Table of Contents

1.0 Purpose

The purpose of this procedure is to define the processes within the Quality Management System related to Corrective and Preventative Actions (CAPA). This system is used to collect and analyze information, investigate quality and product problems, and identify and execute effective corrective and/or preventive actions that address the root cause of the problem.

2.0 Scope

This procedure applies to the Biopharmaceutical Development Program (BDP) at the Frederick National Laboratory for Cancer Research when investigating quality events and identifying CAPA.

3.0 Authority and Responsibility

3.1 QA Management

- Defines this procedure.
- Approves CAPA
- Participates in the Management Review of CAPA

3.2 Quality Assurance

- Reviews trends associated with quality systems
- Initiates an Issue Review that may result in a CAPA
- Investigates quality events
- Leads the root cause investigation
- Determines the need for CAPA from other quality systems

- Initiates a CAPA
- Tracks and trend all action items
- Reports to management
- Evaluates the effectiveness of action items

3.3 BDP Management

- Provides information in support of the investigation
- Participates in the root cause investigations
- Approves CAPA
- Participates in the management review of CAPA
- Approves completed action items

3.4 BDP Staff

- Provides information in support of a CAPA investigation
- Performs Action Items as assigned

4.0 Definitions

Correction or Containment: Action to eliminate the symptom of a problem.

Corrective Actions: An action that is performed to eliminate the root cause of a deviation, issue, or undesirable situation to prevent its recurrence.

CAPA Program: A quality system that includes a structured approach to any quality event and implemented corrective and preventive actions. Actions from the CAPA are reserved for quality events that are systemic, pervasive or that requires long term actions, significant investigation and/ or system related corrective actions. CAPA actions, also identified as action items can be containment actions, corrections, corrective actions or preventative actions

Preventative Actions: An action that is preformed to prevent the occurrence of an undesirable situation.

Product Impact: The effect or possible effect of the deviation on a product's safety, identity, strength, quality, or purity. Product impact can be positive (improving product quality) or negative (decreasing product quality).

Quality Events: A deviation, out-of-specification, environmental monitoring or engineering event, or other issue that occurs and is evaluated for product impact.

Root Cause: The factor that caused or set in motion the cause and effective reaction that led to the deviation/Quality Event. Corrective Actions address and eliminate this factor eliminating recurrence.

