IPA

Innovation, Quality and Global Reach

Investigations for Non-Conformities Guideline

Focus on Batch Failure Investigations

Investigations for Non-Conformities Guideline

Focus on Batch Failure Investigations

February 2019

Published by:
Indian Pharmaceutical Alliance
A-205 Sangam
14B S V Road, Santacruz (W)
Mumbai 400 054
India
E-mail: dgshah@vision-india.com

February 2019

Printed by:
Spenta Multimedia Pvt Ltd
Peninsula Spenta, Mathuradas Mill Compound
N. M. Joshi Marg, Mumbai 400 013

Preface

The IPA launched its Quality Forum (QF) in April 2015 to help Indian pharmaceutical manufacturers to achieve parity with global benchmarks in quality. The QF made a commitment to a multi-year journey to address key issues facing the industry and develop best practices. McKinsey & Company joined this journey as a knowledge partner.

The QF focused on several priority areas in the last four years, namely, Data Reliability, Best Practices & Metrics, Culture & Capability, Investigations, etc. It took upon itself the challenge of developing a comprehensive set of guidelines for several of these topics. In this book, we focus on best practices for *Investigation of Non-conformities*. We had released a comprehensive set of *Data Reliability Guideline* in February 2017 and *Process Validation Guideline* and *Good Documentation Practice Guideline* in February 2018.

The six participating companies in the QF nominated senior managers to study the best practices and frame the guidelines. They are: S V Gopalakrishnan, Shirish Belapure and Arunava Ghosh (Cadila Healthcare); Sanjay Gorana, Gopi Reddy and Rachel Princess (Cipla); K V Raghu and Sairam Philkana (Dr Reddy's); Pradeep Chakravarty, Alok Ghosh and Indrajit Bose (Lupin); Sanjay Deshmukh, Jila Breeze and Jigar Marfatia (Sun); and Jayendra Tripathi, Rakesh Sheth and Sweety Shah (Torrent). They were assisted in this task by Vivek Arora and Jyoti Saini of McKinsey. The IPA wishes to acknowledge their concerted effort over the last 24 months. They shared current practices, benchmarked these with the existing regulatory guidances from the USFDA and other regulatory bodies such as UKMHRA, WHO, etc., developed a robust draft document and got it vetted by a leading subject matter expert and regulatory agencies. The IPA acknowledges their hard work and commitment to quality.

The IPA also wishes to acknowledge the CEOs of six member-companies who have committed their personal time, human resources and provided funding for this initiative.

This document, to be released at the IPA's 4th India Pharmaceutical Forum 2019 in Mumbai, will be hosted on the IPA website www.ipa-india.org to make it accessible to all manufacturers in India and abroad.

Mumbai
February 2019

Investigations for Non-Conformities Guideline

February 2019

Contents


Mn
Fe
Ru
CH3
O
250
200
11
12

Investigations for Non-Conformities Guidelines

1. Purpose

To provide a general procedure and guidance for conducting investigations of various non-conformities at manufacturing sites in order to identify the root cause and recommend corrective and preventive actions.

2. Scope

This SOP is a generalized procedure applicable to all the investigations carried out at manufacturing sites for non-conformities like batch failures, market complaints, system failures, equipment failures, Out-of-Specification results, Out-of-Trend results, deviations, Out-of-Calibration results, observation(s) outside acceptable range, incidences in QC testing, non-conformance with regulatory requirements, etc.

However, for the specific procedure for each of the Quality Management Systems, the respective SOPs, e.g., handling of deviation, CAPA, OOS, OOT, etc. are to be followed.

3. Responsibility

- All employee and personnel involved in GMP functions, e.g., manufacturing, quality, engineering, IT, warehousing and distribution of pharmaceutical components, intermediates, drug substances or drug products, etc. are responsible for reporting any incident involving non-conformity.
- The head of the respective department or typically an individual from the department where the non-conformance has occurred shall be the investigation leader.
- The investigation leader shall have the responsibility to carry out the investigation in coordination with QA and the investigation team (cross-functional team when required) once it is confirmed that the non-conformity has occurred in that function. He will also lead the team in developing, executing and documenting the investigation plan, data collection and analysis, root cause determination and investigation conclusions. The investigation leader shall review completed investigations with QA and obtain approval of the investigations.
- The composition of the investigation team will be decided during evaluation of the problem statement, and members will be chosen from applicable departments, e.g., Engineering, Development, Quality Control (QC), Quality Assurance (QA), Production and other relevant departments as required, and the relevant departments shall assist in the investigation process.
- Departmental/Functional heads shall ensure adequate resource allocation so that investigations can be concluded in a timely and effective manner.
- Site QA head or his designee shall be responsible for review and approval of:
  - The investigation protocol when a separate investigation protocol is required to be made.
  - Investigation report.
  - Investigation extension, if required.

    Site QA Head or designee shall also communicate the findings of the major investigations to Management periodically based on the Management review SOP. Site QA shall also be responsible for sharing the applicable investigation details to other sites to implement CAPA across respective sites in the organization.

4. Definitions

- **Non-conformity:** Any occurrence which is a departure from a standard procedure, specification shall be considered as non-conformity. This includes, but is not limited to, system failures, equipment failures, batch failures, market complaints, deviations, stability failures, Out-of-Specification results, Out-of-Calibration results, incidents, non-conformance to regulatory requirements, failure of any input material, product or process to meet standard acceptance limit and other failure and/or deviations.

- **Immediate action:** This is defined as action taken immediately to salvage the situation and to prevent the non-conformity from spreading further. Immediate action may involve some remedial actions.

- **Remedial action:** This is defined as action taken to improve a situation and to fix or correct a non-conformance, and return the process, product, or materials to an acceptable state of control or quality.

- **Corrective action:** This is defined as action taken to eliminate the cause of a detected non-conformity or other undesirable situation. Corrective action is taken to prevent recurrence of the problem (ISO 9000:2005).

- **Preventive action:** This is defined as action taken to eliminate the cause of a potential non-conformity or other undesirable potential situation. Preventive action is taken to prevent occurrence of the problem (ISO 9000:2005).

- **Major impact:** Any non-conforming condition that has the potential to impact the safety, quality, identity, purity or strength of an affected item, i.e., product or input material, is considered to have a major impact.

- **Minor impact:** Any non-conforming condition that does not have the potential to impact the safety, quality, identity, purity or strength of an affected item, i.e., product or input material, is considered to have a minor impact.

- **Root cause:** The underlying reason for the non-conformance which is confirmed by evidence of a known sequence of events and observations is known as the Root Cause.

- **Most probable cause:** A most likely root cause that cannot be established beyond doubt, but is adequately and substantially supported by data gathered during the investigation with the application of sound and logical approaches is considered to be the Most Probable Cause. A most probable cause is identified through investigation in cases where the level of certainty required in order to establish the root cause could not be reasonably determined.

- **Investigation report:** This refers to the report on each non-conforming condition which provides and lists the non-conformance or deviation, item(s) affected, investigation details, disposition, corrective action, preventive action and evidence of closure for the non-conformance.

- **Initiating department:** This is the department that initiates the investigation. Typically, this is the department in which the quality event or the non-conformity occurred.

- **Risk assessment:** This consists of a systematic process of organizing information to support a risk decision to be made within a risk management process. It consists of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards.

5. Procedure

Identification of non-conformity and initiation of investigation:

- If any incidence of non-conformance or deviation from approved process or specification occurs at the manufacturing site, it shall be logged as per the respective SOP. Different sources of non-conformity include, but are not limited to, deviation handling, market complaints, Out-of-Specification, Out-of-Trend, etc.
- An individual (referred to as the Investigation Initiator) who observes or identifies an incident in which a non-conformance, discrepancy, or failure of Good Manufacturing Practice has occurred, must record the incident on an appropriate document (i.e., Investigation Form or Worksheet) and must notify a higher level of supervision. In case the individual does not have access to the means to document the non-conformance, he will notify the matter to the higher level of supervision or a Quality Assurance individual for documentation and further action. The information to be documented in the investigation form or worksheet is provided in below section (refer Defining the Non-conformity).
- The initiator or the department supervisor shall take immediate action (i.e., containment action) to stop the variant condition from continuing and shall notify QA of the non-conformity, and decide immediate course of action and potential product impact based on available information.
- The initiator and QA shall make an assessment of the variant condition to determine the impact of the non-conformance on safety, quality, identity, purity and strength of the affected product.
- Based on the assessment by the initiating department and QA, any component(s)/bulk products/ finished product which might have been affected by the failure shall be quarantined and stored as per the respective product storage condition till the investigation is completed and the decision regarding disposal is made.
- QA shall review the non-conformance document, verify the impact of the non-conformance and classify the non-conformance as 'Major' or 'Minor' as per the applicable SOP followed at the respective manufacturing sites.
- QA shall determine whether an interruption or suspension of the activities is required.
- **Investigation:**

  Investigation shall be carried out by the initiating Department where the non-conformity has occurred. When required, a cross-functional team shall be identified by the respective Department Head and QA Head to carry out the detailed investigation. By preference, the team members shall be those who are relevant Subject Matter Experts on process, equipment or system under evaluation. Support of an external agency and subject matter experts may be taken for supporting the investigation if needed. The respective Department Head and Head QA shall ensure that the investigation is completed within a pre-defined time line.

  The investigation shall be documented in the formats provided in the respective SOP.
  The investigation shall include steps defined below.

  — Defining the non-conformity:

  The non-conformance observed shall be fully documented, e.g.,:

  - **The product under investigation:** full description to be provided of the product involved, product code, B. No./Lot No.as appropriate.

- **Quality system problem under investigation:** full description of the quality process that was involved in the problem to be provided.
- **Process problem:** full description to be provided of the process involved and details of the event that occurred, e.g., 'process temperature observed below 5°C from lower limit.'
- **The event description leading to the investigation:** the event that occurred to be described in as much detail as available including site or place of occurrence, date/time of occurrence, circumstances surrounding the event, how it was detected, etc. This shall also include date of the initiation of the investigation, actual observations, acceptable range, equipment/system details, personnel involved and other relevant information.
- **The area effected:** the process area associated with the problem to be described, e.g., compression or functional area.
- **The linking source, if applicable:** description to be provided of the events that initiated the investigation, and relevant links should be provided to source documents as available, e.g., the complaint number, qualification/validation discrepancy number, etc.

— Data collection:

All the relevant data related to the non-conformance shall be collected and documented. The data collection shall include review of various documents relevant to the non-conformity, which may include, but shall not be limited to, the following;

- Review of similar incidences/failures in last two (2) years.
- History of the product.
- Batch production and control records.
- Equipment log books.
- Material usage and inventory records.
- Test data.
- Maintenance records.
- Cleaning records.
- Training records.
- Relevant environmental monitoring records as applicable.
- Records of various utilities used.
- Stability data.
- Product development reports.
- Validation/Qualification reports.
- Equipment/Instrument calibration records.
- Standard operating procedures.
- Annual product reviews.
- Interview/s with operating personnel.

Heads of respective departments, the investigation team (as applicable) and QA shall decide upon the relevant documents that are required to be reviewed for the investigation. If required, the

relevant persons of the investigation team may visit the site/place to understand the situation and also review/evaluate the relevant procedure/practices followed.

— Data analysis:

The data collected during the review shall be analyzed using techniques like trend analysis, histograms, Pareto analysis, regression analysis, etc. as appropriate.

— Root cause analysis:

Root cause shall be established based on the observations during investigation and analysis of available data using tools like Cause-and-Effect diagram, FMEA, 5 Whys, Fault Tree analysis, etc. If the root cause cannot be established based on the available data, the most probable cause(s) shall be identified using the knowledge of the process and available data. Some examples of standard investigation tools/techniques are provided in Annexure 1.

— Experimentation to confirm causes:

If the root cause is not established based on the available data, then experiments may be planned or review of unit operation may be carried out to collect additional data to confirm the root cause. Before carrying out the experiment, the objective and the experimental plan shall be clearly defined and documented in the experiment protocol which shall be reviewed and approved by QA. The results of the experimental study shall be documented, evaluated and approved by QA in order to draw the conclusions.

If the investigation report indicates human error as the cause for the non-conformance, then further evaluation shall be done with respect to following aspects:

- Clarity of instructions in procedures.
- Adequacy of training.
- Adequacy of supervision.
- Experience of the person.
- Negligence/dereliction of duty.
- Past history of such incidences in last two (2) years.
- Fatigue.
- Any circumstantial trigger, e.g., receiving more than usual work assignments on that day.
- Psychological state of the person on that day.
- Adequacy of the infrastructural support for job delivery, e.g., in hardware design, whether there is any inherent problem with the machine that is responsible for the non-conformity.

— The investigation team/QA shall review investigation documentation for accuracy and ensure that the intended scope, type of classification, level of investigation and other parameters are appropriate. If not, this shall be discussed immediately with the Department Head and the QA Head.

— When required, an investigation plan shall be developed which would contain a step by step description of the investigation approach, responsibilities and target completion date of each step. The investigation plan shall be updated based on feedback from Department Head and QA.

- **Risk evaluation:**

  Risk evaluation of the non-conformance shall be conducted as per Risk Management Procedure. The output of risk evaluation shall provide the significance of the issue as it relates to other product/ material/sites, acceptability of release of the product and justification for continued manufacturing.

- **Impact assessment:**

  A detailed impact of the observed non-conformance on the product quality shall be assessed. The impact assessment, when applicable, shall also be extended to all the batches of the same product and/or related products which are still within the shelf life period. Some examples where such impact analysis needs to be carried out are as follows, but such analyses are not limited to these areas alone:

  — Confirmed failure during long term stability study.

  — Calibration failure.

  Risk assessment shall be conducted as a part of impact assessment. The Investigator along with a cross-functional team shall participate in this process. Risk assessment consists of the identification of hazards, analysis and evaluation of risks associated with exposure to those hazards. The outcome of a risk assessment is either a quantitative estimate of risk (numerical probability of risk) or a qualitative description of a range of risk (such as 'high', 'medium', or 'low').

