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A Detailed Case Study on Deviation, Out-of-Specification(OOS) and CAPA Generation in Pharmaceutical Industry

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Abstract:- 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).*

I. 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].

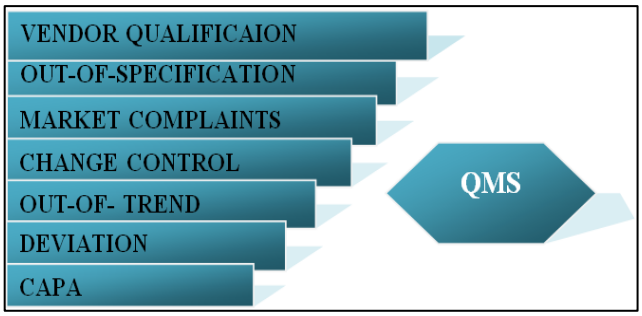

Fig 1 Documents of QMS

II. 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.

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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].

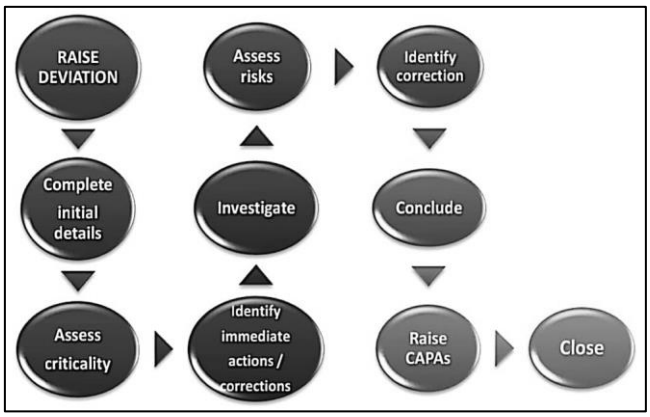

Fig 2 Key Process for Deviation

➢ *Types of Deviation*

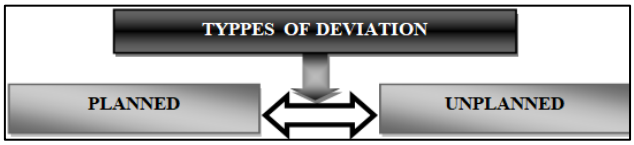

Fig 3 Types of Deviation

- *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.

- *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:*

- *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.

- *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.

- *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.

- *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].