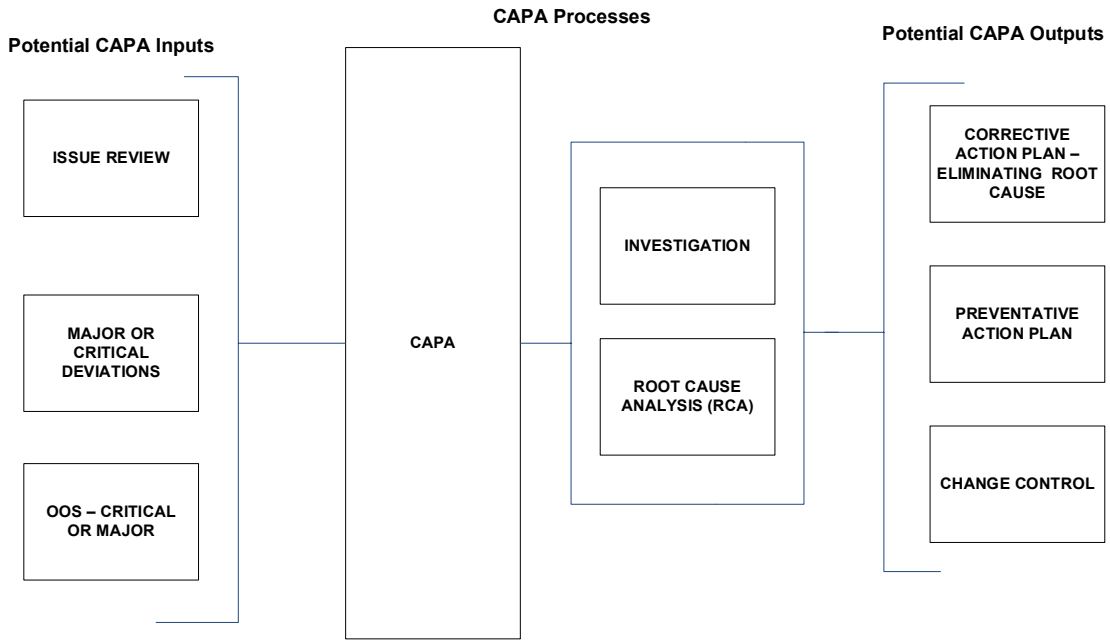
5.0 Overview

In general, the CAPA form in MasterControl is reserved for issues that are more serious in nature, widespread or are related to critical product problems. The CAPA form is used in the Quality Management System to investigate and implement actions. For the purposes of this SOP, CAPA refers to the use of the CAPA form in the eQMS and are those events that that are of increased risk. These could arise from a variety of quality systems (e.g., major or critical deviations, etc.). The CAPA form formalizes the root cause investigation, team, and the investigation record.

BDP's quality management systems are structured to identify and correct the root cause of a quality event. The level of documentation and investigation is proportionate to the level of risk associated with a quality event. Not all quality events require a CAPA form.

Below shows ***potential*** inputs to the CAPA process.

CAPA SYSTEM



A structured approach is used in the investigation process and the root cause analysis when a quality the event is identified. The assessment included in the CAPA form includes an investigation that examines the facts, the frequency of occurrence and evaluates the risk. Correction, containment, and corrective and preventative actions result from all quality events and are identified in the QMS as action items. Most of these action items are implemented within the quality system where they are identified.

6.0 CAPA Form

6.1 CAPA Numbering

The eQMS system automatically assigns an CAPA form number to any CAPA launched. With the following format:

CAPA-YYYY-NNNN

CAPA= identifies the form as a CAPA investigation

YYYY = the year the deviation was launched

NNNN= consecutive numbering starting at 0001

6.2 Current Step

The current step is always identified on the form header. As the form moves through the workflow, the current step is identified for the user.

6.3 Step Due Date

The due dates are calculated by the system for each step based on predefined times. If due dates cannot be met, the user can request and extension by choosing the  icon. See Section 6.16 for details regarding extension requests.

6.4 CAPA Title

Enter a title that is relevant to the event. This field is editable at other steps.

6.5 Workflow

Below represents the issue workflow

For specifics about each of the steps in the workflow:

- See Section 6.8 for Root Cause Investigation.
- See Section 6.9 for CAPA Plan.
- See Section 6.10 for Plan Approval.
- See Section 6.11 for Plan Implementation.
- See Section 6.13 for Effectiveness Checks.
- See Section 6.14 for Management Review.
- See Section 6.15 for Final QA Review.

6.6 General Information

- All required fields for each step are indicated with a red Asterix (*).
- During each step, the form can be saved and returned to later

- If required information is not complete, the system will not allow the user to sign off on the step. Additional required information is highlighted in red.
- If additional information is needed, a user may sign off on each section as Work in Progress to complete the section later.
- QA modifies each of the steps in the workflow to ensure the correct review and approval process.
- Users can [Save] or Sign off as [Work in Progress] to save. If multiple users are collaborating to complete a form at any step, its best to sign off as [Work in Progress] to unlock the form for others to input data.
- Users sign off as [Data Complete] when the current step is completed and the form can be moved to the next step.

6.7 Issue Summary Tab

6.7.1 Responsibility for Completion of the Issue Summary Tab

As the initiator of the CAPA, Quality Assurance is responsible for the completion of the information on this Tab of the form.

6.7.2 Event Information

Upon initiation of a CAPA Investigation, complete the event information. If this CAPA is transferred from another Quality System (Issue review or Deviation) relevant details are transferred from the previous forms by the system.