  If impact assessment calls for filing FAR and/or product/batch recall, the action shall be taken as per the respective SOP. If there is no impact on the involved batches or other batches or products, the conclusion shall be documented with appropriate justification.

- **Review of investigation and CAPA:**

  The non-conformity investigation report shall be prepared by the respective department and reviewed by Department Head, Investigation Team and other relevant departments as applicable. The investigation report shall contain the following:

  — Summary of findings of the investigation.

  — Reference to protocols and any other documentation of results.

  — Evidence that supports conclusions of the investigation.

  — Impact assessment.

  — Immediate measures that are planned and recommended based on the identified root cause or the most probable cause. The immediate measures may include remedial measures as well.

  — Requirement of corrective action and preventive action.

  The investigation report and supporting documents shall then be forwarded to QA to determine adequacy and completeness. QA shall review the investigation, the root cause of the non-conformity as identified based on the investigation and the necessity of corrective action and preventive action. Corrective action shall include action to eliminate the root cause and preventive action shall focus on elimination of probable causes. If corrective action and/or preventive action is not recommended by the investigation team based on the investigation findings and the type of non-conformities, then scientific justification/rationale shall be provided in the investigation report for not recommending corrective action and/or preventive action.

— Formulating Corrective and Preventive Action plan:

Corrective and preventive action should result in product and process improvements and enhanced product and process understanding. The Corrective and Preventive Action plan shall be adequately documented along with methods for evaluating the effectiveness of the measures and acceptance criteria.

— Implement actions:

Effectiveness of CAPA may be checked by doing trial runs with laboratory/commercial scale batches. Planned CAPA shall be implemented following Change Control procedures. Implementation in commercial production shall be done in conformance with the regulatory pathway.

- **Completion of investigation:**

QA shall close the investigation. The investigation must be completed within thirty (30) working days of detection of the non-conformance. However, investigations which may require more than thirty days for completion can be extended based on rationale/justification duly approved by QA and as per procedure defined in respective SOPs. The investigations, in such cases, shall be completed as per the new timeline decided. An interim investigation report with status as on date shall be submitted in such cases.

Once the investigation has been closed, it may be reopened to amend the original report as a result of additional data or information related to the original investigation. Such amendments shall be approved by the same functions that approved the original investigation.

- **Monitoring of CAPA effectiveness:**

All corrective and preventive action plans shall be implemented within the target completion date mentioned in CAPA. In case the CAPA could not be implemented within the target completion date in a few cases, a revised target date should be documented along with justification and approved by Site Quality Head.

— **Evaluation of the implementation:**

After implementation, an evaluation of the change implemented shall be made to confirm that the change objectives have been achieved and there was no deleterious impact on product quality. Specific methods defined in the CAPA plan shall be used to measure the effectiveness of the CAPA. The results shall be documented and evaluated to see whether the CAPA is effective in eliminating the cause. Such evaluation may call for validation of specific steps or stability study. If monitoring of effectiveness is not required, the decision regarding the same shall be documented in the investigation report along with the scientific rationale supporting the decision.

— When required, monitoring the effectiveness of CAPA including the review mechanism shall be based on effectiveness plan defined in the investigation report. The plan shall define appropriate review time period or number of batches of a product or products as applicable.

— If the effectiveness plan for the stated CAPA is successful, the effectiveness plan must be closed within thirty (30) working days of the check for effectiveness.

— If the effectiveness plan for the stated CAPA is not successful, the Department Head, the investigation team (if necessary) and QA shall find out the reason for the same. The investigation may be reopened to identify further causes, to carry out impact assessment and to take CAPA.

— Long-term monitoring of CAPA effectiveness shall be done through use of established site review systems such as Annual Product Review, Validation Review and Trend Analysis Review as mentioned in specific SOPs as well as Site Quality Reviews.

- **Trending of investigation:**

— QA shall carry out the trend analysis of the investigations as per the frequency defined in respective Non-conformance SOP, e.g., handling of deviation, OOS, etc. in order to look for emerging trend.

— The trend data shall be compared with past two (2) years' trend and shall include the effectiveness check of CAPA.

— Any emerging trend(s) shall be brought to the notice of Management.

6. Abbreviations

- **CAPA**—**C**orrective **A**ction **P**reventive **A**ction
- **API**— **A**ctive **P**harmaceutical **I**ngredient
- **FMEA**—**F**ailure **M**ode and **E**ffect **A**nalysis
- **OOS**—**O**ut **o**f **S**pecification
- **OOT**—**O**ut **o**f **T**rend
- **SOP**—**S**tandard **O**perating **P**rocedure
- **QA**—**Q**uality **A**ssurance
- **CQA**—**C**orporate **Q**uality **A**ssurance
- **PDL**—**P**rocess **D**evelopment **L**ab

(This page is intentionally left blank)

ANNEXURES

Annexure 1: Investigation tools/ techniques to carry out root cause investigations

Following three investigation tools/techniques (whichever is applicable) can be used to find out root cause of failure during process investigation:

1. 6M/ISHIKAWA/Fishbone diagram.
2. Fault Tree Analysis (FTA).
3. Five WHY technique.

1. 6M/ISHIKAWA/Fishbone diagram/Cause and effect diagram technique

Purpose: to break down (in successive layers of detail) root causes that potentially contribute to a particular effect.

Ishikawa diagrams (also called fishbone diagrams, herringbone diagrams, cause-and-effect diagrams, 6M or Ishikawa) are causal diagrams that show the causes of a specific event. Common uses of the Ishikawa diagram are in product design and quality defect prevention- in order to identify potential factors causing an overall effect. Each cause or reason for imperfection is a source of variation. Causes are usually grouped into major categories to identify these sources of variation.

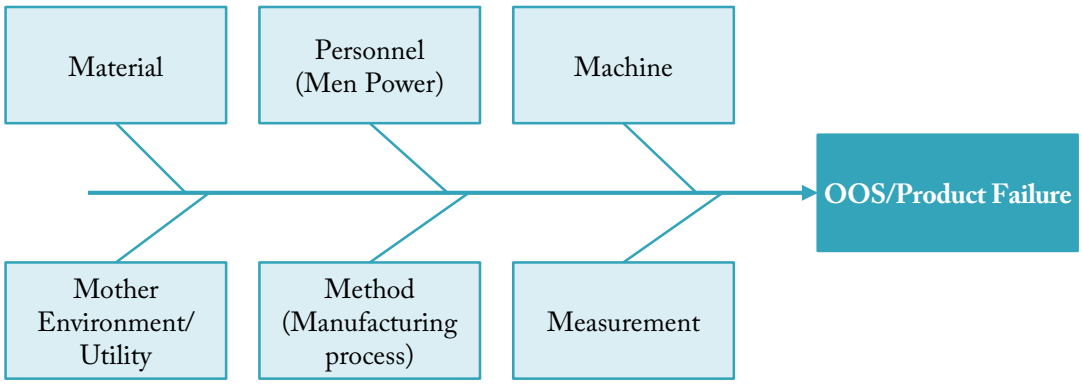
The categories typically include:

- **People:** any person/s involved with the process.
- **Methods:** how the process is performed and the specific requirements for carrying out the process, such as policies, procedures, etc.
- **Machines:** any equipment, computers, tools, etc. required to accomplish the job.
- **Materials:** raw materials, parts, etc. used to produce the final product.
- **Measurements:** data generated from the process that are used to evaluate its quality.
- **Environment/Milieu:** the conditions, such as location, time, temperature, and culture in which the process operates.

An Ishikawa diagram, in fishbone shape, will show factors of equipment, process, people, materials, environment and management, all affecting the overall problem. Smaller arrows connect the sub-causes to major causes.

Causes: Causes are often categorized, such as to the 6M's, as described below. Cause-and-effect diagrams can reveal key relationships among the variables, and the possible causes provide additional insight into process behavior. Causes can be derived from brainstorming sessions. These groups can then be labeled as categories of the fishbone. They will typically be one of the traditional categories mentioned above but may be something unique to the application in a specific case. Causes can be also traced back to root causes with the 5 Whys technique.

Basic ISHIKAWA/Fishbone diagram/Cause and effect diagram



One should check the factors given below. However, other factors may also have an impact.

- Personnel/Men power/Man:
  - Skill, knowledge, competence and attitude.
  - Adequacy of supervision & support.
  - Clarity about job role.
  - Experience, training.
  - Shift in which the activity done.
  - Conduct work environment.
  - Availability of tools/equipment.
- Materials:
  - Change in source of materials.
  - Change in process.
  - Age of materials vs. stability.
  - Materials packing.
  - Test result at incoming stage/retest.
  - Storage condition.
  - Correctness of quality.
  - Quality trend.
- Machine:
  - Age of equipment.
  - Calibration and maintenance history.
  - Whether machine operating correctly.
  - Machine capability.
  - Operating parameters.
- Measurement:
  - Method validation.
  - Analyst training.

- Instrument calibration.
- Standard used.
- Frequency of inspection.
- Other analysis done along with the failing batch.
- Execution of methodology.

- Method:
  - Whether the process is well defined.
  - Critical control points & adequacy of control parameters.
  - Robustness of the process.
  - Experience, training.
  - Process capability.
  - Recent change, if any.
  - Deviation in execution.
  - Trend analysis of process parameters.
  - Safety mechanism and challenges.
- Mother environment/Milieu:
  - Impact of environment condition on the process.
  - Control of environment condition.
  - Impact of environmental condition on the material.

2. Fault Tree Analysis (FTA) technique

Fault Tree Analysis (FTA) is a top down, deductive failure analysis in which an undesired state of a system is analyzed using logic to combine a series of lower-level events.

The fault tree analysis tool is an approach that assumes failure of the functionality of a product or process. This tool evaluates system or sub-system failures one at a time but can combine multiple causes of failure by identifying causal chains.

The fault tree analysis tool is a graphical representation of the major faults or critical failures associated with a product, i.e., the causes for the faults. The results are represented pictorially in the form of the tree of fault modes.

At each level in the tree, combination of fault modes are described with logical operators (and, or, if then, except, not, etc.). FTA relies on the expert process understanding to identify casual factors.

FTA analysis involves five steps:

a. Defining the undesired event to study:

An expert with a wide knowledge of the design of the system or a system analyst is the best person who can help define and number the undesired events. Undesired events are used then to make the FTA, on the principle of one event for one FTA; no two events will be used to make one FTA.

b. Obtaining an understanding of the system:

Once the undesired event is selected, all causes with probabilities of affecting the undesired event are studied and analyzed.

System analysts can help with understanding the overall system. System designers have full knowledge of the system and this knowledge is very important for not missing any cause affecting the undesired event. For the selected event all causes are numbered and sequenced in the order of occurrence and are used subsequently for the next step which is the drawing up or constructing the fault tree.

c. Constructing the fault tree:

After selecting the undesired event and having analyzed the system so that all the causing effects (and if possible their probabilities) are known, the fault tree may now be constructed. Fault tree is based on 'AND' and 'OR' gates which define the major characteristics of the fault tree.

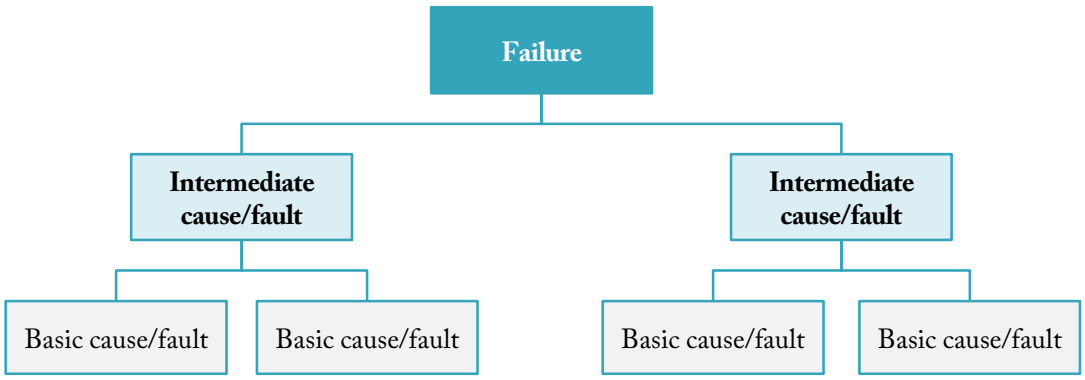
d. Evaluating the fault tree:

After the fault tree has been constructed for a specific undesired event, it is evaluated and analyzed for any possible improvement, i.e., to study the risk management and also to find ways for system improvement. This step functions as an introduction to the final step wherein the objective is to control the causes identified. In short, in this step it is important to identify all possible causes affecting the system in a direct or an indirect way.

e. Controlling the identified causes:

This step is very specific and differs largely from one system to another, but the main objective remains constant: after identifying the cause/s all possible methods are pursued to decrease the probability of occurrence.

Basic fault tree structure



3. Five WHYs Technique

5 Whys is an iterative interrogative technique used to explore the cause-and-effect relationships underlying a particular problem. The primary goal of the technique is to determine the root cause of a defect or problem by repeating the question "Why?". Each answer forms the basis of the next question. The "5" in the name derives from an anecdotal observation on the number of iterations needed to resolve the problem. This is used to explore the cause and effect relationships underlying a particular problem. This technique is useful for simple or moderately difficult problems.

Following steps shall be followed for this technique:

- **Step 1:** A team of people should be assembled who are knowledgeable about the area of non-conformance. It is important to include as many members as possible.
- **Step 2:** A full description should be written out about what is known about the problem. For this purpose, a flip chart presentation board, paper, or any other suitable medium should be used. It is very important to describe the problem as completely as possible refine the definition with the team, and achieve agreement on the definition of the problem at hand.
- **Step 3:** The team asks questions related to issues that impact the problem, and records the answers which may lead to the solution to the problem as described.
- **Step 4:** If the answers provided from Step 3 (above) does not solve the problem, the team should repeat steps 3 and 4 until a logical solution is provided.
- **Step 5:** If the answer provided from 3 (above) appears to be likely to solve the problem, the team should record its agreement and attempt a resolution using the agreement.