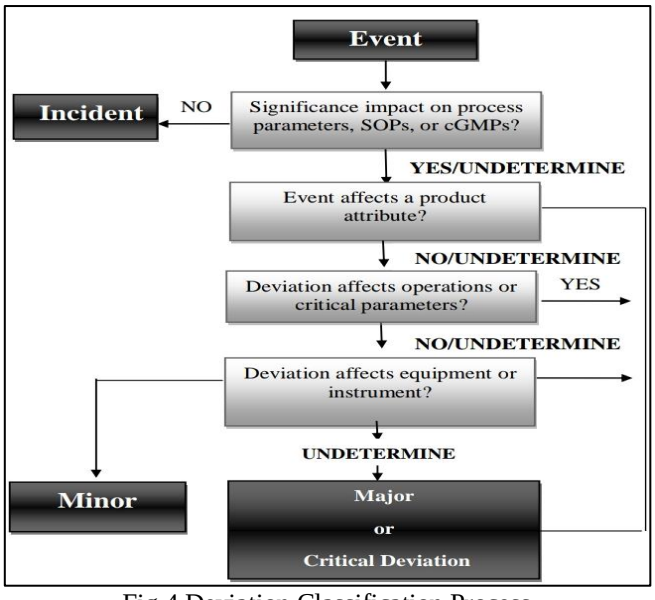

Fig 4 Deviation Classification Process

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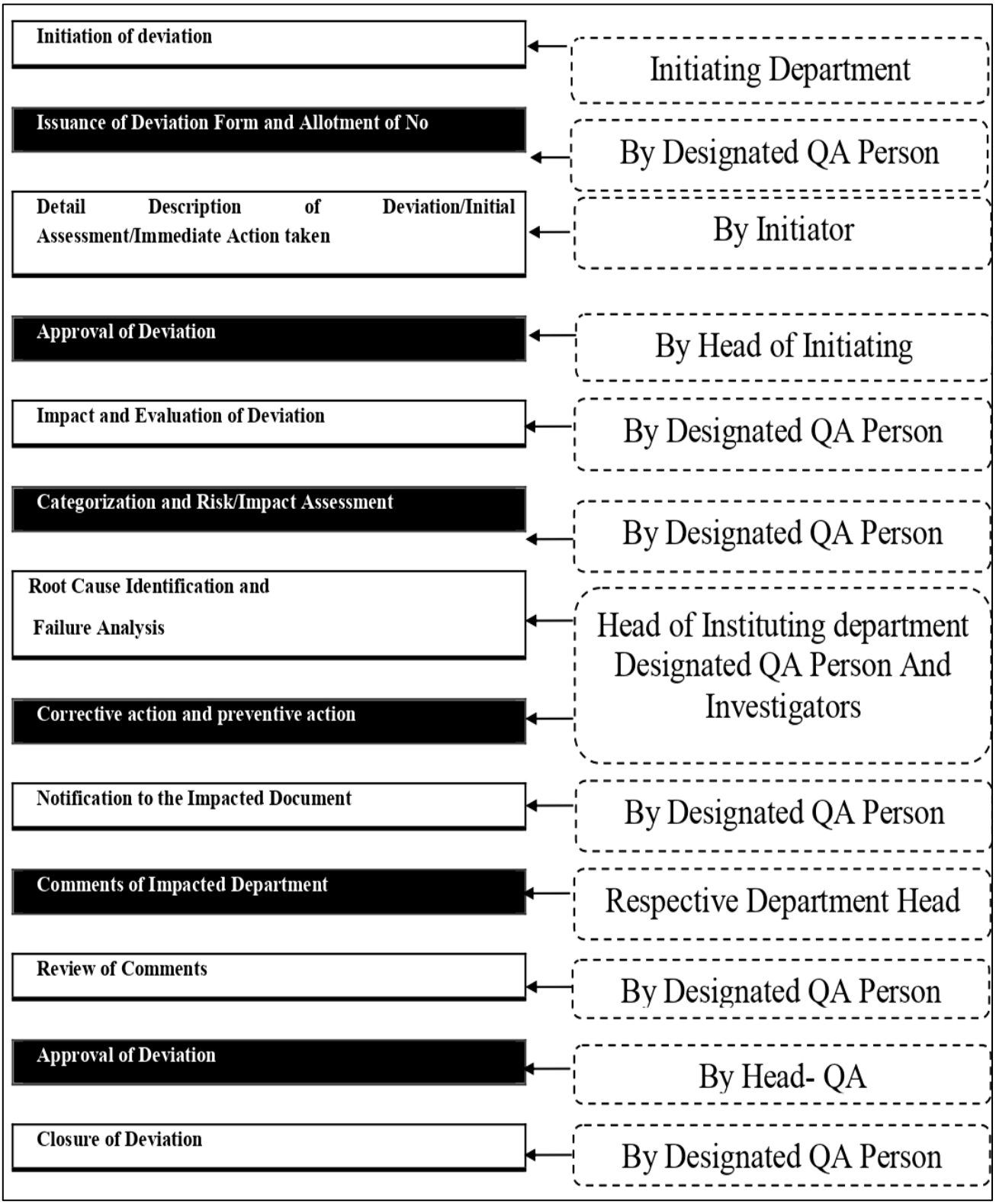

Fig 5 Flow Chart for Deviation Handling

- *Documents*

Table 1 Documents of Deviation

Format No.	Title
01	Format For Deviation Form
02	Format For Deviation Control Register
03	Format For Extended Review of Deviation

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- *Format 01*

Table 2 Format of Deviation

FORMAT FOR DEVIATION FORM		
Deviation applicable for : Document/System/Equipment/Instrument/Facility/Product/Process/Material/Method/Specification Mention title and relevant Document No./ Protocol No./ Equipment No./ Instrument No./ Batch No./ A.R. No./ Item Code		
Deviation : Planned/Unplanned		
Current Procedures : (Use separate sheet if required)		
Description of the deviation : (Use separate sheet if required)		
Justification for planned deviation/Investigation of unplanned deviation: (Use separate sheet if required)		
Initiated By :	Name : Department :	(Sign & Date)
		Page 01 of 03

FORMAT FOR DEVIATION FORM		
Comments by HOD (Initiating Department) :		
(Sign & Date) :		
Root Cause :		
Date & Sign of Investigating team : (Quality Assurance and Concern Department)		
Corrective and Preventive Action by HOD- Initiating Department :		
(Sign & Date) :		
Evaluation of Investigation Summary, Root Cause Analysis, CAPA Approval or Rejection (By Quality Assurance Head) :		
Classification of Deviation : (Quality Assurance Head)	MAJOR	MINOR
Approved / Rejected : (Sign & Date)		
Change Control Initiation (If required) :		
		Page 02 of 03

FORMAT FOR DEVIATION FORM	
Deviation Form No :	
Closure by Quality Assurance Head	
(Sign & Date)	
	Page 03 of 03

- *Format 02*

Table 3 Format for Deviation Control Register

Format For Deviation Control Register							
Date	Originating Department	Nature of deviat-ion	Product/Batch No.	Description of deviation	Justification/Investigation for approval	Deviation No.	Sign & date (QA)

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- *Format 03*

Table 4 Format for Extended Review of Deviation

Format For Extended Review of Deviation	
Deviation No. :	
If root cause of the deviation is not identified or deviation is not closed within the specified period as per SOP then perform additional review at intervals specified in SOP	
1st review of deviation : Department Head (Sign & Date)	 Quality Assurance Head (Sign & Date)
2nd review of deviation : Department Head (Sign & Date)	 Quality Assurance Head (Sign & Date)
3rd review of deviation : Department Head (Sign & Date)	 Quality Assurance Head (Sign & Date)

III. 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.

- *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.