- **Originating Department:** This identifies the department in which the issue originates. If the issue is a systemic quality issue, this should be identified as Quality Assurance.
- **Source:** This categorizes the system that identified the issue. This includes but is not limited to:
  - Audit
  - Customer Complaint
  - Deviation
  - Event Report
  - Non-Conformance
  - OOS/OOT
  - Issue Review
  - Other
- **Other Source :** Either provides additional information when the source identified is other or provides additional information about the source. (e.g. Internal Audit MMIC 2019, or External Audit by XYZ Audit team June 23-25 2020.)

6.7.3 Provide Event Specifics

- What, Where, When, Weight or Scope of Impact, and Who
- Patient or Donor ID (if applicable)

Complete the questions regarding the quality event.

Questions Yes or No required

- *Does the issue involve or impact the development, manufacture, or distribution of a product?* If **YES**, then the product information and the quantity is required. Include units with the product quantity. Manufacturing of a product includes the QC tests that are performed to quantify or qualify the product.
- *Does the issue involve or impact a project?* If **YES**, then choose from the list of projects.
- *Does the issue involve or impact a process?* If **YES**, then choose from the list of processes. A description will auto populate. If not on the list, you may free type the process and description. Include the MPR, MPR Revision and Step number.
- *Does the issue involve or impact in-use equipment?* If **YES**, then include the Equipment ID Number (MEF Number), and the equipment description.
- *Does the issue involve or impact a supplier or vendor?* If **YES**, then select the vendor or vendors that are involved or impacted.

6.7.4 Event Category

The category is a pre-defined drop-down list created to group related issue types. Sources include but are not limited to:

- Quality
- Environmental
- Health and Safety
- Resource (supply chain or human resource)

6.7.5 Preliminary Investigation Summary

Information from previous forms, (e.g., deviation or issue review) may pre-populate these fields. Fields can be updated as needed.

- **Issue Statement:** This is carried over from any previous deviation or issue review form. The issue statement concisely defines the event or events so that the significance can be understood by those reviewing the CAPA.

- **Issue Category:** The issue category is a pre-defined drop-down list created to group related issue types.
- **Preliminary Investigation Summary:** Clearly and concisely summarizes the facts of the investigation.
- **Preliminary Investigation Results:** This section should detail the results of the investigation. Conclusions reached should be included.
- **Preliminary Identified Cause:** This is a predetermined list identifying the cause of the issue. This is used for trending purposes. Choose from
  - Machine
  - Man
  - Materials
  - Measurement
  - Method
  - Mother Nature (Environment)
- **Impacted Department** Select the departments that are impacted by the CAPA. For example, if this is a review of a recurring trend from the internal audit process, select all departments in which the trend has been identified.
- Attach any Supporting Materials as attachments, or if the supporting materials are part of the eQMS system, these can be linked. Examples of supporting materials may include pictures of non-conforming product, emails detailing a customer complaint or trend analysis.

6.8 Root Cause Investigation Tab

6.8.1 Responsibility for the Root Cause Investigation Tab

The Investigation Team includes representation from all departments impacted by the CAPA and is led by QA. The team completes the information on this tab, and will sign off as information is completed to move it to the next step.

6.8.2 Investigation Team Members

List all Areas and Team Members represented.

6.8.3 Investigation Method

The system defines two of the most commonly used methods, Comparative Analysis and the 5 Whys. The Investigation Team can use either of these methods or choose another method.

6.8.3.1 Comparative Analysis

This method is often called the is/is not method. The team walks through a series of questions provided by the system. The team documents where they did and did not see the problem occur, when it occurred, and further describes the scope of the problem. The likely causes and tests to verify this as the cause are included in the summary.

6.8.3.2 5 Whys

This method is often used to troubleshoot simple to moderately difficult problems. The core idea of the 5 Whys system is how it sounds. The team is guided though the exercise by asking pointed questions, all starting with why? In this method, the questions are added as well as the answers.

6.8.3.3 Other Method

If another method of root cause analysis is chosen, the team must document the method used and include a record of how the root cause was determined by including the information in the Supporting Materials - Attachments. Other methods may include but are not limited to Failure Mode and Effects Analysis, Cause and Effect Diagrams, Pareto Charts, Fault Trees or Process Analysis. It may be appropriate to use more than one method.