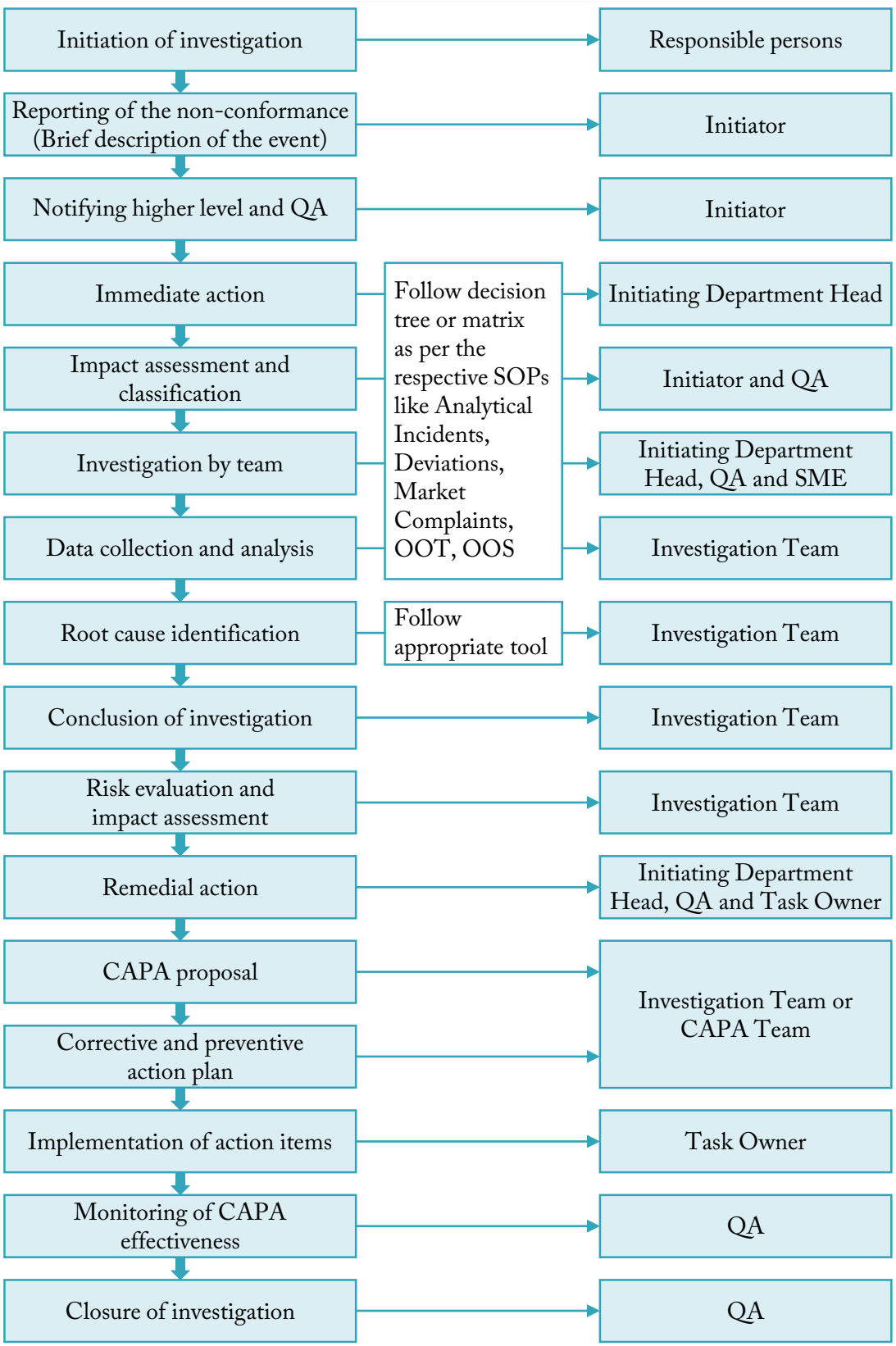
Example:

Problem: Dissolution failure in tablets.

- **Why?** – High disintegration time.
- **Why?** – Over lubrication.
- **Why?** – More mixing in force feeder.
- **Why?** – Slow machine speed with high feeder RPM.
- **Why?** – Parameters not defined in BMR.

The iterative questioning demonstrated in this example could be taken further to a sixth, seventh, or even higher level, but in practice, five iterations of asking why is generally sufficient to get to a root cause. The key is to encourage the trouble-shooter to avoid assumptions and logic traps and instead trace the chain of causality in direct increments from the effect through any layers of abstraction to a root cause that still has some connection to the original problem. It should be noted that, in this example, the fifth why suggests a broken process or an alterable behavior, which is indicative of reaching the root-cause level. It is interesting to note that the last answer points to a process. This is one of the most important aspects in the 5 Whys approach - the real root cause should point toward a process that is not working well or does not exist.

Annexure 2: Flowchart for investigations of non-conformances



References

- ICH Q9: Quality risk management.
- ICH Q10: Pharmaceutical quality system.

Batch Failure Investigations

February 2019

Contents


Mn
Fe
Ru
CH3
O
250
200
11
12

Batch Failure Investigations

1. Purpose

To provide a general guidance:

- For conducting investigations of batch failure of the formulation at any stage of manufacturing and/or analysis in the laboratory.
- For identifying the root cause and recommending corrective and preventive actions.

2. Scope

This guidance is applicable to the investigations carried out at manufacturing sites for batch failure of the formulation at any stage of manufacturing and/or analysis in the laboratory. However, this guidance can also be used for investigating other quality issues, e.g., market complaints, out-of-trend results, product deviations, etc. where applicable.

The procedure is not applicable to:

- In-process tests that are conducted for monitoring or adjusting a process, (e.g., moisture content of granules during drying process).
- Tests such as sterility tests or microbiological limit tests done on the finished product.

3. Responsibility

- QA shall have the responsibility of carrying out investigation in coordination with manufacturing and investigation teams (and cross-functional teams when required). QA will also lead the teams in developing, executing and documenting the investigation plan, data collection and analysis, root cause determination and investigation conclusions.
- Analyst is responsible for performing the analysis as described in the approved standard test procedures (STP), reporting the OOS results, aborting tests where laboratory errors have been identified and informing the supervisor.
- QC manager is responsible for providing OOS information to QA, performing laboratory investigations, performing re-analysis (if required) after QA approval and take necessary actions during the investigation.
- Investigation teams, based on the gravity of the issue, may include representation from various departments, viz., Engineering, Development, Quality Control (QC), Quality Assurance (QA), Production, etc. Other relevant departments shall assist in the investigation process, if required.
- QA shall review the completed investigations with the investigation teams and approve the investigation reports.
- The organization may have a separate department for investigation.
- Adequate resources shall be provided to ensure that investigations are concluded in a timely and effective manner.
- QA Head or designee shall communicate the findings of the investigations to the Management periodically, based on the Management Review SOP. Site QA shall also be responsible for assessing global applicability of CAPA. If applicable, CAPA shall be implemented across impacted sites in the organization.

- The communication of the batch failure investigation can be by way of direct reporting, or during Monthly Management Reviews, Monthly Quality council Meetings, etc. The communication can be by way of daily, weekly, or monthly reports as appropriate.

A detailed RACI matrix for both laboratory and manufacturing which provides a summary of the roles and responsibilities is included in the Annexures.

4. Definitions

- **Batch failure:** Rejection of a batch at any stage of manufacturing and/or analysis in the laboratory due to failure to meet the predefined standard acceptance limit, which may compromise safety, integrity, strength, quality and purity of product.
- **Assignable cause:** A scientifically justified explanation of the reason for an out-of-specification test result identified and documented during investigation.
- **Batch disposition:** Action to be taken about the batch in question based on the conclusion of the investigation (Release/Reject/Reprocess/Rework/Destruction).
- **Experimental testing:** Testing conducted to identify possible laboratory errors (e.g., instrument malfunction, injection errors, contamination during sample preparation, dilution error and incomplete extraction of drug). Such testing shall be done against an approved testing protocol. The values obtained during such experimental testing will not be used for taking a decision about the batch disposition or reporting of the results.
- **Full scale OOS investigation (Phase - II):** Detailed investigation into manufacturing of the product and design to identify the root cause of failure. This includes review of various records and experimentation where necessary. This also includes extended laboratory investigation, including retesting of the same sample in statistically significant replicates if assignable cause is not identified.
- **Hypothesis testing:** Testing conducted to prove or disprove hypothesis about a probable lab error. Such testing shall be done against an approved testing protocol by recreating the analysis condition and/or repetition of the process which has been identified as the probable cause. The values obtained during such hypothesis testing will not be used for taking a decision about the batch disposition or for reporting of the final results.
- **Human error:** Error associated when a mistake is made by the analyst while attempting to adhere to the steps defined in the test methods or any other operation.
- **Laboratory error:** An error associated with the performance of a test procedure or due to laboratory equipment malfunction or failure.
- **Laboratory investigation:** Investigation carried out to assess the accuracy of laboratory testing and recording in order to identify whether there was any error in the testing of the batch in question that could have resulted in the OOS result. This investigation includes review of sample collection, storage, preparation and testing in the laboratory against the documented procedures.
- **Method/Procedural clarity:** Error associated due to lack of clear instructions in the test method or the SOP that may have caused the unexpected result.
- **Obvious laboratory error:** An observed or readily identifiable error that caused the OOS.
- **Out-Of-Specification (OOS) test result:** A test result that fall outside the established specification or acceptance criteria.
- **Probable cause:** A cause which is likely to have resulted in an out-of-specification test result but has not been scientifically proven.

- **Retesting:**
  - Testing done after identification and correction of laboratory/sampling error.
  - Testing done in case the probable laboratory error is confirmed.
  - Testing done as part of Phase II investigation, in the event that no assignable cause is found.
- **Resample:** A second or additional sample collected from a lot or a batch of drug substance or drug product.
- **Retesting protocol:** A written plan for performance of retests during an OOS investigation. The retest protocol will be based upon sound scientific and statistically valid principles and consider factors such as product history, the nature and purpose of the test from which the original reportable value was obtained, and other relevant consideration.
- **Valid OOS:** An OOS wherein the failure is confirmed through laboratory investigation and/or manufacturing investigation. In case an assignable cause is not identified for failure, the OOS shall be considered as valid.
- **Invalid OOS:** An OOS wherein the initial results are invalidated as the root cause or assignable cause for failure is identified as error in testing in the laboratory and product in question meets with specification.

5. Procedure

- Batch failure during manufacturing (semi-finished/bulk product):

  Batch failure can occur at various stages during product manufacturing (semi-finished/bulk product) due to the following reasons:

  - Manufacturing error which may compromise safety, integrity, strength, quality and purity of product, e.g., dispensing, spillage, etc.
  - Processing error and/or process design, which may compromise safety, integrity, strength, quality and purity of product.
  - In-process check results that are significantly out of specification, which may compromise safety, integrity, strength, quality and purity of product.
  - Any event, which may compromise safety, integrity, strength, quality and purity of product, e.g., water leakage in facility, flood, earthquake, fire, etc.
  - Any other error, e.g., labeling, storage, etc., that may compromise safety, integrity, strength, quality and purity of product.
- Batch failure during manufacturing at the stage of finished product testing/stability testing:

  Batch failure can occur at finish product testing/stability testing due to the following reasons:

  - Material variability.
  - Product robustness.

  Important Note: *batch failure indicates significant lapses in the system where any or all the controls have been missed. The investigation should focus on review of all the six systems, viz. Material System, Production System, Facility and Equipment System, Packaging and Labeling System, Laboratory Control System, and Quality System, in order to arrive at a robust CAPA.*
- **Laboratory investigation:**

  Usually the first indication of batch failure is identified during testing in the laboratory. Whenever a failure result is obtained for any of the specified tests for the release of a batch at an intermediate or final stage, an Out-of-Specification (OOS) result is reported.

OOS is investigated to find whether such failure is the result of error in analysis due to

— Errors in instruments, chemicals and other accessories used for analysis.

— Not following procedures correctly.

— Mistake/s on the part of the analyst.

— A combination of the above.

The following are the pathways for investigation to find out whether the failure result obtained is due to laboratory error:

— Obvious error.

— Sampling error.

— Hypothesis testing.

Each of the above is described in the following sections.

- **Obvious error:**

  Usually obvious errors are detected during the primary investigation in the laboratory with respect to correct transcription of data, using correct glassware, chemicals and standards, and calculation errors.

  These kinds of errors are easy to correct, and root cause of such errors can be easily identified. Where necessary, testing should be carried out after removing the error to obtain correct results for the test.

  Based on the nature of the error, corrective and preventive actions should be taken, including, but not limited to, training of the analyst, correction in the method of analysis and/or laboratory procedures for better clarity, after eliminating conditions that have the potential to cause error.

- **Hypothesis testing:**

  If no obvious error is identified during the preliminary laboratory investigation, hypothesis testing is carried out as a first step. Hypothesis testing involves, but is not limited to, injecting the same sample preparations to ascertain any issues related to the instrument or dilutions during sample preparations.

  If the evaluation of the results of hypothesis testing indicates instrument errors and/or sample preparation or dilution errors, the root cause for such error should be identified and corrective and preventive actions should be implemented to eliminate such errors.

  Retesting of the sample should be carried out after eliminating the identified error to obtain correct results for the test.

- **Extended laboratory investigation:**

  Where no obvious error has been identified and hypothesis testing has not revealed the root cause for the failure, extended laboratory investigation shall be carried out.

  During extended laboratory investigation, all possible reasons which can cause a failure result shall be evaluated. Depending on the nature of failure, the extended laboratory investigation shall include, but shall not be limited to, sample handling and storage, preparation of samples, possible cross-contamination within the laboratory and product degradation pathways (in case of failure of related substances).

  Based on the identified possibilities, hypothesis study should be designed to assess if any of them has caused the failure. The hypothesis study results shall be evaluated against the initial failure result.

  If the evaluation indicates that the initial result was caused due to any of the identified possible errors, then probable/assignable cause for the failure is established and testing should be carried out according to the approved retesting plan.

