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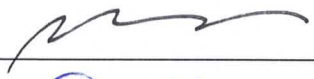
	Name	Date	Signature
Owner	**Sijin Guo**	**20March2025**	
Operation Management	**Baozhong Zhao**	**20March2025**	
Quality Assurance	**Xibo Li**	**20March2025**	

Changes from previous version:

Section	Summary of Changes	Change Control Number
ALL	1. New document	

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1. PURPOSE

The purpose of this SOP is to provide guidance and a framework that facilitates efficient and standardized approach in performing a Root Cause Investigation, including establishing a format for a Root Cause Analysis (RCA) report.

2. SCOPE

This SOP applies to cGMP operations and systems in which the need for a Root Cause investigation has been established, using the guidelines in this procedure.

3. INTERNAL REFERENCES

Document ID	Title
QUA001	Quality Manual
QUA004	Quality Policy
QUA010	Corrective Action and Preventative Action Policy

4. EXTERNAL REFERENCES

Document ID	Title
ICH Q7 (API)	Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients
ICH Q9	Quality Risk Management
ICH Q10	Pharmaceutical Quality System
ISO 9001:2015	Quality Management System Requirements
21 CFR Part 211	Current Good Manufacturing Practice for Finished Pharmaceuticals

5. RESPONSIBILITIES

Job Function and/or Department	Responsibility
All employee	It is the responsibility of all employees, including temporary employees and consultants, involved in recording, or reviewing, information on documents, to provide clear and consistent details on record keeping and follow good documentation practices to support the quality of work.
Root Cause Investigator	It is the responsibility of the personnel assigned to manage and document the root cause investigation as defined in the procedure.
Quality Assurance	It is the responsibility of Quality Assurance to track and monitor the progress of the Root Cause Investigation events and to facilitate all Root Cause Investigations.
Operation Management	It is the responsibility of all department heads to provide resources and personnel to support Root Cause Investigations.

6. DEFINITION

Term	Definition
Root Cause Initiator	Individual who reports the issue and provides the initial information for the investigation.
Root Cause Investigator	Personnel assigned to manage and conduct the root cause investigation: Schedules the investigation meeting with the proper departmental representative(s) who possess the expertise to examine the problem. Author for Investigation and Root Cause Analysis reports. Determines the most appropriate tool(s) and format to use in the analysis and will prepare the appropriate templates, if required. Coordinates the activities required for performing the Root Cause Analysis and ensures that the true root cause is appropriately identified and documented. Develops an appropriate Effectiveness Review Plan. Updates the final Investigation and Root Cause Analysis Report(s), prior to submission to Quality Assurance.
Team Members	Contributes to brainstorming, idea sharing, fact finding, data analysis, and ultimately identifying the root cause of the problem.
Symptom	A sign of disorder that can often be a cause within a chain of events but is not the root cause of an event.
First Level Causes	Causes that directly lead to a problem.
Higher Level Causes	Causes that lead to the First level causes.

Term	Definition
Root Cause	The fundamental, or underlying reason for a symptom, problem, or event. Root Causes are those over which management has control.
Parking Lot	A tool used to document issues that are outside the scope of the effort or activity and when used properly should include the out-of-scope inputs, issues and opportunities from all participants. Parking lot items should be documented in meeting minutes for future consideration.
Fishbone Diagram (or Cause & Effect diagram)	Graphical tools are used to explore and analyze possible causes and their relationship to the effect or problem being studied.
Subject Matter Experts (SMEs)	Individuals having expertise in the areas under analysis – employees or outside experts as required.

7. PROCEDURE

7.1. Recommended Materials and Equipment

The Following materials are recommended for use when performing the root cause investigation:

- Easel size Post-it pad Post-it notes
- Markers (Black or Blue preferred)
- Fishbone Checklist (6-M)
- Process Map poster(s) – if required
- The conference room is large enough to accommodate the Root Cause Analysis team and enough wall space to place (7) easel size stick pad notes (for large scale analyses)

7.2. Triggers for Root Cause Investigations

In general, a Root Cause Investigation should be considered for application to events in which a causative reason is not definitively understood. The program is applied for procedural and compliance events that may deviate from the approved procedure or in situations in which the result is out of trend or out of specification.

Issues needing investigation vary in size, criticality, and complexity; therefore, the requirements for the level (complexity) of Root Cause Analysis will vary as well.