- *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.

- *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:

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- *MHRA Guideline for OOS*
- *CDER Guideline for OOS*

- *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].

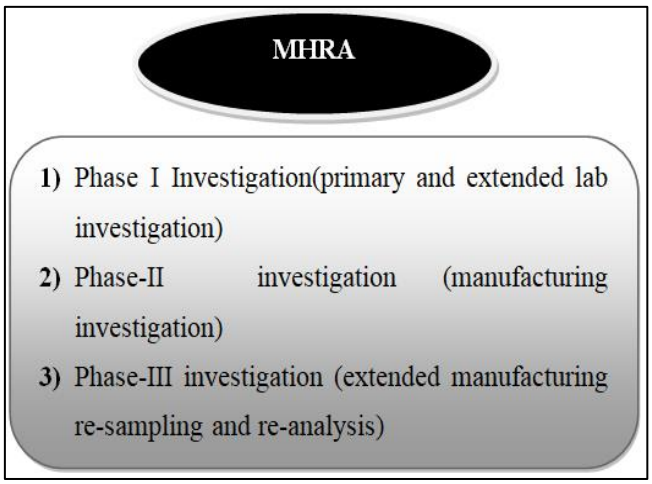

Fig 6 Investigation as per MHRA Guideline

✓ 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 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.

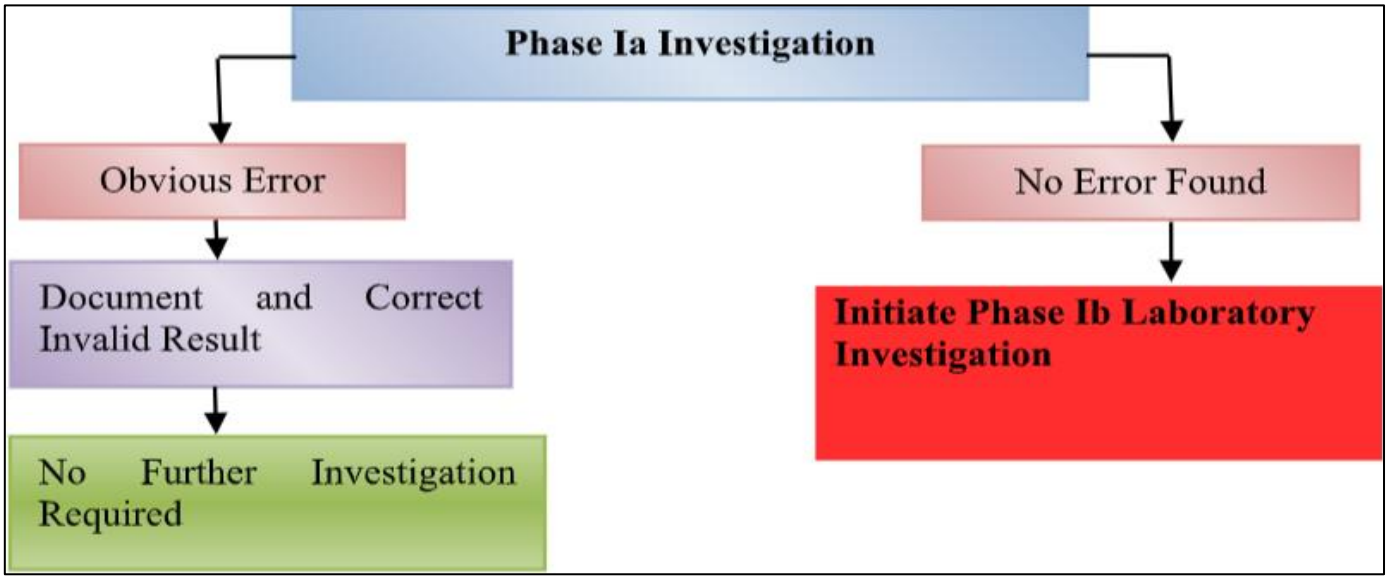

Fig 7 Phase Ia Investigation

✓ 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].