- **Re-testing:**

  Retesting of the original sample is carried out by following exactly the analytical procedure, in case an obvious error or assignable cause is identified during laboratory investigation.

  In case the root cause or assignable cause is not identified after hypothesis and experimental testing, the OOS stands valid. Though error in the laboratory is not ascertained, re-testing may be carried out, wherever feasible, by two analysts with three replicates each in order to prove that the error may be a one-off case.

  Lastly, in case of batch failure, the following three considerations should be kept in mind:

  — Root cause shall be identified for confirmed batch failures. The subsequent batches can be manufactured after removing the cause for failure through appropriate CAPA.

  — In case one batch fails and if the root cause is not identified, then, based on the past history of the product, criticality of failure and thorough Risk Assessment, one batch may be manufactured under close supervision to ensure the batch is manufactured exactly as per the laid down process. Exhaustive testing at in-process stage may be carried out to understand any possible variability. Based on acceptable results, further manufacturing may be continued. However, such a situation (i.e., no root cause identified) should be rare.

  — Wherever batches fail consecutively or frequently, manufacturing shall be ceased, and the product shall be referred back to R&D for further evaluation in order to identify root cause. In such cases, based on the changes suggested to the process, the product shall be taken up for revalidation along with assessment of regulatory filing as necessary. Impact assessment shall be carried out for the batches already on the market with the help of batches on stability and retention samples, in order to conclude whether any further action is warranted on these batches.

  If evaluation of the hypothesis study results does not indicate any laboratory error during initial analysis, then the initial results stand valid. To identify the reason for failure, extensive investigation of manufacturing stages shall be carried out. This is elaborated in the following sections.

6. Investigation of batch failure at various stages (semi-finished/ bulk product) during product manufacturing

- If any incidence of non-conformance or deviation from approved process (Batch Manufacturing Record) or specification occurs during the manufacturing or during in-process or finish product analysis, it shall be logged as per the respective SOP. These incidences of non-conformance may or may not result in batch failure.

- Any individual, who observes or identifies an incident in which a non-conformance, discrepancy, or failure of Good Manufacturing Practice has occurred, must record the incident on an appropriate document (i.e., Investigation form/worksheet) and notify it to his immediate supervisor. Such and individual is known as the Investigation Initiator. In case the individual does not have access to the appropriate document in which to record the non-conformance, he will notify it to his immediate supervisor or a Quality Assurance individual for documentation and further action. The information should be documented in the investigation form/worksheet.

- The initiator or department supervisors will take immediate action (i.e., containment action) to stop the variant condition from continuing and shall notify QA of the non-conformity, and shall decide immediate course of action and potential product impact based on available information.

- The initiator and QA will assess the variant condition to determine the impact of the non-conformance on efficacy, safety, quality, identity, purity and strength of the affected product.

- Based on the assessment by the initiating department and QA, bulk products or finished products which might have been affected by the non-conformance shall be quarantined and stored as per respective product storage conditions till the investigation is completed and disposition decision is made.
- QA shall review the non-conformance document, verify the impact of the non-conformance and classify the non-conformance (as 'Major' or 'Minor') as per the applicable SOP followed at the respective manufacturing sites.
- QA shall determine whether a suspension of activities is required.
- **Investigation:**

  Investigation shall be carried out by the initiating department where the non-conformity has occurred. When required, a cross-functional team shall be identified by the respective Department Head and QA Head to carry out detailed investigation. Preferably, the team members shall be those who are relevant Subject Matter Experts on the process, equipment or the system under evaluation. Support of external agency and subject matter experts may be taken for supporting the investigation if needed. The respective Department Head and Head QA shall ensure that the investigation is completed within a pre-defined time line.

  The investigation shall be documented in the formats provided in the respective SOP. The next sections define how different steps of investigations should be carried out.

  — Defining the non-conformity:

  The non-conformance observed shall be fully documented, e.g.,

  - **The product under investigation:** description of the product involved should be provided, including product code, B. No., Lot No., etc., as appropriate.
  - **Quality problem under investigation:** the quality process that was involved in the problem should be described.
  - **Process problem:** the process involved and details of the event that occurred should be provided, e.g., process temperature observed to be below 5°C from lower limit.
  - **The event description leading to the investigation:** the event that occurred should be described in as much detail as available including site or place of occurrence, date and time of occurrence, circumstances surrounding the event, how it was detected, and other relevant information. This description shall also include date of the initiation of the investigation, actual observations, acceptable range, equipment and system details, personnel involved, and other relevant information.
  - **The area effected:** the process, e.g., compression or functional area associated with the problem, should be clearly indicated.
  - **The linking source, if applicable:** the source that initiated the investigation should be indicated, and links provided to source documents as are available, e.g., the complaint number, qualification and/or validation discrepancy number, etc.

  — Data collection:

  All relevant data related to the non-conformance shall be collected and documented. Data collection shall include review of various documents relevant to the non-conformity, which may include, but should not be limited to, the following:

  - History:
    - — Review of similar incidences and/or failures in last 2 years.
    - — History of the product.
    - — Annual Product Reviews.

- Batch specific reviews:
  - Batch production and control records.
  - Equipment logbooks.
  - Material usage and inventory records.
  - Test data.
  - Maintenance records.
  - Cleaning records.
  - Training records.
  - Relevant environmental monitoring records as applicable.
  - Records of various utilities used.
  - Product details.
  - Stability data.
  - Product development reports.
  - Validation and/or qualification reports.
- Quality system documents:
  - Equipment/Instrument Calibration records.
  - Standard Operating Procedures.
- Others:
  - Interviews with operating personnel.

Heads of respective departments, the investigation team as applicable and QA shall decide which are the relevant documents required to be reviewed for the investigation. If required, the relevant persons of the investigation team may visit the site/place to understand the situation and review and evaluate the relevant procedure and practices followed.

— Data analysis:

The data collected during the review shall be analyzed using techniques like trend analysis, histograms, Pareto analysis, regression analysis, etc., as appropriate.

— Root cause analysis:

Root cause shall be established based on the observations during investigation and analysis of available data using tools like Cause and Effect diagram, FMEA, 5 Whys, Fault Tree Analysis, etc. If the root cause cannot be established based on the available data, the most probable cause(s) shall be identified using the knowledge of the process and available data.

— Experimentation to confirm causes:

If the root cause is not established based on the available data, then experiments may be planned, or review of unit operation may be carried out to collect additional data to confirm the root cause. Before carrying out experiment, the objective and the experimental plan shall be clearly defined and documented, and the experiment protocol reviewed and approved by QA. The results of the experimental study shall be documented, evaluated and approved by QA to draw conclusions.

— If the investigation report indicates human error as the cause of the non-conformance, then further evaluation shall be done with respect to following aspects:

- Clarity of instructions in procedures.
- Adequacy of training.
- Experience of the person.
- Fatigue.

- Any circumstantial trigger, e.g., receiving more than usual work assignments on that day.
- Psychological state of the person on that day.
- Negligence or dereliction of duty.
- Adequacy of supervision.
- Past history of such incidences in last two years.
- Adequacy of infrastructural support for job delivery, e.g., in hardware equipment.
- Any inherent design problem with the machine that is responsible for the non-conformity.

The above list is not exhaustive; however, such a list can be developed by companies based on their experience.

— The investigation team and QA shall review investigation documentation for accuracy and ensure that the intended scope, type of classification, and level of investigation is appropriate. If not, this shall be immediately discussed with Department Head and QA Head.

— When required, the investigation plan shall be developed which would contain a step-by-step description of the investigation approach, responsibilities and target completion date of each step. The investigation plan shall be updated based on feedback from Department Head and QA.

- **Risk evaluation:**

Risk evaluation of the non-conformance shall be conducted by a cross-functional team and appropriate SME, as per Risk Management Procedures. The QA shall have final authority to accept or reject the conclusion. The conclusion of risk evaluation will be appropriately communicated to stakeholders (refer RACI matrices). If the risk evaluation concludes that there is a significant risk wherein the efficacy, safety, integrity, strength, quality and purity of product have been compromised, the batch stands rejected.

The risk evaluation shall provide the significance of the issue as it relates to other product/material/sites, together with justification for continued manufacturing.

- **Impact assessment:**

The responsibility for carrying out and communicating impact assessment shall be the same as detailed under Risk evaluation (refer above paragraph). The impact of the batch failure on the product quality shall be assessed in full detail. The impact assessment, when applicable, shall also be extended to all the batches of the same product and/or related products, which are still within the shelf-life period. Some examples where such impact analysis needs to be carried out are given below. However, this is not an exhaustive list, and impact analysis may need to be carried in other instances as well.

— Confirmed failure during long-term stability study:

Risk assessment shall be conducted as a part of impact assessment. The investigator along with the cross-functional team shall participate in this process. The outcome of a risk assessment is either a quantitative estimate of risk (numerical probability of risk) or a qualitative description of a range of risk (such as “high”, “medium”, or “low”).

If impact assessment calls for filing FAR and/or product/batch recall, the action shall be taken as per the respective SOP. If there is no impact on the involved batches or other batches or products, the conclusion shall be documented with appropriate justification.

- **Non-conformity investigation report review and decision on CAPA:**

The non-conformity investigation report shall be prepared by the respective department and reviewed by Department Head, investigation team and other relevant departments as applicable. The investigation report shall contain the following:

— Summary of investigation finding.

— Reference to protocols and any other documentation of results.

— Evidence that supports the investigation.

— Impact assessment.

— Immediate measures, that shall be planned based on the identified root cause or most probable cause. The immediate measures may also include remedial measures.

— Requirement of corrective action and preventive action.

The investigation report and supporting documents shall then be forwarded to QA to determine adequacy and completeness. QA shall review the investigation, the root cause of the non-conformity identified based on the investigation results, and necessity for corrective action and preventive action.

Corrective action shall include action to eliminate the root cause and preventive action shall focus on elimination of probable causes. If corrective action and/or preventive action are not recommended by the investigation team based on the investigation findings and the type of non-conformities, scientific justification or rationale shall be provided in the investigation report for not recommending corrective action and/or preventive action.

— Formulate Corrective and Preventive Action plan:

  • Appropriate CAPA will be formulated by the cross-functional team and SME.

  • QA will have the final authority to accept or reject the CAPA.

  Corrective and preventive action should result in product and process improvements and enhanced product and process understanding. The Corrective and Preventive Action plan shall be adequately documented along with methods for evaluating the effectiveness of the measures and acceptance criteria.

— CAPA Implement:

  Planned CAPA shall be implemented following change control procedures. Implementation in commercial production shall be done in conformance with regulatory requirements.

  Validity of CAPA may be checked by doing trial runs, laboratory and/or commercial scale batches.

  The implementation of CAPA shall be the responsibility of the function where non-conformance was initiated. If required, help of SME can be taken. QA shall periodically monitor the progress of implementation. Appropriate escalation to higher management will be done by taking up the matter in predefined forums, meetings, reports, etc.

- **Completion of investigation:**

  QA shall close the investigation. The investigation should be completed within 30 (thirty) working days of detection of the non-conformance. However, investigations which may require more than 30 days for completion can be extended based on rationale or justification duly approved by QA and as per procedure defined in respective SOPs. In such cases, the investigations shall be completed as per the new timeline decided. An interim investigation report with status as on date shall be provided in such cases.

- **Reopening of a closed investigation:**

  Once the investigation has been closed, it may be reopened to amend the original report because of additional data or information related to the original investigation. These amendments shall be approved by the same functions that approved the original investigation.

- **Monitoring of CAPA effectiveness:**

  All corrective and preventive action plans shall be implemented within the target completion date mentioned in CAPA. In those cases where the CAPA could not be implemented within the target completion date, the revised target dates must be documented along with proper justification, and approved by site Quality Head.

  — After implementation, an evaluation of the change implemented shall be made, in order to confirm that the change objectives have been achieved and there was no deleterious impact on product quality. Specific methods defined in the CAPA plan shall be used to measure the effectiveness of the CAPA. The results shall be documented and evaluated to see whether the CAPA is effective in eliminating the cause. Such evaluation may call for validation of specific steps or stability study. If effectiveness monitoring is not required, this must be documented in the investigation report along with the scientific rationale.

  — When required, monitoring the effectiveness of CAPA including the review mechanism shall be based on the effectiveness plan defined in the investigation report. The plan shall define the appropriate review period or the number of batches of a product or products, as applicable.

  — If the effectiveness plan for the stated CAPA is successful, the effectiveness plan should be closed within 30 working days of the check for effectiveness.

  — If the effectiveness plan for the stated CAPA is not successful, the Department Head, investigation team if applicable and QA shall find out the reason for the same. The investigation may be reopened to identify further causes, carry out impact assessment, and take CAPA.

  — Long-term monitoring of CAPA effectiveness shall be done through use of established site review systems such as Annual Product Review, Trend Analysis Reviews as mentioned in specific SOPs and Site Quality Reviews.

- **Trend analyses of investigations:**

  — QA shall carry out the trend analyses of investigations as per the frequency defined in respective Non-Conformance SOPs, e.g., Handling of Deviation, OOS, etc. in order to study whether there is indication of any trend.

  — The trend data shall be compared with past two years' trend and shall include effectiveness check of CAPA.

  — Any emerging trend(s) shall be brought to the notice of the Management.

7. Investigation of batch failure during finish product testing/stability

The OOS results found during the analysis of any of the tests mentioned in the specification shall be investigated. Once the laboratory investigation confirms that no error has occurred in the analysis, the matter will be handed over to manufacturing for possible root cause investigation in the manufacturing process or processes.

- Common tests for most of the dosage forms are:

  — Assay.

  — Related Substance.

- Specific tests for Tablets:

  — CU – Tablets, capsules.

  — Weight variation.

  — Disintegration.

- Dissolution.
- Hardness.
- Thickness.
- Friability.

- Specific tests for liquid injectable:
  - CU – Eye/Ear Drops, Injectable.
  - Foreign particles.
  - Glass particles.

The procedure followed for investigations should be same as detailed in the guideline (refer page no 30).