6.8.4 Root Cause Category & Subcategory

The results from the root cause analysis are recorded by category and sub-category.

- Machine
- Man
- Materials
- Measurement
- Method
- Mother Nature (Environment)

There may be multiple root causes identified. Choose the one that had the greatest impact or that poses the most risk as the primary root cause. Any actions assigned should prioritize the elimination of this root cause. The subcategories auto-populate from the category chosen and provide the CAPA owner with additional information in developing action items.

6.8.5 Root Cause Description

In the root cause description, include a description of the primary root cause and any other causes determined during the Root Cause Analysis. During the CAPA Plan Step, the CAPA owner assigns action items that must address the Root Cause.

6.8.6 CAPA Owner Assignment

After completion of the root cause analysis, the CAPA is assigned to a department and CAPA plan owner. The CAPA is also assigned a CAPA Category for trending purposes.

6.8.7 Everyone in this step is required to sign off as [Data Complete] to move the CAPA to the next step.

6.9 CAPA Plan and Implementation Tab – The Plan

A CAPA Plan is developed by the CAPA Plan Owner. This section describes the sub tabs under CAPA Plan and Implementation. In each section below the CAPA Plan Owner completes the fields and outlines the plans to address the root cause identified.

6.9.1 Corrective Action Plan Sub Tab

6.9.1.1 Corrective Action Plan and Planned effectiveness checks are outlined. The corrective action plan details the actions that are necessary to address the root cause of the CAPA. Planned actions may be long term actions (e.g. the purchase of capital equipment) or shorter term actions (e.g. all staff training or the inclusion of another control step in the process).

6.9.1.2 For a CAPA that impacts suppliers answer the questions listed regarding the status of Supplier acceptance. Examples of a supplier related CAPA would include the data integrity of testing results or labels that were no longer adhering to the final product vials.

6.9.1.3 Planned effectiveness checks are outlined. These are action items assigned to evaluate the success of the CAPA plan. Effectiveness checks should include a notification for review during an internal audit but may also include verification or validation, monitoring activities done by the departments. Effectiveness checks should include minimum test requirements. For example, an effectiveness checks for an EM investigation may include a monitoring period of 3 months, 3 lots, or other end points.

6.9.1.4 Answer the question if the Action Plan will eliminate or diminish the root cause.

6.9.1.5 Corrective Action Plan/ Implementation Action Items are detailed for the approvers to review and approve. The information includes the Task Type (e.g. corrective, containment, or preventative), a brief description of that the assignee will need to do, the task assignee and a realistic due date.

Action Items are **not** launched (Task Reference assigned) until **after** the plan has been approved.

6.9.2 Preventative Action Plan Sub Tab

If, as part of the root cause analysis, other undesirable situations are identified, a preventative action plan is also launched. For example if the root cause from vials breaking during the filling process is damage to the equipment, the corrective action would be to repair the equipment, but the preventative action would be to implement periodic checks of the equipment to prevent the damage to the equipment. Alternately an example of a labels purchased by one supplier no longer sticking to final product vials, a preventative action may be to monitor the labels of the second source used as well.

6.9.2.1 Preventative Action Plan and Planned effectiveness checks are outlined. The corrective action plan details the actions that are necessary to address the root cause of the CAPA. Planned actions may be long term actions (e.g. the purchase of capital equipment) or shorter term actions (e.g. all staff training or the inclusion of another control step in the process).

6.9.2.2 For a CAPA that impacts suppliers, answer the questions listed regarding the status of Supplier acceptance.

6.9.2.3 Planned effectiveness checks are outlined. These are action items assigned to evaluate the success of the CAPA plan. Effectiveness checks should include a notification for review during an internal audit but may also include verification or validation, monitoring activities done by the departments. Effectiveness checks should include minimum test requirements.