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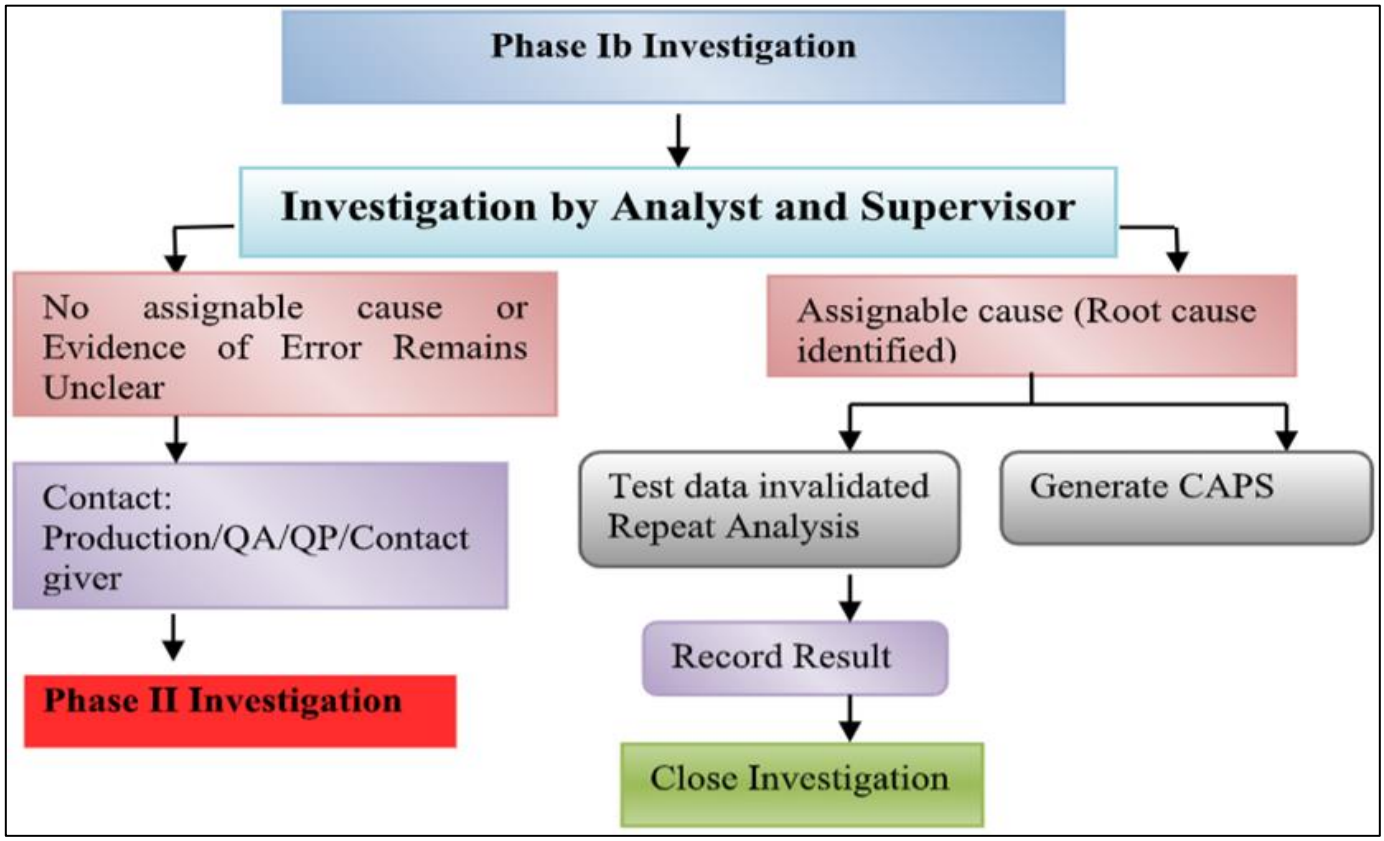

Fig 8 Phase Ib Investigation

- *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.