A checklist-based approach is recommended in order to conduct manufacturing investigations. The checklist has been designed for every Critical Quality Attribute (CQA) based on all possible elements that can contribute for a possible CQA failure. The possible elements are grouped into three levels and the levels are in an increasing order of the possibility of finding a root cause.

Level 1 will represent the elements which are the obvious causes for a failure and would not need an experimental hypothesis to prove the cause of the failure.

Level 2 represents the immediate and multiple possible causes for a failure and may not need an experimental hypothesis to prove the cause of the failure.

Level 3 represents the distant and multiple possible causes for a failure but would need an experimental hypothesis to prove the cause of the failure.

The checklists can be found in the Annexures.

Note: *The above-mentioned checklists are generic in nature and can be modified to suit specific nature of dosage forms. The content of each checklist can also be used to generate a checklist for any other dosage forms.*

8. Investigation Governance

The governance mechanism has been provided under each step of investigation.

However, a summary of the roles and responsibilities for both laboratory and manufacturing is provided in the Annexures in the form of RACI matrices.

9. Abbreviations

- **CAPA**—**C**orrective **A**ction **P**reventive **A**ction
- **API**— **A**ctive **P**harmaceutical **I**ngredient
- **FMEA**—**F**ailure **M**ode and **E**ffect **A**nalysis
- **OOS**—**O**ut **o**f **S**pecification
- **OOT**—**O**ut **o**f **T**rend
- **SOP**—**S**tandard **O**perating **P**rocedure
- **QA**—**Q**uality **A**ssurance
- **CQA**—**C**orporate **Q**uality **A**ssurance
- **PDL**—**P**rocess **D**evelopment **L**ab

ANNEXURES

Annexure 1: Investigation checklist for Assay

Checklist is applicable for following dosage forms: Tablets (IR/ER/DR/MR/SR)/Capsules (Hard Gelatine/Soft Gelatine)/Suppositories/Biphasic Semi solid (Ointments/creams)/Injectable (Liquid/Lyophilized)/Transdermal patches/Oral Liquids (Solutions/Syrups/Suspensions)/Nasal preparations (Spray/drops)/Aerosols (MDI)/Dry powder for inhalation (DPI)/Eye/Ear Drops

Checkpoint	Obser-vation		Direct root cause		Caustive factor		Remark
	Yes	No	Yes	No	Yes	No	
LEVEL I							
Were the input materials used as per BOM?							
Was quantity of API used as per BOM?							
Were the quantities of all the excipients used as per BOM?							
Were all the manufacturing steps followed as per BMR?							
Were process parameters in line with the specified range in BMR?							
Were the environmental conditions and controls during manufacturing (Temperature/RH/Light) as per requirements?							
Were the environmental conditions and controls during quarantine (Temperature/RH/Light) as per requirements?							
Was the storage of input materials used in the batch as per requirements?							
Were the utilities associated with major equipment satisfactory?							
Was the storage condition of the product at intermediate stage satisfactory?							
Is there any correlation between degradation study data with process steps?							
Was there any possibility of confusion of dispensing of material with addition of material?							

Checkpoint	Obser-vation		Direct root cause		Caustive factor		Remark
	Yes	No	Yes	No	Yes	No	
LEVEL II							
Was there any deviation related to this product? If so, was this deviation a cause for failure?							
Sampling							
▪ Was the right sampling technique used?							
▪ Was the right sampling tool used?							
▪ Was the sampling done as per procedure? (This refers to the prerequisite and sampling steps).							
▪ Was the sample handled as per the requirement? (This refers to storage and duration).							
▪ Was the sampling done in the container or enclosure as mentioned in the procedure?							
Was there any change with respect to material source?							
Was there any change in the material with respect to physical properties (such as particle size/bulk density/tapped density/viscosity, etc.)?							
Was there any change with respect to manufacturing process of the drug product?							
Was there any change with respect to equipment used in the production of the product?							
Was there any change in packaging components?							
Is the compatibility of accessories for the product established?							
Was preventive maintenance of the equipment executed as per schedule? (RS)							
Was there any breakdown of machines or utility during processing?							
Had the batches exceeded the hold time at any stage?							
LEVEL III							
Human Errors							
Is there clarity of instructions in the procedures?							
Was training adequate?							

Checkpoint	Obser-vation		Direct root cause		Caustive factor		Remark
	Yes	No	Yes	No	Yes	No	
Was supervision adequate?							
Was the relevant person experienced?							
Was there any sign of negligence?							
Could fatigue play a role in this failure?							
Any circumstantial trigger, i.e., receiving more than usual work assignment on that day.							
Was the infrastructural support for job delivery adequate, e.g., hardware design? (This is important to consider in case there is any inherent problem with the machine that is responsible for the variant condition).							
LEVEL IV							
Was potential cause of segregation during manufacturing process and handling?							
Was there any modification in the equipment?							
Is there any emerging point from review of the product development report which can be correlated to the failure?							
History of processing equipment used in the product.							
Review of forced degradation study for the product.							
History of change in packaging.							
Is there any emerging point from the review of the same product with modified process in any other market?							
Are the CPPs process ranges defined in the BMR supported with data?							
Review of historical data of input materials.							
Is there any history of failure in this parameter in the past two years?							
Sampling							
▪ Was the right sampling technique used?							

Annexure 2: Investigation checklist for related substance

Checklist is applicable for following dosage forms: Tablets (IR/ER/DR/MR/SR)/Capsules (Hard Gelatine/Soft Gelatine)/Suppositories/Biphasic Semi solid (Ointments /creams)/Injectable (Liquid/ Lyophilized)/Transdermal patches/Oral Liquids (solution/Syrups/Suspensions)/Nasal preparation (Spray /drops)/Aerosols (MDI)/Dry power for inhalation (DPI)/Eye/Ear Drops

Checkpoint	Obser-vation		Direct root cause		Caustive factor		Remark
	Yes	No	Yes	No	Yes	No	
LEVEL I (Contamination)							
Was the cleaning of the equipment ensured at all stages?							
Was the cleaning of holding containers ensured during processing or transfer?							
Was the hold time period for dirty equipment exceeded?							
Was the hold time period for cleaned equipment exceeded?							
Were cleaning aids used as per procedure?							
Was cleaning of accessories of the equipment used ensured?							
Were input materials used as per BOM?							
Was storage of input materials used in the batch adequate with respect to integrity of container?							
Was storage of drug product or intermediate stage material adequate with respect to integrity of container?							
Was there any possibility of confusion of dispensing of material with addition of material?							
Was the person handling multiple activities and/or products at the same time?							

Checkpoint	Obser-vation		Direct root cause		Caustive factor		Remark
	Yes	No	Yes	No	Yes	No	
LEVEL II (Contamination)							
Were the utilities attached to the equipment intact and/or clean?							
Was the air handling unit of the area intact?							
Was the sampling tool used dedicated, or was cleaning of the same ensured?							
Was the batch manufactured after breakdown maintenance?							
Was there any possibility of leakage or contamination from equipment?							
Was there any possibility of contamination from the area or utility in the product?							
Was there any deviation related to this product? If so, was this deviation a cause of contamination?							
LEVEL I (Degradation)							
Were the input materials used as per BOM?							
Were the quantities of all the excipients used as per BOM?							
Were all the manufacturing steps followed as per BMR?							
Were process parameters in line with the specified range in BMR?							
Were the environmental conditions and controls during manufacturing (Temperature/ RH/Light) as per requirements?							
Were the environmental conditions and controls during quarantine (Temperature/RH/ Light) as per requirements?							
Was storage of input materials used in the batch as per requirement?							
Was the storage condition of the product at intermediate stage satisfactory?							
Is there any correlation of degradation study data with process steps?							
Was the impurity level in API (degradation product) out of trend?							

Checkpoint	Obser-vation		Direct root cause		Caustive factor		Remark
	Yes	No	Yes	No	Yes	No	
LEVEL II (Degradation)							
Was there any deviation related to this product? If so, was this deviation a cause for failure?							
Was there any change with respect to the manufacturing process of the drug product?							
Was there any change in packaging component?							
Is the compatibility of accessories for the product established?							
Had the batches exceeded the hold time at any stage?							
LEVEL III							
Human Errors							
Is there clarity of instructions in procedures?							
Was training adequate?							
Was supervision adequate?							
Was the person experienced?							
Was there any sign of negligence?							
Was there any dereliction of duty?							
Could fatigue play a role in this failure?							
Any circumstantial trigger, i.e., receiving more than usual work assignment on that day.							
Psychological state of the person on that day.							
Was the infrastructural support for job delivery adequate, e.g., hardware design? (This is important to consider in case there is any inherent problem with the machine that is responsible for the variant condition).							

Checkpoint	Obser-vation		Direct root cause		Caustive factor		Remark
	Yes	No	Yes	No	Yes	No	
LEVEL IV							
Was there any modification in the equipment?							
Is there any emerging point from review of product development report which can be correlated to the failure?							
History of processing equipment used in the product.							
Review of forced degradation study for the product.							
History of change in packaging.							
Is there any emerging point from review of the same product with modified process in any other market?							
Is there any history of failure in the past two years?							

Annexure 3: Investigation checklist for content uniformity/weight variation (solid oral dosages)

Checklist is applicable for following dosage forms: Tablet/Capsule

Checkpoint	Obser-vation		Direct root cause		Caustive factor		Remark
	Yes	No	Yes	No	Yes	No	
LEVEL I							
Were the input materials used as per BOM?							
Were the quantities of all the excipients used as per BOM?							
Were the quantities of all the APIs used as per BOM?							
Were all the manufacturing steps followed as per BMR?							
Were process parameters in line with the specified range in BMR?							
Were the environmental conditions and controls during manufacturing and storage (Temperature/RH) as per requirements?							
Was the storage of input materials used in the batch as per requirement?							
Was the storage condition of the product at intermediate stage satisfactory?							
Was the storage container of product at intermediate stage satisfactory?							
Was there any possibility of spillage while dispensing of material, especially binders?							
Were granulation parameters, viz. mixing time, granulation end point, within validated limit?							
Was Compression/Filling M/c machine speed run at validated speed?							
Was there any mechanical malfunctioning?							
Was the recipe of compression/filling machine (PLC) as per the predefined recipe?							
Was there any prolonged stoppage?							

Checkpoint	Obser-vation		Direct root cause		Caustive factor		Remark
	Yes	No	Yes	No	Yes	No	
Was there any deviation in the process?							
Was there any spillage of material during manufacturing?							
Was there any breakdown in the machine?							
Were controls on the manufacturing, hold, transfer and filling satisfactory?							
Was the execution of batch as per defined parameters (blending/mixing time/RPM of turret, force feeder/compaction force/hopper feed level, etc.) and defined sequence?							
LEVEL II							
Were the monitoring and measuring devices associated with compression/filling machine in calibrated state?							
Was there any deviation related to this product? If so, was this deviation a cause for failure?							
Was preventive maintenance of equipment done as per schedule?							
Was there any change with respect to material source or material grade, especially for binder?							
Was there any change in the material with respect to physical properties, such as particle size, bulk density, tapped density, etc.?							
Was there any change with respect to the manufacturing process of the drug product (For example wet granulation to direct compression or dry granulation).							
Was segregation of fines and granules carried out during handling at the in-process stages?							
Was there any change with respect to equipment used in the product (especially compression/filling machine)?							
Was preventive maintenance of equipment executed as per schedule?							
Did the batches exceed the hold time at any process stage?							
Were there any interruptions in process steps?							
Was the state of calibration of equipment within the specified window?							
Was there any possibility of mix-up at the dispensing and/or granulation?							

Checkpoint	Obser-vation		Direct root cause		Caustive factor		Remark
	Yes	No	Yes	No	Yes	No	
LEVEL III							
Human Errors							
Is there clarity of instructions in procedures?							
Was training adequate?							
Was supervision adequate?							
Was the person experienced?							
Was there any sign of negligence?							
Could fatigue play a role in this failure?							
Any circumstantial trigger, i.e., receiving more than usual work assignment on that day.							
Was the infrastructural support for job delivery adequate, e.g., hardware design? (This is important to consider in case there is any inherent problem with the machine that is responsible for the variant condition).							
LEVEL IV							
Was potential cause of segregation of particles (Granules/Fines) during manufacturing process and handling?							
Was there any modification in the equipment?							
History of processing equipment used in the product.							
Is there any history of failure in this parameter in the past two years?							

Annexure 4: Investigation checklist for (liquid dosages – injectable/eye/ear drops)

Checklist is applicable for following dosage forms: Injectables/Eye/Ear Drops

Checkpoint	Obser-vation		Direct root cause		Caustive factor		Remark
	Yes	No	Yes	No	Yes	No	
LEVEL I							
Was there any discrepancy reported during the machine start up process?							
Was machine speed run at validated speed?							
Was there any mechanical malfunctioning?							
Was the filters assembly attached online satisfactory?							
Was the recipe of filling machine (PLC) as per predefined recipe?							
Was there any fluctuation in pressure for pressure dosing vessel?							
Was there any prolonged stoppage?							
Was there any deviation in the process?							
Was there any breakdown in the machine?							
Was the online checkweigher qualified?							
Was the in-process weight checking found satisfactory?							
Was the centering of the filling nozzle satisfactory?							
LEVEL II							
Were the monitoring and measuring devices associated with the filling machine in calibrated state?							
Were the physical parameters of the liquid being filled (viscosity) as per requirement?							

Checkpoint	Obser-vation		Direct root cause		Caustive factor		Remark
	Yes	No	Yes	No	Yes	No	
Was rejection after interventions in line with usual trend?							
In case of peristaltic pump, was the condition of tubes found satisfactory?							
LEVEL III							
Human Errors							
Is there clarity of instructions in procedures?							
Was training adequate?							
Was supervision adequate?							
Was the person experienced?							
Was there any sign of negligence?							
Could fatigue play a role in this failure?							
Any circumstantial trigger, i.e., receiving more than usual work assignment on that day.							
Was the infrastructural support for job delivery adequate, e.g., hardware design? (This is important to consider in case there is any inherent problem with the machine that is responsible for the variant condition).							
LEVEL IV							
Was there any modification in the equipment?							
History of processing equipment used in the product.							
Is there any history of failure in this parameter in the past two years?							