7.3. Initiating an investigation and Root Cause Analysis

7.3.1. Generating an RCA

An investigation and root cause analysis determined necessary after description of the problem and consultation with Quality Assurance.

7.3.2. Describing the problem

The initiator is to provide all pertinent information (description of the problem) to the RCA investigator (if not the same person).

7.3.3. The description of the problem shall include the following:

1. What happened?
2. When did the event occur?
3. When was it discovered?
4. Who was involved? (reference job title only, not personal name)
5. Where did it happen?
6. What were the consequences?
7. Is there data available for analysis?
8. Has the problem been contained?

7.4. Investigation and Root Cause Analysis Meeting

The Root Cause Analysis meeting is required to be performed within five business days from the initiation

of the quality event.

The Root Cause investigator identifies the cross-functional team representatives who possess the expertise required to examine the problem and then schedules the initial meeting.

Some investigations may require additional meetings, such as lab experimentation, testing, vendor documentation. Etc. may be required to identify the root cause.

7.5. Actions during meeting

During the investigation and Root Cause Analysis meeting the RCA investigator will:

- Lead the team to define the problem statement, the impact assessment, potential corrective/preventive action plans, and the effectiveness review plan
- Work with the team to gather data to define the problem

7.6. Defining the Problem

The RCA investigator will work with the team to gather data to define the problem.

The problem statement (**TABLE 1**) should be clearly defined and short. For example, Material failed to meet specification for moisture, Drum of XYZ leaked onto Solution Preparation Floor.

TABLE 1: PROBLEM STATEMENT WORKSHEET

Problem Definition: (Re)define the problem using Is/Is Not. Definition should answer who, what, when, where, how much.	
Is: (observation)	Is Not: (comparison)
What?	**What?**
What is the object/process/ product affected? What exactly is wrong? What defects are observable?	What similar things could be affected but are not? What else could be wrong but are not? What other defects could be observable but are not?
Who?	**Who?**
Who is affected? Who is impacted? Who is involved?	Who could be affected but not affected? Who isn't involved?
Where?	**Where?**
Where do you see the problem occur? Consider: where in the organization, physical building location, on the product/object, in process/system.	Where else could you expect to see this problem occur?
When?	**When?**
When was the problem first seen? When in process flow is the problem occurring?	When could the problem have occurred? When in the process could the problem occur (earlier/later)?
How Much?	**How Much?**
How often? How many products? Is there a trend?	How often could it have been impacted? What trend(s) might you have expected to see but don't?

7.7. Identify Possible Causes

Once the problem statement has been properly identified, the next step is to identify all possible causal factors to determine if the causes of the problem are known or unknown.

7.7.1. Known Causes:

Document the known causes to be analyzed in the subsequent steps.

7.7.2. Unknown Causes:

The team will need to brainstorm the possible causes of the problem. This can best be done by using the Fishbone or Cause-and-Effect method (**FIGURE 1**).

The 6-M Checklist in (**TABLE 2**) is useful for guiding the possible cause idea generation process.

