approach will enhance assay reliability and reduce errors in future testing.

4. Discussion

Details on OOS, CAPA, and Deviation has described here. Every deviation from the approved processes should documented for continuous improvement and compliance with Good Manufacturing Practice (GMP). A full investigation of any OOS is required by Food and Drug Administration (FDA) part 211.192, including documentation of outcomes and follow-up. Handling deviations is an essential component of the quality management system (QMS), which is necessary for ensuring the product's quality by continually enhancing it. If the deviation occurs, it requires immediate action as part of Corrective and Preventive intervention (CAPA). The main problem for a system is how the staff responds to any deviations/OOS that occur. It depends on the degree of training, qualifications, dedication, and support from the company's higher authorities.

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