Annexure 5: Investigation checklist for disintegration test (solid oral dosage)

Checklist is applicable for following dosage forms: Tablets/Capsules (Hard Gelatine/Soft Gelatine)

Checkpoint	Obser-vation		Direct root cause		Caustive factor		Remark
	Yes	No	Yes	No	Yes	No	
LEVEL I							
Were the input materials used as per BOM?							
Were the quantities of all the excipients used as per BOM?							
Were all the manufacturing steps followed as per BMR?							
Was there any change in physical parameters/ state of the input materials for the functional excipients?							
Were process parameters in line with the specified range in BMR?							
Were the environmental conditions and control during manufacturing (Temperature/RH) as per requirements?							
Was the storage of input materials used in the batch as per requirement?							
Was the storage condition of the product at intermediate stage satisfactory?							
Was the storage container of product at intermediate stage satisfactory?							
Was there any possibility of spillage while dispensing of material, especially disintegrants?							
Was the storage condition of all input materials as per specification?							
Were granulation parameters, viz. mixing time, kneading time, binder addition time, granulation end point, etc. within validated limits?							
Was PSD of the granules/blend after final blending within limit?							

Checkpoint	Obser-vation		Direct root cause		Caustive factor		Remark
	Yes	No	Yes	No	Yes	No	
Were the process parameters of granulation, drying and blending within limit?							
Were the in-process parameters during packing (leak test, sealing temperature, etc.) satisfactory?							
LEVEL II							
Were compression parameters within specified limits? (These include compaction force, turret speed, RPM, tooling, CAM size used, physical state of tooling, etc.).							
Was there any deviation related to this product? If so, was this deviation a cause for failure?							
Sampling							
▪ Was sampling done as per procedure? (Prerequisite and sampling steps to be included)							
▪ Was the sample handled as per the requirement (Storage and duration to be mentioned)							
▪ Was the sampling done in the container/ enclosure as mentioned in the procedure?							
Was there any change with respect to material source, especially for disintegrants?							
Was there any change in the material with respect to physical property (such as particle size, bulk density, tapped density, etc.?							
Was there any change in the manufacturing process of the drug product? (For example, wet granulation to direct compression or dry granulation).							
Was the segregation of fines and granules carried out during handling at the in-process stages?							
Was there any change with respect to equipment used in the product, especially in the compression/filling machine?							
Was preventive maintenance of equipment executed as per schedule?							
Was there any breakdown of machines or utility during processing?							

Checkpoint	Obser-vation		Direct root cause		Caustive factor		Remark
	Yes	No	Yes	No	Yes	No	
Had the batches exceeded the hold time at any process stage?							
Were there are any Interruptions in-process steps?							
Was the state of calibration of equipment within the specified window?							
Was there any possibility of confusion at the dispensing or granulation operations?							
Was the end-point determination for granulation/mixing carried out as defined in the procedure?							
LEVEL III							
Human Errors							
Is there clarity of instructions in procedures?							
Was training adequate?							
Was supervision adequate?							
Was the person experienced?							
Was there any sign of negligence?							
Could fatigue play a role in this failure?							
Any circumstantial trigger, i.e., receiving more than usual work assignment on that day.							
Was the infrastructural support for job delivery adequate, e.g., hardware design? (This is important to consider in case there is any inherent problem with the machine that is responsible for the variant condition).							
LEVEL IV							
Was there a potential cause of segregation of particles (Granules/Fines) during manufacturing process and handling?							
Was there any modification in the equipment?							
Was there any emerging point from the review of the Product Development Report which can be correlated to the failure?							
History of processing equipment used in the product.							
History of variation of process parameters.							

Checkpoint	Obser-vation		Direct root cause		Caustive factor		Remark
	Yes	No	Yes	No	Yes	No	
History of change in packaging.							
Is there any emerging point from the review of the same product with modified process in any other market?							
Are the CPPs process ranges defined in the BMR and are these supported with data?							
Review of historical data of input materials.							
Was there any history of failure in this parameter in the past two years?							

Annexure 6: Investigation checklist for dissolution test (solid oral dosage)

Checklist is applicable for following dosage forms: Tablets (IR/ER/DR/MR/SR)/Capsules (Hard Gelatine)

Checkpoint	Obser-vation		Direct root cause		Caustive factor		Remark
	Yes	No	Yes	No	Yes	No	
LEVEL I							
Were the input materials used as per BOM?							
Was the quantity of API used as per BOM?							
Were the quantities of all the excipients used as per BOM?							
Were all the manufacturing steps followed as per BMR?							
Were the process parameters in line with the specified range in BMR?							
Were the environmental conditions and control During manufacturing (Temperature/RH/ Light) as per requirements?							
Were the environmental conditions and control (Temperature/RH/Light) during quarantine as per requirements?							
Was the storage of input materials used in the batch as per requirement?							
Were the utilities associated with major equipment satisfactory?							
Was the storage condition of the product at intermediate stage satisfactory?							
Was material reconciliation at the processing stage within the particular stage of manufacturing as per specifications?							
Was verification of in-process tests/parameters at manufacturing (LOD/moisture content/ particle size distribution of blend) carried out as per specifications?							

Checkpoint	Obser-vation		Direct root cause		Caustive factor		Remark
	Yes	No	Yes	No	Yes	No	
Was there any change in the physical parameters of the input material of the functional excipient (e.g., viscosity/PSD)?							
Was the curing time of the pellets satisfactory?							
Was there any Interruption in process?							
Were Critical Process Parameters with respect to equipment (Air flow, bed temperature, pan speed, spray rates, verification of scrubber unit parameters) satisfactory?							
Were the order of addition of materials in the processing steps in line with BMR?							
LEVEL II							
Was there any deviation related to this batch? If so, was this deviation a cause for failure?							
Sampling							
▪ Was the right sampling technique used? (For in-process dissolution of pellets).							
▪ Was the right sampling tool used? (For in-process dissolution of pellets).							
▪ Was sampling done as per procedure (prerequisite and sampling steps)? (For in-process dissolution of pellets).							
▪ Was the sample handled as per the requirement (storage and duration)? (For in-process dissolution of pellets).							
Was there any change with respect to material source?							
Was there any change in the material with respect to physical properties (such as particle size/bulk density/tapped density/viscosity, etc.)?							
Was there any change with respect to the manufacturing process of the drug product?							
Was there any change with respect to the equipment used in the product?							
Was the transfer of material between the equipment and processing steps satisfactory?							

Checkpoint	Obser-vation		Direct root cause		Caustive factor		Remark
	Yes	No	Yes	No	Yes	No	
Was there any change in packaging component?							
Was preventive maintenance of the equipment executed as per schedule? (RS)							
Was there any breakdown of machines or utility during processing?							
Had the batches exceeded the hold time at any stage?							
LEVEL III							
Human Errors							
Was there clarity of instructions in procedures?							
Was training adequate?							
Was supervision adequate?							
Was the person experienced?							
Was there any sign of negligence?							
Could fatigue play a role in this failure?							
Was there any circumstantial trigger, i.e., receiving more than usual work assignment on that day.							
Was the infrastructural support for job delivery adequate, e.g., hardware design? (This is important to consider in case there is any inherent problem with the machine that is responsible for the variant condition).							
LEVEL IV							
Was Potential cause of segregation during manufacturing process and handling?							
Was there any modification in the equipment?							
Was there any emerging point from the review of the Product Development Report which can be correlated to the failure?							
History of processing equipment used in the product.							
History of change in packaging.							

Checkpoint	Obser-vation		Direct root cause		Caustive factor		Remark
	Yes	No	Yes	No	Yes	No	
Was there any emerging point from the review of the same product with modified process in any other market?							
Were the CPPs process ranges defined in the BMR, and are these supported with data?							
Review of historical data of input materials.							
Was there any history of failure in this parameter in the past two years?							
Review of failure related to the same parameter in other strengths of the same product.							

Annexure 7: Investigation checklist for hardness test (solid oral dosage)

Checklist is applicable for following dosage forms: Tablets (IR/ER/DR/MR/SR)/Capsules (Hard Gelatine)

Checkpoint	Obser-vation		Direct root cause		Caustive factor		Remark
	Yes	No	Yes	No	Yes	No	
LEVEL I							
Were the input materials used as per BOM?							
Were the quantities of all the excipients used as per BOM?							
Were all the manufacturing steps followed as per BMR?							
Were there any changes in the physical parameters and state of the input materials, particularly for functional excipients like binders?							
Were the process parameters in line with the specified range in BMR?							
Were the environmental conditions and control (Temperature/RH) during manufacturing and storage as per requirements?							
Was the storage of input materials used in the batch as per requirement?							
Was the storage condition of product at intermediate stage satisfactory?							
Was the storage container of product at intermediate stage satisfactory?							
Was there any possibility of spillage while dispensing of material, especially binders?							
Were granulation parameters, viz. mixing time, kneeding time, binder addition time, granulation end point, etc., within validated limits?							
Was the PSD of the granules and blend after final blending within limit?							

Checkpoint	Obser-vation		Direct root cause		Caustive factor		Remark
	Yes	No	Yes	No	Yes	No	
Were the process parameters of granulation, drying and blending within limits?							
Were compression parameters (compaction force, turret speed, RPM, tooling, CAM size used, physical state of tooling, etc.) within validated limits?							
Were compaction forces, screw RPM, feed rate, rollers used, mesh size used, RPM (roll compactor, and hardness of the compacted slug within validated range/Limit?							
LEVEL II							
Was there any deviation related to this product? If so, was this deviation a cause for failure?							
Sampling							
▪ Was the right sampling technique used?							
▪ Was the right sampling tool used?							
▪ Was sampling done as per procedure? (Prerequisite and sampling steps)							
▪ Was the sample handled as per the requirement (storage and duration)?							
▪ Was the sampling done in the container or enclosure as mentioned in the procedure?							
Was there any change with respect to material source or material grade, especially for binder?							
Was there any change in the material with respect to physical properties (such as particle size, bulk density, tapped density), etc.?							
Was there any change with respect to the manufacturing process of the drug product? (For example wet granulation to Direct compression or dry granulation).							
Was the segregation of fines and granules carried out during handling at the in-process stages?							
Was there any change with respect to equipment used, especially compression and filling machines, in the product?							
Was preventive maintenance of equipment executed as per schedule?							

Checkpoint	Obser-vation		Direct root cause		Caustive factor		Remark
	Yes	No	Yes	No	Yes	No	
Was there any breakdown of machines or utility during processing?							
Had the batches exceeded the hold time at any process stage?							
Were any Interruptions in process steps?							
Was the state of calibration of equipment within the specified window?							
Was there any possibility of a mix-up at the dispensing and granulation stages?							
Was the testing method adequate?							
Was the testing methodology followed as per the procedure defined?							
Was the end-point determination carried out as defined in the procedure?							
LEVEL III							
Human Errors							
Is there clarity of instructions in procedures?							
Was training adequate?							
Was supervision adequate?							
Was the person experienced?							
Was there any sign of negligence?							
Could fatigue play a role in this failure?							
Any circumstantial trigger, i.e., receiving more than usual work assignment on that day.							
Was the infrastructural support for job delivery adequate, e.g., hardware design? (This is important to consider in case there is any inherent problem with the machine that is responsible for the variant condition).							
LEVEL IV							
Was Potential cause of segregation of particles (Granules/Fines) during manufacturing process and handling?							
Was there any modification in the equipment?							

Checkpoint	Obser-vation		Direct root cause		Caustive factor		Remark
	Yes	No	Yes	No	Yes	No	
Is there any emerging point from the review of the Product Development Report which can be correlated to the failure?							
History of processing equipment used in the product.							
History of variation of process parameters.							
History of change in packaging.							
Is there any emerging point from the review of the same product with modified process in any other market?							
Are the CPPs process ranges defined in the BMR and are these supported with data?							
Review of historical data of input materials.							
Is there any history of failure in this parameter in the past two years?							

Annexure 8: Investigation checklist for friability – Tablets

Checklist is applicable for following dosage forms: Tablets

Checkpoint	Obser-vation		Direct root cause		Caustive factor		Remark
	Yes	No	Yes	No	Yes	No	
LEVEL I							
Were the input materials used as per BOM?							
Were the quantities of all the excipients used as per BOM?							
Were all the manufacturing steps followed as per BMR?							
Was there any change in physical parameters or state of the input materials, especially functional excipients like binders?							
Were process parameters in line with the specified range in BMR?							
Were the environmental conditions and control (Temperature/RH) during manufacturing and storage as per requirements?							
Was the storage of input materials used in the batch as per requirement?							
Was the storage condition of the product at intermediate stage satisfactory?							
Was the storage container of the product at intermediate stage satisfactory?							
Was there any possibility of spillage during dispensing of material, especially binders?							
Were granulation parameters, viz. mixing time, kneading time, binder addition time, granulation end point, within validated limit?							
Was the PSD of the granules or blend after final blending within limit?							
Were the process parameters of granulation, drying and blending within limit?							

Checkpoint	Obser-vation		Direct root cause		Caustive factor		Remark
	Yes	No	Yes	No	Yes	No	
Were compression parameters (compaction force, turret speed, RPM, tooling, CAM size used, physical state of tooling, etc.) within validated limits?							
Were compaction forces, screw RPM, feed rate, rollers used, mesh size used, RPM (roll compactor), and hardness of the compacted slug, within validated range/limit?							
LEVEL II							
Was there any deviation related to this product? If so, was this deviation a cause for failure?							
Sampling							
▪ Was the right sampling technique used?							
▪ Was the right sampling tool used?							
▪ Was sampling done as per procedure? (Prerequisite and sampling steps)							
▪ Was the sample handled as per the requirement for storage and duration?							
▪ Was the sampling done in the container or enclosure as mentioned in the procedure?							
Was there any change with respect to material source or material grade, especially for binder?							
Was there any change in the material with respect to physical properties, such as particle size, bulk density, tapped density, etc.?							
Was there any change with respect to manufacturing process of drug product? (For example wet granulation to direct compression or dry granulation).							
Was the segregation of fines and granules carried out during handling at the in-process stages?							
Was there any change with respect to equipment used, especially compression and filling machines in the product manufacturing?							
Was preventive maintenance of equipment executed as per schedule?							
Was there any breakdown of machines or utility during processing?							