FIGURE 1: FISHBONE DIAGRAM

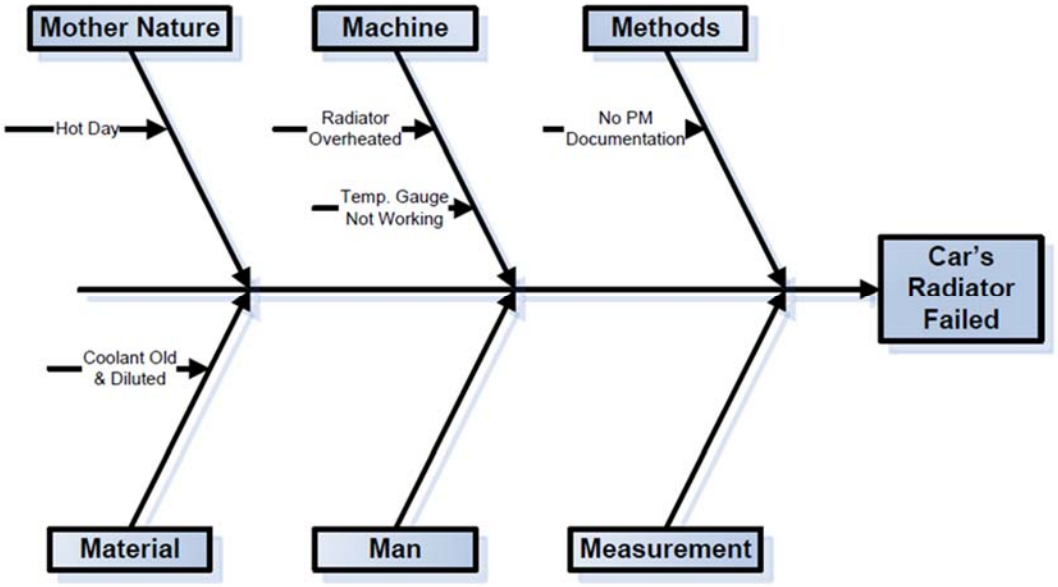


TABLE 2: 6-M CHECKLIST

Man (Operator)	Machine (Equipment & Facilities)
• Does operator follow standards (SOP and/or TM)? • Is operator work efficiency acceptable? • Is operator problem-conscious? • Is operator responsible? Accountable? • Is operator qualified? • Is operator experienced? • Is operator assigned to the right job? • Is operator willing to improve? • Does operator maintain good working relations? • Is operator healthy?	• Does it meet production requirements? • Does it meet process capabilities? • Is the inspection adequate? • Is the maintenance, PM adequate? • Is operation often stopped due to mechanical trouble? • Does it make any unusual noises? • Is the layout adequate? • Are there enough machines? • Is everything in good working order?
Material	**Method**
• Are there any mistakes in volume? • Are there any mistakes in grade? • Are there any mistakes in the brand name? • Are there impurities mixed in? • Is the inventory level adequate? • Is there any waste in material? • Is the handling adequate? • Is the quality standard adequate? • Was there a change in lot#? • Is there any visible change in material	• Are the work standards (SOP and/or TM) adequate? • Are they documented? • Has the operator been trained in the method? • Is it a safe method/SOP • Is it a robust method/SOP? • Is it an efficient method/SOP? • Is the sequence of work adequate? • Is the set-up adequate?
Measurement	**Mother Nature (Environment)**

• Can the accuracy of the instrument be confirmed? • Is the equipment/instrument calibrated? • If development work (i.e. D.O.E.) has been performed, does the measurement data make sense?	• Are the environmental conditions (temperature & humidity) adequate? • Are the lighting and ventilation adequate?

7.8. Capturing input

The members of the investigation team use post-it notes and markers and write down their possible cause ideas and place them on the most appropriate branches or sheets of the fishbone diagram.

It is critical that all team members input be captured and recorded.

Some of the potential Root Causes may not at first seem applicable and focus on the specific problem. These potential causes may be broader scoped and cross-functional nature.

7.9. Summarize the brainstorming input

Once the possible cause brainstorming input is complete, the Root Cause Investigator will read aloud all the inputs to the team to check for understanding and proper categorization among the 6-M. Team evaluation or comments on appropriateness should be delayed until later analysis to ensure that no ideas are eliminated prematurely.

Some inputs may be moved to other fishbone branches as deemed appropriate by the team. Input that represents the same thoughts is to be captured as one that best summarizes that idea.

7.10. Prioritize the potential causes

Based on the quantity of potential root causes identified through the brainstorming process, detailed examination of ALL potential causes may be time prohibitive and inefficient.

The team can prioritize the MOST LIKELY causes by using multi-voting to identify the top possible causes. All potential causes of receiving votes should be examined in detail.

7.11. Examine the causes

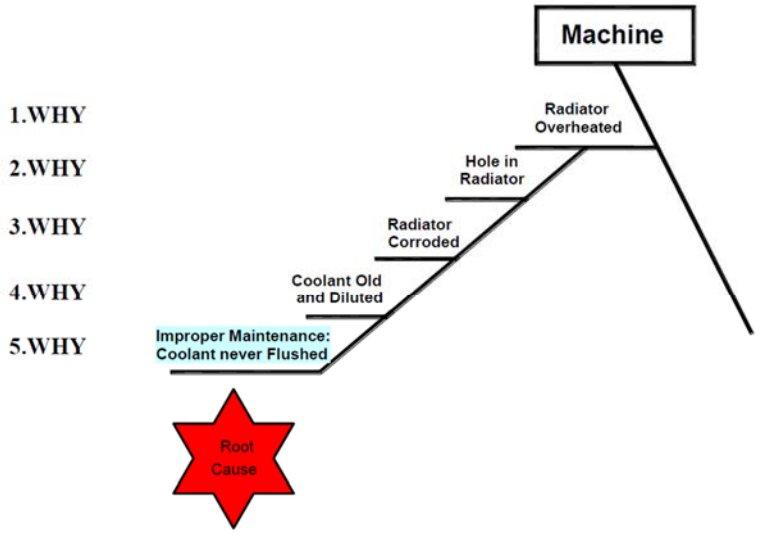
The team will next examine each of possible causes, identified via the multi-voting/prioritization process, utilizing the 5 Whys approach to help drill down through the symptoms to identify the potential root cause of the problem.