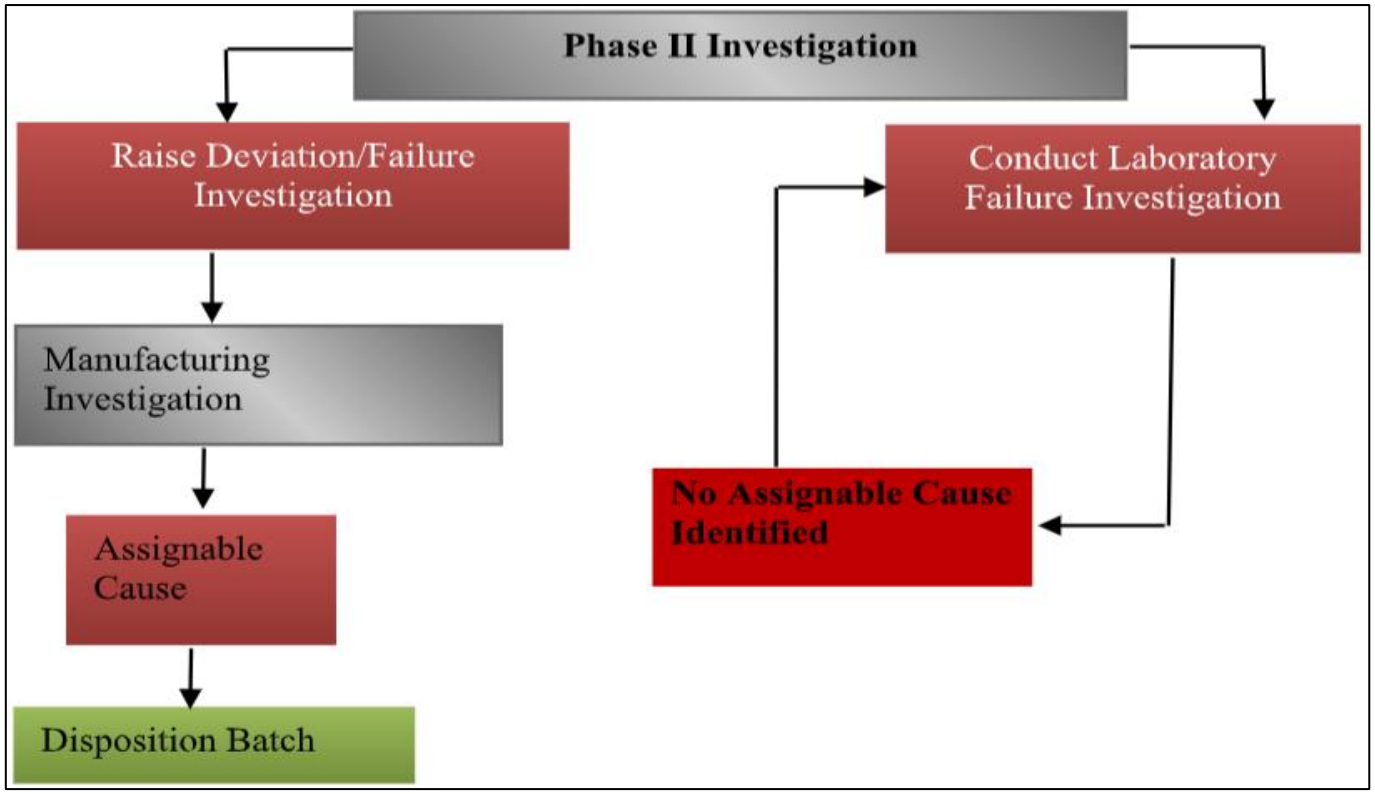

Fig 9(A) Phase II Investigation

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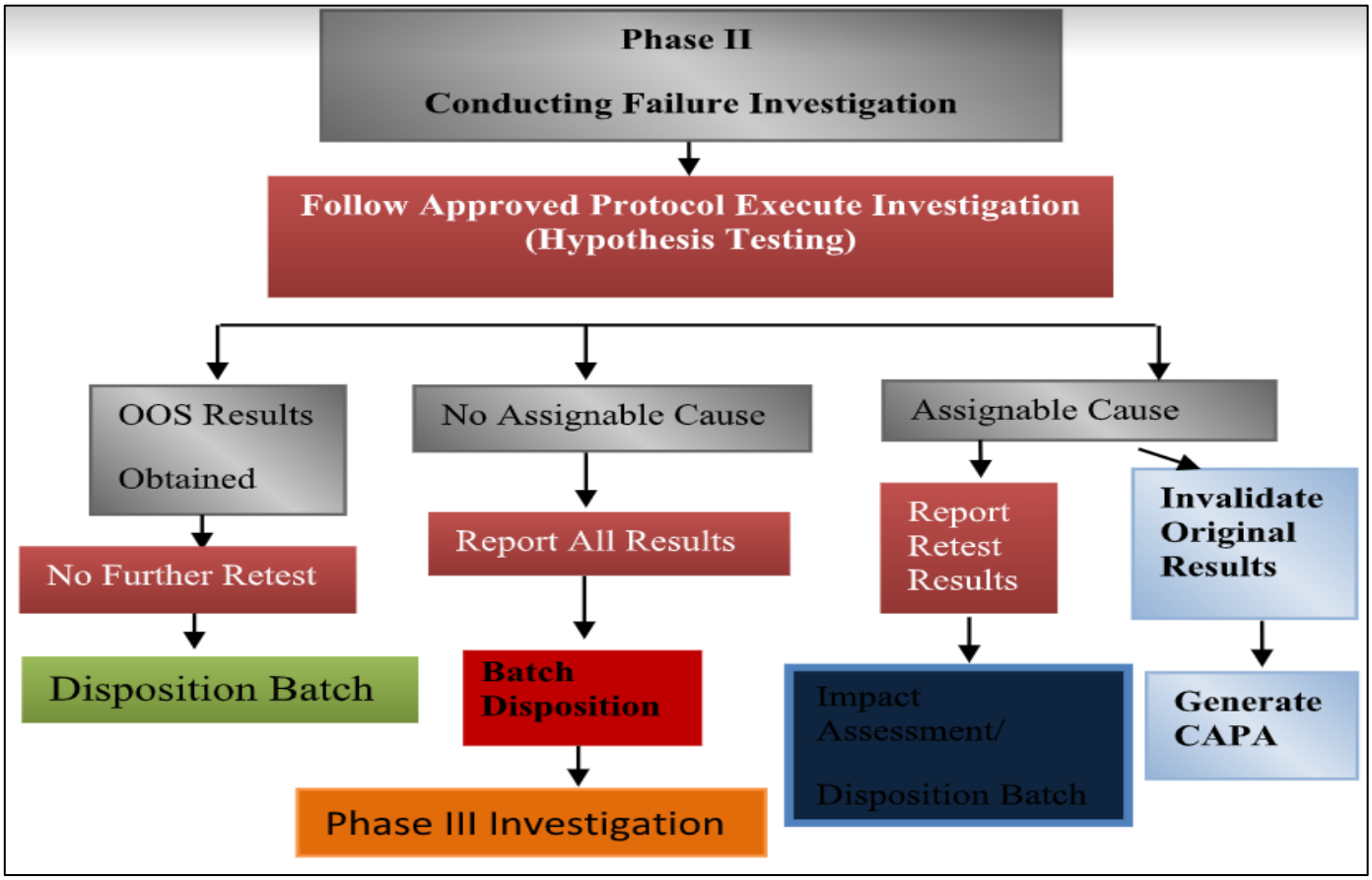