Checkpoint	Obser-vation		Direct root cause		Caustive factor		Remark
	Yes	No	Yes	No	Yes	No	
Had the batches exceeded the hold time at any process stage?							
Were there any Interruptions in process steps?							
Was the state of calibration of equipment within the specified window?							
Was there any possibility of a mix-up during dispensing and granulation?							
Was the testing method is adequate?							
Was the testing methodology followed as per the procedure defined?							
Was the end-point determination carried out as defined in the procedure?							
LEVEL III							
Human Errors							
Is there clarity of instructions in procedures?							
Was training adequate?							
Was supervision adequate?							
Was the person experienced?							
Was there any sign of negligence?							
Could fatigue play a role in this failure?							
Any circumstantial trigger, i.e., receiving more than usual work assignment on that day.							
Was the infrastructural support for job delivery adequate, e.g., hardware design? (This is important to consider in case there is any inherent problem with the machine that is responsible for the variant condition).							
LEVEL IV							
Was Potential cause of segregation of particles (Granules/Fines) during manufacturing process and handling.							
Was there any modification in the equipment?							
Is there any emerging point from the review of the Product Development Report which can be correlated to the failure?							

Checkpoint	Obser-vation		Direct root cause		Caustive factor		Remark
	Yes	No	Yes	No	Yes	No	
History of processing equipment used in the product.							
History of variation of process parameters.							
History of change in packaging.							
Is there any emerging point from the review of the same product with modified process in any other market?							
Are the CPPs process ranges defined in the BMR, and are these supported with data							
Review of historical data of input materials.							
Is there any history of failure in this parameter in the past two years?							

Annexure 9: Investigation checklist for content uniformity (liquid – injectable/eye and ear drops)

Checklist is applicable for following dosage forms: Injectable/Eye/Ear Drops

Checkpoint	Obser-vation		Direct root cause		Caustive factor		Remark
	Yes	No	Yes	No	Yes	No	
LEVEL I							
Was there any discrepancy reported during machine start-up process?							
Was the machine speed run at validated speed?							
Was there any mechanical mal functioning?							
Was the filters assembly attached online satisfactory?							
Was the recipe of filling machine (PLC) as per predefined recipe?							
Was there any fluctuation in pressure for pressure dosing vessel?							
Was there any prolonged stoppage?							
Were there any deviations in the process?							
Was there any spillage of material during manufacturing?							
Was there any breakdown in the machine?							
Were the quantities of input material satisfactory?							
Were controls on the manufacturing, hold, transfer and filling stages satisfactory?							
Was filter validation with product available and satisfactory?							
Was compatibility with tubing and other contact parts established?							
Was the process temperature and/or pressure dependent?							

Checkpoint	Obser-vation		Direct root cause		Caustive factor		Remark
	Yes	No	Yes	No	Yes	No	
Was the execution of the batch as per defined parameters (RPM/temperature/ homogenization, etc.) and defined sequence?							
Was the curing of primary packing material (where applicable) done as per defined procedure?							
LEVEL II							
Were the monitoring and measuring devices associated with filling machine in calibrated state?							
Were the physical parameters of the liquid being filled (i.e., viscosity) as per requirement?							
Was the preventive maintenance of equipment done as per schedule?							
Were the primary packing materials used as specified?							
LEVEL III							
Human Errors							
Was there clarity of instructions in procedures?							
Was training adequate?							
Was supervision adequate?							
Was the person experienced?							
Was there any sign of negligence?							
Could fatigue play a role in this failure?							
Any circumstantial trigger, i.e., receiving more than usual work assignment on that day.							
Was the infrastructural support for job delivery adequate, e.g., hardware design? (This is important to consider in case there is any inherent problem with the machine that is responsible for the variant condition).							
LEVEL IV							
Was there any modification in the equipment?							
History of processing equipment used in the product							
Was there any history of failure in this parameter in the past two years?							

Annexure 10: Investigation checklist for foreign particulate matter

Checklist is applicable for following dosage forms: Injectable/Eye/Ear Drops

Checkpoint	Obser-vation		Direct root cause		Caustive factor		Remark
	Yes	No	Yes	No	Yes	No	
LEVEL I							
Was there any discrepancy reported during the machine start-up process?							
Were the washing machine parameters (pressure) within specified range?							
Was the interlock challenge test of washing machine satisfactory?							
Was the compressed air clarity testing found satisfactory?							
Was the washed vial movement covered under LAF prior to depyrogenation tunnel?							
Were replacement frequency, recycle water inspection, vial in-process for clarity and other processes found satisfactory?							
Were the filters attached on washing machine intact condition or were they damaged?							
Were rejection rates of input glass vial or ampoule for particulate matter within the prescribed range?							
Did the review of washing nozzle, blockage, nozzle-centering and other equipment prove satisfactory?							
Was there any physical observation carried out inside the depyrogenation tunnel?							
Was there any Immediate physical damage to HEPA of tunnel, or the intactness as per PAO test, or the filter media sealant?							
Was the pressure differential of tunnel found satisfactory?							
Was the pressure differential of room with respect to tunnel found satisfactory?							

Checkpoint	Obser-vation		Direct root cause		Caustive factor		Remark
	Yes	No	Yes	No	Yes	No	
Were the dead plate of tunnel, tunnel conveyor physical view, and cleaning of conveyor found satisfactory?							
Was HEPA of depyrogenation tunnel intact?							
Was washing cycle of rubber stoppers satisfactory?							
Was the supplier of ready-to-use rubber stopper qualified?							
Was a study available for leachability with rubber stopper and product?							
Was there any deviation in the process?							
Was there any break down in the machine?							
Was the detected foreign particle identified as one of the component of drug product? If yes, then please check the following:							
▪ Was the pH of product within specification?							
▪ Were the quantities of the input material satisfactory?							
Were controls on the manufacturing, hold, transfer and filling stages satisfactory?							
Was the validation of the filter with the product available and satisfactory?							
Was the quality of glass material used satisfactory?							
Was the quality of processing aid satisfactory?							
LEVEL II							
Were the physical parameters of the liquid being filled (viscosity) as per requirement?							
Were the controls on the HEPA life-cycle management on equipment as well as in the area satisfactory?							
Were controls on ORABS satisfactory?							
Was the container closure leach ability and extractable study available?							
Were the controls on gloves (filling line) satisfactory?							
Was the review of online NVPC satisfactory?							

Checkpoint	Obser-vation		Direct root cause		Caustive factor		Remark
	Yes	No	Yes	No	Yes	No	
Was the review of rubber stopper cleaning efficiency satisfactory?							
Were the gowning system, handling of broken objects, removal of vials after any breakage, etc. satisfactory?							
Was the qualification and intervention procedure, e.g., removal of vials after every intervention defined?							
In the case of lyophilized product, specific instructions are required, like handling of partially stoppered vials, loading to lyophilizer, review points of lyophilizer such as filter intactness, leak tests, etc. Were these instructions found satisfactory?							
Was the review of different material introduced in the aseptic processing area carried out and found satisfactory?							
Was the review of flushing gas like nitrogen found satisfactory with respect to particulate matter and integrity of filter?							
Was the review of number of sterilisation cycle found satisfactory?							
Was the physical condition of gasket (tank) and gasket satisfactory?							
Was intactness of filling tank, storage of filling tank, and tank breathing filter integrity satisfactory?							
Was there any possibility of filtered solution contamination during sampling?							
LEVEL III							
Human Errors							
Was there clarity of instructions in procedures?							
Was training adequate?							
Was supervision adequate?							
Was the person experienced?							
Was there any sign of negligence?							
Could fatigue play a role in this failure?							
Any circumstantial trigger i.e., receiving more than usual work assignment on that day.							

Checkpoint	Obser-vation		Direct root cause		Caustive factor		Remark
	Yes	No	Yes	No	Yes	No	
Was the infrastructural support for job delivery adequate, e.g., hardware design? (This is important to consider in case there is any inherent problem with the machine that is responsible for the variant condition).							
LEVEL IV							
Was there any modification in the equipment?							
History of processing equipment used in the product.							
Was there any history of failure in this parameter in the past two years?							

Annexure 11: Investigation checklist for glass particles

Checklist is applicable for following dosage forms: Injectable/Eye/Ear Drops

Checkpoint	Obser-vation		Direct root cause		Caustive factor		Remark
	Yes	No	Yes	No	Yes	No	
LEVEL I							
Was there any discrepancy reported during the machine start-up process?							
Were the washing machine parameters (pressure) with-in specified range?							
Was the interlock challenge test of the washing machine satisfactory?							
Was the washed vial movement covered under LAF prior to depyrogenation tunnel?							
Were the replacement frequency, recycle water inspection, and vial in-process for clarity found satisfactory?							
Was in-process rejection rate for glass particles within the specified range?							
Were the washing machine parameters (Pressure) with in specified range?							
Were the filters attached on washing machine intact or damaged?							
Was the review of washing nozzle, blockage, nozzle centering, etc. satisfactory?							
Was there any physical observation made inside the depyrogenation tunnel?							
Was there any immediate physical damage to HEPA of tunnel?							
Was the intactness as per PAO test satisfactory?							
Were the rejection rates of input glass vial and ampoule for particulate matter within specified range?							
Was there any physical observation inside the de-pyrogenation tunnel?							

Checkpoint	Obser-vation		Direct root cause		Caustive factor		Remark
	Yes	No	Yes	No	Yes	No	
Was HEPA of depyrogenation tunnel intact?							
Were there any deviations in the process?							
Was there any break down in the machine?							
Was quality of glass material used satisfactory?							
LEVEL II							
Was the container leachability study available?							
Were the gowning system, handling of broken objects, removal of vials after any breakage, etc. satisfactory?							
Were the qualification and intervention procedures, like removal of vials after every intervention, defined?							
LEVEL III							
Human Errors							
Was there clarity of instructions in procedures?							
Was training adequate?							
Was supervision adequate?							
Was the person experienced?							
Was there any sign of negligence?							
Could fatigue play a role in this failure?							
Any circumstantial trigger i.e., receiving more than usual work assignment on that day.							
Was the infrastructural support for job delivery adequate, e.g., hardware design? (This is important to consider in case there is any inherent problem with the machine that is responsible for the variant condition).							
LEVEL IV							
Was there any modification in the equipment?							
History of processing equipment used in the product.							
Was there any history of failure in this parameter in the past two years?							

Annexure 12: OOS Investigation – Phase I

OOS Reference No.:		Date of OOS occurrence:	
SECTION A: OOS REPORTING			
Product/Material Name		QC Ref. No.	
Batch No.		Mfg. Date	
Specification No.		Expiry/Retest Date	
Test Name		Test Method No.	
Packing configuration			
Stage of testing *(Select the applicable option)*	☐ Raw material/Packing material ☐ In-process/Intermediate release testing ☐ Finished product ☐ Stability study ☐ Cleaning/Process validation ☐ Hold time Test point: _____ Months Condition: Accelerated/Intermediate/Long Term ☐ Others (specify the stage)		
Details of OOS Test Results (state result and specification limit)			
Details of abnormal observations noted during the testing, if any			
Name of Analyst		Name of Initiator	
		Signature & Date	

OOS Reference No.:			
Was similar OOS reported for this Product/Material earlier? If yes, state the assignable cause identified and corrective/preventive actions taken.			
Name of QA In-charge		**Signature & Date**	

SECTION B: LABORATORY INVESTIGATION

(The list is not exhaustive and it can be extended to other possible errors)

(To be completed by Section In-charge of QC)

Sr. No	Check Parameters	Observations (Yes/No/NA)	Comments
1.	General		
1.1	Any unusual occurence in lab? (e.g., power failure)		
1.2	Was the method discussed with the analyst?		
1.3	Correct analytical method used?		
1.4	Analyst was trained to perform the test?		
1.5	Correct glassware used for dilutions?		
1.6	Glassware was properly cleaned?		
1.7	Instrument used are qualified?		
1.8	Is there any abnormality or malfunction of instrument observed?		
1.9	Instruments used within calibration validity period		
	Instrument Used (Name & ID) / **Calibration Due**		
1.10	Instrument setup & operation as per standard operating procedure?		
1.11	Use of appropriate grade of chemical and reagents within the validity period?		
1.12	Correct normality/molarity of volumetric solutions used?		
	VS used / **Valid up to date** / **Strength**		

OOS Reference No.:					
Sr. No	Check Parameters			Observations (Yes/No/NA)	Comments
2.	**Sample/Standards Preparation**				
2.1	Sample and Standard preparations done as per the test method?				
2.2	Is any weighing error identified?				
2.3	Correct potency of standard used in calculation? Standard is within validity period?				
	Std(s) Used	**Valid up to date**	**Potency**		
2.4	Is the sample properly shaken, sonicated or heated/warmed as per method of analysis?				
2.5	Are the sample/standard dilutions correctly performed as per method of analysis?				
2.6	Any noticeable difference noted in sample/ standard preparation?				
2.7	Are the samples filtered/centrifuged/membrane filtered correctly before introduction into instrument or analysis by classical method?				
2.8	Are samples/standards preparations stored under correct environment/time before analysis?				
2.9	Tablets/granules are ground properly?				
2.10	Any errors in calculation and transcription?				
3.	**Chromatography**				
3.1	Correct Column Used (e.g., column make, Dimension, Particle Size, End capped/Non-End capped, Pore Size, Carbon Loading)?				
3.2	Any leakages observed in the fittings?				
3.3	Correct instrument parameters used (e.g., for HPLC – type of detector, flow rate, oven temp., wavelength, injection volume, sample temp. For GC – type of detector, flow rate, oven temp. injection volume, injection temp, detector temp.)?				
3.4	Mobile phase preparation is as per the method (check for composition, pH, and air bubbles)?				
3.5	System suitability acceptance criteria were met during the analysis?				
3.6	Any unusual or unexpected response observed with standard or test preparations?				