7.11.1. 5 Whys example (**FIGURE 2**)

Example: Why did the Radiator Overheat?

- 1st Why > Why did the radiator overheat? > There was a hole in the radiator.
- 2nd Why > Why was there a hole in the radiator? > The Radiator was corroded.
- 3rd Why > Why did the radiator corrode? > The coolant was old & diluted.
- 4th Why > Why was the coolant old & diluted? > The Cooling system was not maintained.
- 5th Why > Why wasn't the cooling system maintained? > There was no documentation that recommended this type of maintenance.

FIGURE 1: USE FIVE WHY TO IDENTIFY ROOT CAUSE



NOTE: For significant impact root causes associated with operator or human error, drill down further by answering the questions that focus on the areas of Direction, Competence, Opportunity, and Motivation (**Error! Reference source not found.Error! Reference source not found.**).

TABLE 3: HUMAN ERROR ROOT CAUSE ANALYSIS

Focus Area	Investigation	Summary of Finding	Conclusions
Direction	1. Were expectations and/or instructions communicated to the employee(s)? 2. How were these expectations/instructions communicated? 3. Were the expectations/instructions provided in a clear, orderly and logical manner? 4. Were the instructions given in this case consistent with direction given in the past for the same tasks and/or procedures? 5. Did the employee(s) raise any concerns or questions regarding direction given to accomplish this task? 6. Is there any additional information indicating direction was the root cause or contributed to this event?		
Competence	1. Did the employee(s) have the technical and/or functional skills and knowledge to perform the work correctly? 2. If yes, how is having these skills and knowledge documented and/or substantiated? 3. If no, did the employee(s) communicate that they did not have the skills and knowledge necessary to complete the task? 4. Has the employee demonstrated competency by performing the task successfully? 5. Is there any additional information indicating competence was the root cause or contributed to this event?		

Focus Area	Investigation	Summary of Finding	Conclusions
Opportunity	1. Did the employee(s) assigned to complete the task have the resources needed to perform or accomplish the task? Assess each of the following: a. Tools b. Material(s) c. Information/procedures d. Time e. Access f. Authority 2. If no, what resource(s) was/were not provided and why? 3. Was the function, system, or procedure too complex for an employee to routinely perform without error? 4. Were there simultaneous tasks or expectations of the employee(s) assigned such that the employee could not successfully complete each task? 5. Is there any additional information indicating opportunity was the root cause or contributed to this event? For example: Was the facility and environment appropriate to rule out other potential root causes?		

7.12. Reaching consensus and selecting the most likely root causes.

Once all the possible causes have been drilled down and examined the team will select the most likely candidates as the root cause and contributing causes for the problem. The consensus reaching process can be done be utilizing multi-voting

7.13. Selecting root cause and/or contributing causes

Once the data has been analysed the team will ascertain which, if any, of the root cause candidates have been verified. If verified, the team will move on to the solution's determination. If the data does not support the chosen causes as being root cause the team should return to the list of all possible causes or brainstorm to identify other candidates. If during the examination causes which may not be identified as the root cause but may have significantly contributed to the occurring are identified, these contributing causes should be considered during the solution determination phase.

7.14. Developing the Root Cause Solution Plan

Once the team has reached consensus on which possible causes are the root cause(s) and contributing causes and have verified these based on the supporting data and detailed analysis (where applicable), then the team will develop corrective and preventive action plans to resolve the problem.

The Root Cause Analysis corrective action plan may include a follow-up effectiveness review plan to ensure that the problem has been contained, and the selected possible Root Cause(s) were the true Root Causes of the problem.

Corrective actions are managed through the CAPA system. The proposed Corrective Actions/Preventive Actions (CAPA) are documented in the accompanying quality event investigation report (see section **Error! Reference source not found.**).

7.15. Documenting the RCA

Not all RCA tools work well for all situations and with investigations with significant impact there may be an obvious root cause that can be confirmed using very simple techniques.