Fig 9(b) Phase II Investigation

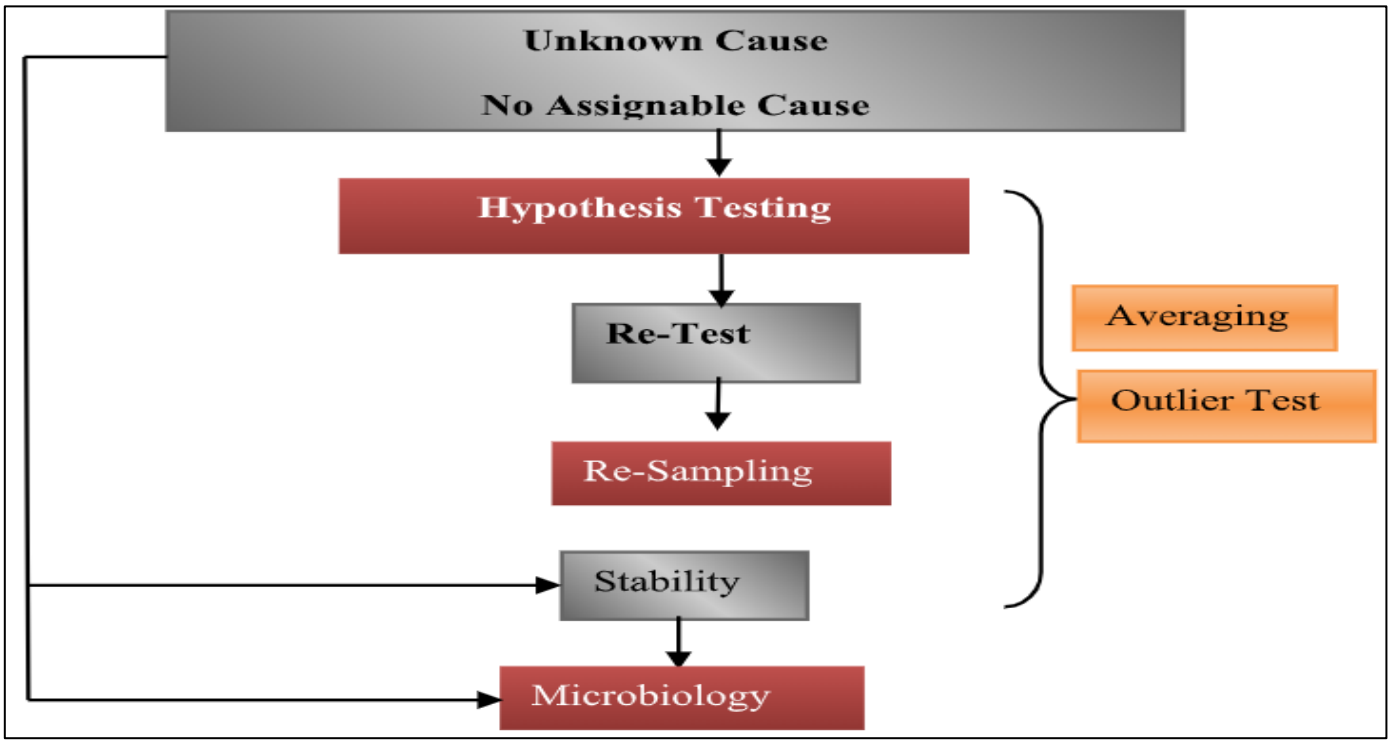

Fig 9(c) Phase II Investigation

- 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].

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- *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].

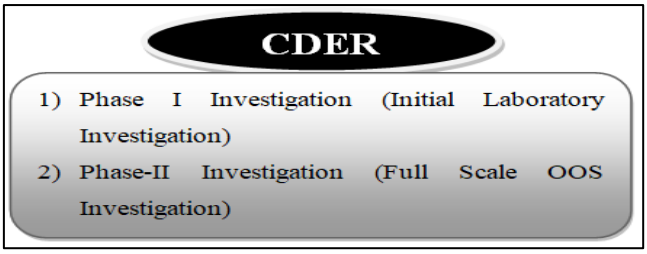

Fig 10 Investigation as per CDER Guideline

✓ *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.