OOS Reference No.:			
Sr. No	Check Parameters	Observations (Yes/No/NA)	Comments
4.	**Dissolution**		
4.1	Correct instrument parameters used (apparatus type, speed, bath temperature, time, medium used, and volume)?		
4.2	Dissolution medium degassed?		
4.3	Sample withdrawn correctly?		
4.4	Correct filter used?		
5.	**Microbiological assay** (Note: Relevant points stated under Sr. nos. shall also be checked, as applicable)		
5.1	Was media from single prepared lot used in the assay?		
5.2	Was there any malfunction or breakdown of incubator?		
5.3	Was temperature of incubator during incubation period as per requirement?		
5.4	Are the zones of inhibition/exhibition clearly defined?		
5.5	Is merging of zones seen?		
5.6	Was zone reading done as per SOP?		
5.7	Is the Zone reader/Vernier calipers in calibrated state?		
6.	**Sample handling/storage (as applicable)**		
6.1	Any noticeable difference in sample appearance?		
6.2	Sample handling was done appropriately?		
6.3	Sample storage was done appropriately?		
7.	**Stability Study**		
7.1	Any malfunction or breakdown of stability chamber?		
7.2	Any failure of utilities (power, water, UPS)?		
7.3	Any deviation in temperature/humidity monitoring?		
7.4	Any damage to pack?		
7.5	Any deviation from SOP for sample pull out time?		
7.6	Were samples, after pull out, stored as per the conditions specified in the SOP?		
7.7	Were samples analyzed within the specified time period as in the SOP?		
7.8	Any change in method of analysis or specification?		

<table>
<tr><th colspan="5">OOS Reference No.:</th></tr>
<tr><th>Sr. No</th><th>Check Parameters</th><th colspan="2">Observations
(Yes/No/NA)</th><th>Comments</th></tr>
<tr><td>8.</td><td>Any other (Specify)</td><td colspan="2"></td><td></td></tr>
<tr><td>9.</td><td colspan="4">Any other findings (review of method validation data, trend data, etc.)</td></tr>
<tr><td rowspan="6">10.</td><td colspan="4">a) Laboratory error identified : Yes/No

If yes, describe the error:

Experimental testing required: (Yes/No/NA)</td></tr>
<tr><td>QC Analyst
(Sign & Date)</td><td colspan="2">QC In-charge of
(Sign & Date)</td><td>QA In-charge of
(Sign & Date)</td></tr>
<tr><td colspan="4">Experimental Testing Details:</td></tr>
<tr><td colspan="4">Test Protocol Reference no.:

Description of the experimental testing:</td></tr>
<tr><td colspan="4">Outcome of experimental testing:</td></tr>
<tr><td colspan="4">Retesting required: Yes/No</td></tr>
<tr><td></td><td colspan="2">QC In-charge of
(Sign & Date)</td><td colspan="2">QA In-charge of
(Sign & Date)</td></tr>
<tr><td></td><td colspan="4">b) In case of error related to sample handling/storage:</td></tr>
<tr><td></td><td colspan="4">Reason for re-sampling:</td></tr>
<tr><td></td><td colspan="4">Sampling SOP Reference No.:</td></tr>
</table>

OOS Reference No.:		
	Re-Sampling plan:	
	Total number of containers	
	Number of containers to be sampled	
	Sample quantity from each container	
	Remarks or Special instructions (if any):	
	QC/QA In-charge (Sign & date)	**Approved by: QA In-charge** (Sign & date)
11.	If error is not concluded in point number 10, identify probable errors (if any): Probable error : Yes/No/Not Applicable Hypothesis testing required : Yes/No/Not Applicable	
	QC In-charge (Sign & date)	**Approved by: QA In-charge of** (Sign & date)
12.	**HYPOTHESIS TESTING**	
	Test Protocol Reference no.: Description of the hypothesis:	
	Outcome of testing:	
	LABORATORY ERROR DENTIFIED (After hypothesis testing): Yes /No	

<table>
<tr><td colspan="4">OOS Reference No.:</td></tr>
<tr><td></td><td colspan="3">If yes, describe the error identified:

Retesting required : Yes/No</td></tr>
<tr><td></td><td colspan="3">If No, proceed for Phase II investigation:</td></tr>
<tr><td></td><td colspan="2">QC In-charge
(Sign & Date)</td><td>Approved by: QA In-charge
(Sign & Date)</td></tr>
<tr><td>13.</td><td colspan="3">a) RETESTING (In case of laboratory error/sampling handling or storage error identified)</td></tr>
<tr><td></td><td colspan="3">Test: _____

Results Of retesting:_____

Specification limit: _____

Complying with Specification: Yes/No ; If No, proceed for laboratory investigation as per point no.14 below.</td></tr>
<tr><td></td><td>QC Analyst
(Sign & Date)</td><td>QC In-charge of
(Sign & Date)</td><td>QA In-charge
(Sign & Date)</td></tr>
<tr><td></td><td colspan="3">b) Retesting (In case of Raw/Packing material failure where no cause is identified):

Test: .....</td></tr>
<tr><td></td><td>Analyst I</td><td>Analyst II</td><td rowspan="4">Average:_____

% RSD:_____

Specification Limit: _____.</td></tr>
<tr><td></td><td>1.</td><td>1.</td></tr>
<tr><td></td><td>2.</td><td>2.</td></tr>
<tr><td></td><td>3.</td><td>3.</td></tr>
<tr><td>14.</td><td colspan="3">LABORATORY INVESTIGATION

(The list is not exhaustive and it can be extended to other possible errors)

(To be completed by Section In-charge of QC)</td></tr>
</table>

Sr. No	Check Parameters			Observations (Yes/No/NA)	Comments
14.1	**General**				
OOS Reference No.					
14.1.1	Any unusual happening in lab? (e.g., power failure)				
14.1.2	Was the method discussed with the analyst?				
14.1.3	Correct analytical method used?				
14.1.4	Analyst was trained to perform the test?				
14.1.5	Correct glassware used for dilutions?				
14.1.6	Glassware was properly cleaned?				
14.1.7	Instrument used are qualified?				
14.1.8	Is there any abnormality or malfunction of instrument observed?				
14.1.9	Instruments used within calibration validity period				
	Instrument Used (Name & ID)		**Calibration Due**		
14.1.10	Instrument setup and operation as per standard operating procedure?				
14.1.11	Use of appropriate grade of chemical and reagents within the validity period?				
14.1.12	Correct normality/molarity of volumetric solutions used?				
	VS used	**Valid up to date**	**Strength**		
14.2	**Sample/Standards Preparation**				
14.2.1	Sample and Standard preparations done as per the test method?				
14.2.2	Is any weighing error identified?				
14.2.3	Correct potency of standard used in calculation? Standard is within validity period?				
	Std(s) Used	**Valid up to date**	**Potency**		
14.2.4	Is the sample properly shaken, sonicated or heated/ warmed as per method of analysis?				

OOS Reference No.			
Sr. No	Check Parameters	Observations (Yes/No/NA)	Comments
14.2.5	Are the sample/standard dilutions correctly performed as per method of analysis?		
14.2.6	Any noticeable difference noted in sample/standard preparation?		
14.2.7	Are the samples filtered/centrifuged/membrane filtered correctly before introduction into instrument of analysis by classical method?		
14.2.8	Are samples/standards preparations stored under correct environment/time before analysis?		
14.2.9	Tablets/granules are ground properly?		
14.2.10	Any errors in calculation and transcription?		
14.3	**Chromatography**		
14.3.1	Correct Column Used (e.g., column make, Dimension, Particle Size, End capped/Non-End capped, Pore Size, Carbon Loading)?		
14.3.2	Any leakages observed in the fittings?		
14.3.3	Correct instrument parameters used (e.g., for HPLC – type of detector, flow rate, oven temp., wavelength, injection volume, sample temp. For GC – type of detector, flow rate, oven temp., injection volume, injection temp, detector temp.)?		
14.3.4	Mobile phase preparation is as per the method (check for composition, pH, air bubbles)?		
14.3.5	System suitability acceptance criteria were met during the analysis?		
14.3.5	Any unusual or unexpected response observed with standard or test preparations?		
14.4	**Dissolution**		
14.4.1	Correct instrument parameters used (apparatus type, speed, bath temperature, time, medium used, volume)?		
14.4.2	Dissolution medium degassed?		
14.4.3	Sample withdrawn correctly?		
14.4.4	Correct filter used?		
14.5	**Microbiological Assay** (Note: Relevant points stated under Sr. nos. shall also be checked, as applicable)		
14.5.1	Was media from single prepared lot used in the assay?		
14.5.2	Was there any malfunction or breakdown of incubator?		
14.5.3	Was temperature of incubator during incubation period as per requirement?		
14.5.4	Are the zones of inhibition/exhibition clearly defined?		
14.5.5	Is merging of zones seen?		
14.5.6	Was zone reading done as per SOP?		
14.5.7	Is the Zone reader/Vernier calipers in calibrated state?		

OOS Reference No.			
Sr. No	Check Parameters	Observations (Yes/No/NA)	Comments
14.6	**Sample handling/storage (As applicable)**		
14.6.1	Any noticeable difference in sample appearance?		
14.6.2	Sample handling was done appropriately?		
14.6.3	Sample storage was done appropriately?		
14.7	**Stability Study**		
14.7.1	Any malfunction or breakdown of stability chamber?		
14.7.2	Any failure of utilities (power, water, UPS)?		
14.7.3	Any deviation in temperature/humidity monitoring?		
14.7.4	Any damage to pack?		
14.7.5	Any deviation from SOP for sample pull out time?		
14.7.6	Were samples, after pull out, stored as per the conditions specified in the SOP?		
14.7.7	Were samples analyzed within the specified time period as in the SOP?		
14.7.8	Any change in method of analysis or specification?		
15.	**Any other (Specify)**		
16.	**Any other findings (review of method validation data, trend data etc.):**		

OOS Reference No.			
17.	**Laboratory error identified:** Yes/No (Select the option below) ☐ Instrument error ☐ Method/Specification error ☐ Sample storage ☐ Input material ☐ Others (specify): ☐ Analyst error ▪ Was the analyst involved in same error during the last 12 months period ☐ Yes/No (if Yes specify the error): Previous analyst qualification date: ▪ If the analyst involved in this OOS had a same error during past 12 months, the analyst will undergo the "Analyst Re-qualification". Describe the error in detail: If No, proceed for Phase II investigation:		
	QC Analyst (Sign & Date)	**QC In-charge of** (Sign & Date)	**QA In-charge of** (Sign & Date)
	Retesting Required: Yes / No		
	QC In-charge of (Sign & Date)	**QA In-charge of** (Sign & Date)	

OOS Reference No.:			
18.	RETESTING *(In case of laboratory error/sampling handling or storage error is identified)*		
	Test: _____ Results of retesting:_____ Specification limit: _____ **Complying with Specification:** Yes/No; If no proceed for Phase II investigation.		
	QC Analyst (Sign & Date)	**QC In-charge of** (Sign & Date)	**QA In-charge** (Sign & Date)
19.	**IMPACT ASSESSMENT**		
	QC In-charge (Sign & Date)	**QA In-charge** (Sign & Date)	

OOS Reference No.:		
20.	SUMMARY AND CONCLUSION	
21.	☐ OOS Valid ☐ OOS Invalid ☐ Investigation inconclusive	
	CAPA (Corrective Action and Preventive Action) taken (if applicable) :	
	QC In-charge (Sign & Date)	**QA In-charge** (Sign & Date)
OOS Reference No.:		
	LIST OF ATTACHMENTS:	

Annexure 13: RACI Matrix

Key steps in Investigation & RACI Matrix - Laboratory				
Step	**Responsibility**	**Accountability**	**Consulting**	**Information**
Issue Identification/ Surfacing	Analyst	Section Head	-	QA
Investigation	QA & QC	QC Head	ARD/SME	SQA/SH
Root Cause	QA & QC	QA	ARD/SME	SQA/SH
Risk Assessment/ Impact Assessment	QA & QC	QA	ARD/SME	CQA/COH/ RA/CEO*
CAPA Identification	QA & QC	QA	ARD/SME	SQA/SH
CAPA Implementation	QC	QC Head	ARD/SME	COH/SQA/SH/ CEO*
CAPA Effectiveness	QC	QA	-	SQA/SH

SME - Subject Matter Expert; ARD - Analytical R&D; CFT - Cross Functional Team; IE - Instrument Engineer; SQA - Site Quality Head; SH - Site Head;
COH - Corporate Operations Head; RA - Regulatory Affairs;
** if applicable in case of batch rejection/recall/Over due CAPA*

Reporting
Direct Reporting
Monthly Report/Review
Quality Council/Management Review Meeting

Key steps in Investigation & RACI Matrix - Manufacturing				
Step	**Responsibility**	**Accountability**	**Consulting**	**Information**
Issue Identification/ Surfacing	Doer/Observer	IRM	-	QA
Investigation	QA/Concerned Function	QA	SME/CFT	SQA/SH
Root Cause	QA/Concerned Function	QA	SME/CFT	SQA/SH
Risk Assessment/ Impact Assessment	CFT	QA	SME	CQA/COH/ RA/CEO*
CAPA Identification	CFT	QA	SME	COH/SQA/SH
CAPA Implementation	Concerned Function	QA	SME	COH/SQA/SH/ CEO*
CAPA Effectiveness	QA	QA	Concerned Function	COH/SQA/SH

*** if applicable in case of batch rejection/recall/Over due CAPA*

Reporting
Direct Reporting
Monthly Report/Review
Quality Council/Management Review Meeting

(This page is intentionally left blank)

Published by:
Indian Pharmaceutical Alliance
A-205 Sangam
14B S V Road, Santacruz (W)
Mumbai 400 054 India
E-mail: dgshah@vision-india.com