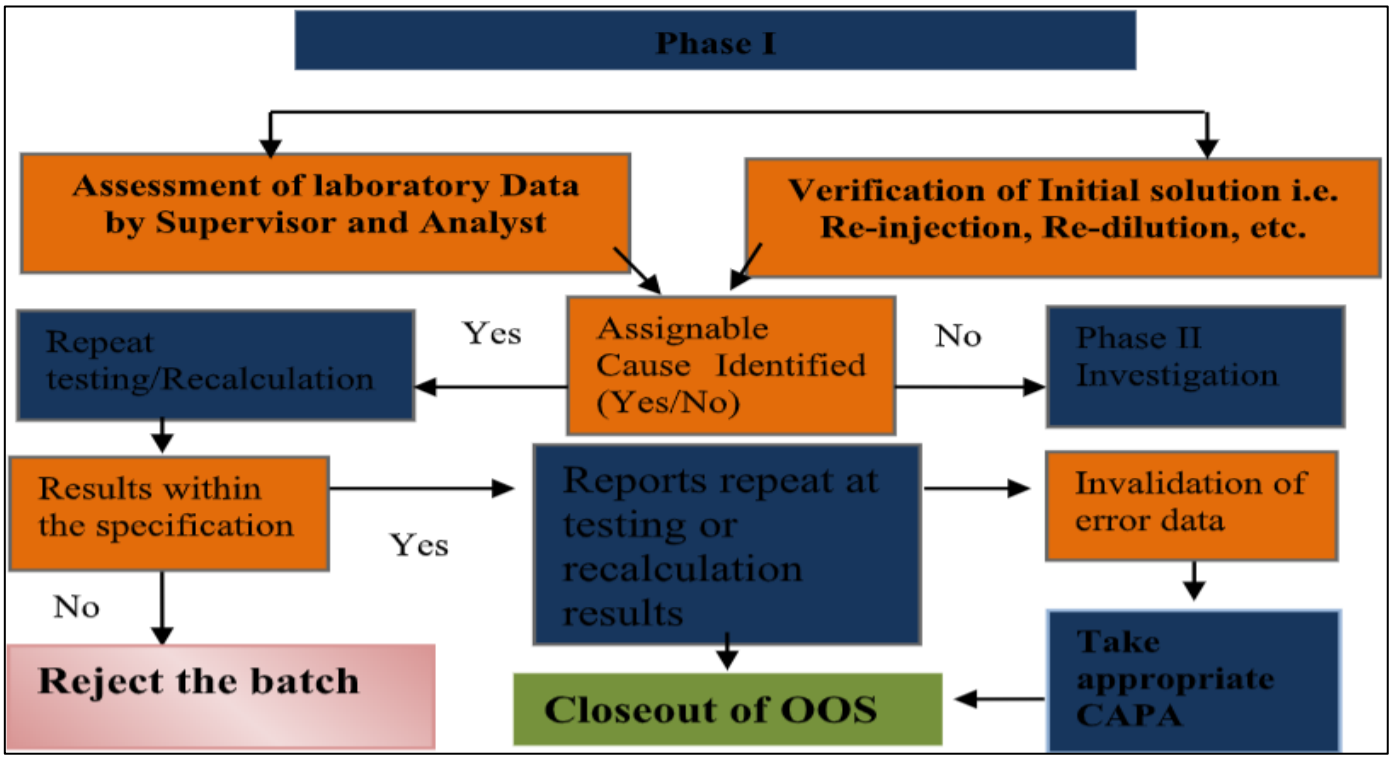

Fig 11 Phase I Investigation

✓ *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:-

- Review of Production
- Additional Laboratory Testing

- Re-Testing
- Re-Sampling

- Reporting Testing Results

- Averaging
- Outlier Testing

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- *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.

- *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.

- *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.

- *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.

- *Reporting Test Results:*

Averaging and outlier tests are two techniques for reporting and interpreting test results.

- *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

- *Outliers Tests:*

A statistical technique for identifying extreme data in a collection[11,14,15].

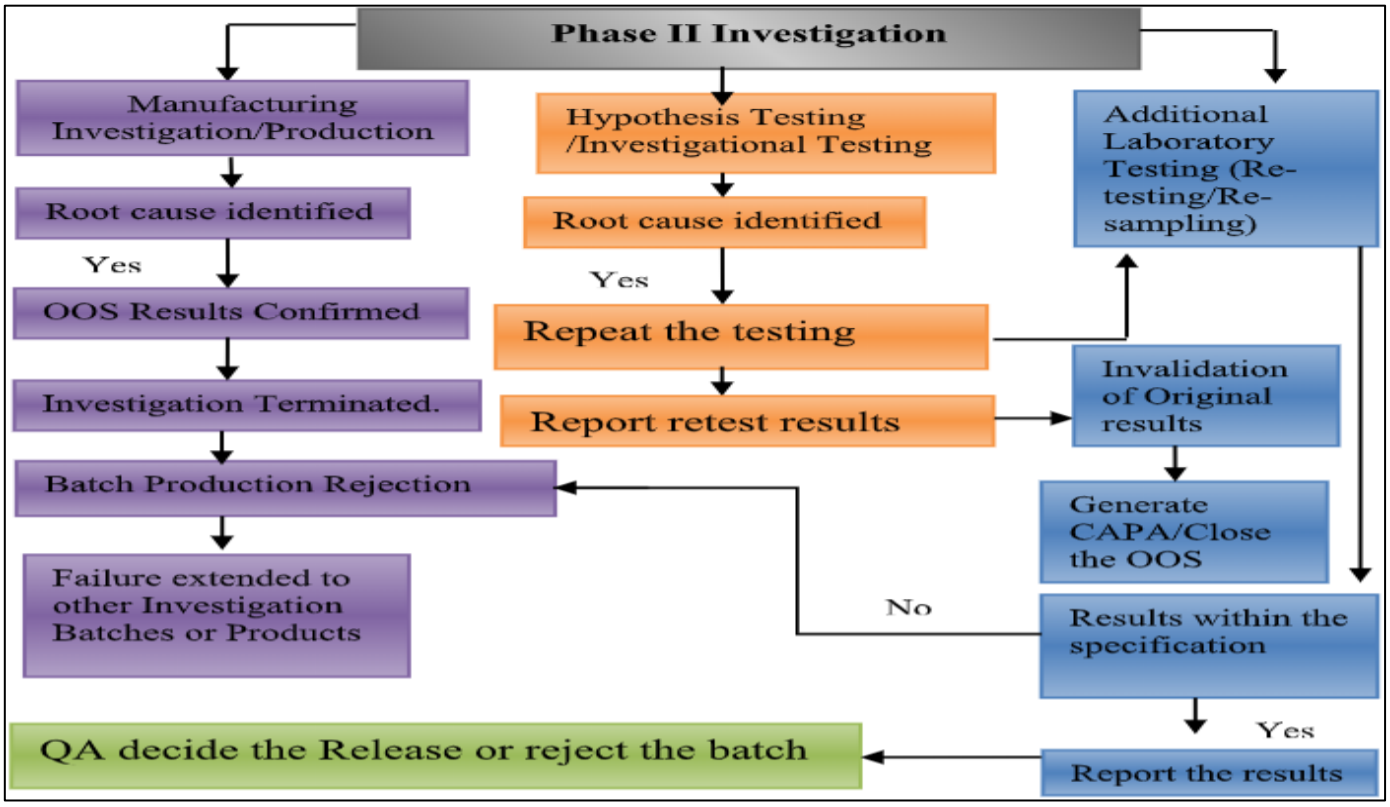

Fig 12 Phase II Investigation (Full Scale Investigation)

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➢ *A Typical OOS Investigation Process Covers the Following:*

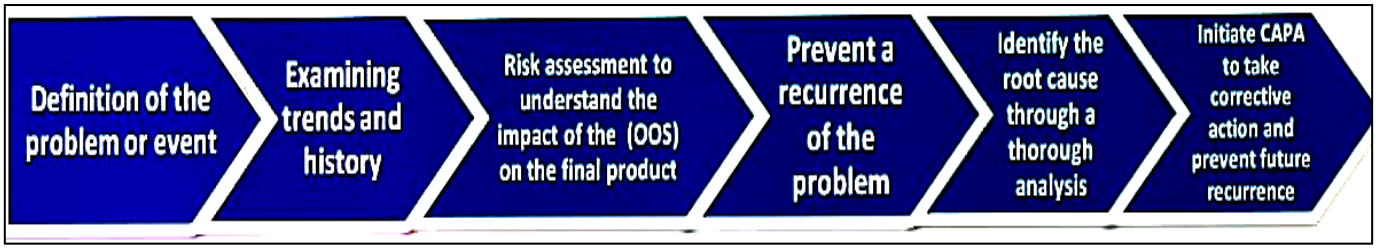

Fig 13 Investigation Process

➢ *Tools for OOS investigation & Related corrective and preventive action:*

- *6M Method for Cause and Effect Analysis:*

Table 5 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.

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

Fig 14 Root Cause Analysis Process

IV. 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:

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- Correction or Remedial Action
- CA
- PA.

- *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.

- *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.

- *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]

V. MATERIAL AND METHOD

➢ *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.

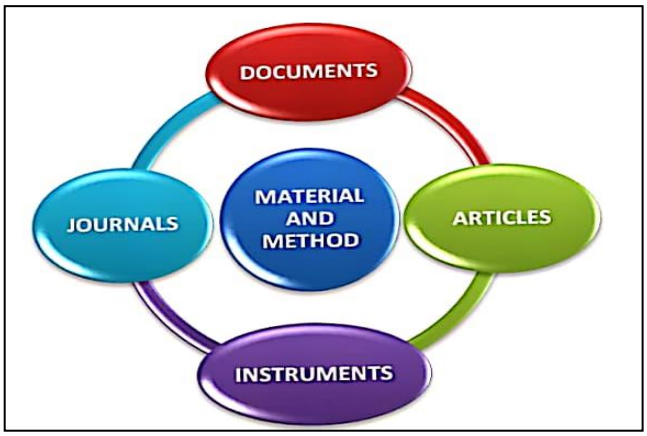

Fig 15 Material and Method

➢ *Method*

To begin work on this project, firstly visited the pharmaceutical industry and reviewed the standard operating procedures and standard guidelines for deviation and 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.

VI. 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

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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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