6.9.2.4 Preventative / Implementation Action Items are detailed for the approvers to review and approve. The information includes the Task Type (e.g. corrective, containment, or preventative), a brief description of what the assignee will need to do, the task assignee, and a realistic due date.

Action Items are **not** launched (Task Reference assigned) until **after** the plan has been approved.

6.9.3 Change Control – Sub Tab

Minimally in this section the CAPA Plan owner needs to determine if a Change Control is needed. This includes either a document change control or any other change control (e.g., Engineering Event).

6.9.4 The CAPA is signed by the CAPA Plan Owner as [Data Complete] and moved to the Plan approval.

6.10 Plan Approval

The CAPA, including the Plan and planned action items, are reviewed and approved by the Director of Regulatory Compliance and any other applicable Department Head(s). The Plan is signed off as Data Approval. If rejected, the CAPA can either be moved back to Root Cause Investigation or CAPA Plan.

6.11 CAPA Plan and Implementation Tab – The Implementation

6.11.1 After the CAPA Plan is approved it moves back to the CAPA Plan Owner for Implementation. During this step, the Plan Owner launches the action items required under the Corrective Action Plan and Preventative Action Plan. See Section 6.12 to launch action items

6.11.2 The CAPA remains in the CAPA Owner's task list until all the action items are completed. After all actions are completed, the CAPA owner signs off as [Data Complete]

6.12 Action Items (Corrective Action Plan and Preventative Action Plan)

6.12.1 Use the  icon near the Task Reference field to initiate the action item to the assignee. An Action Item form launches. Complete the Request Details /Task Instructions in the Header and all the information on the Task Details Tab of the Action Item Form. Supervisors and QA Management are added as Task Approvers.

6.12.2 Action items are acknowledged by the assignee by signing off. They stay in the assignee's task list until complete. The Current Step is indicated as Action Item Completion.

6.12.3 Upon Completion of the Task, the assignee adds completion notes and a task completion date. The assignee must Sign off as [Data Complete] to move the item to the approval step.

6.12.4 The supervisor and QA approve the completion of the task, based on the completion notes. Either can reject and send the task back to the assignee.

6.12.5 Supporting Materials, demonstrating that the action is complete can either be linked, e.g., MasterControl infocards or attached as other documents from outside of the MasterControl system, e.g., photographs, diagrams, or external documents.

6.13 Effectiveness Checks -Tab

6.13.1 QA is responsible for the completion of this step.

6.13.2 QA determines if verification or validation is needed. Notes are included in the CAPA if there is any change from the planned effectiveness checks from the implementation plan. Justification is required if verification or validation is not needed.

6.13.3 Action Items are assigned.

6.13.4 After the completion of the effectiveness checks, the step is signed off as [Data Complete]

6.14 Management Review -Tab

6.14.1 QA is responsible for the completion of this step.

6.14.2 The CAPA is reviewed either during Quality Board or other meeting with Management. Notes are added regarding the review. The CAPA can then be Approved as [Data Complete].

6.14.3 In the event that Management requires an update to the CAPA, QA can reject the CAPA form as far back in the process as necessary. Choose [Data Rejection] and Choose from the list the step.

6.15 Final QA Review - Tab

A final QA Review is done to close and complete the CAPA. QA identifies if the CAPA was effectively implemented. ***If the actions were found to be ineffective, a path forward is outlined and a new CAPA initiated***. This summary includes a rationale for the decision, a reference to the new CAPA number and any Final notes.

6.16 Extension Requests

6.16.1 An extension request is generated for request additional time to complete each a step. The person responsible for the step is responsible to request an extension.

6.16.2 The system auto-generates an extension form that identifies the number of requests that have been generated.

6.16.3 The requestor chooses a requested step due date. This date should be a realistic date to that the task or step can be completed.

6.16.4 **Extension Request Reason** is a dropdown field that the requestor can use for common reasons. If the reason is not included in the drop-down field this is also a free text field.

6.16.5 **Justification:-** This field is used in support of the request reason and should include as much information as possible so that the approvers can make an informed decision.

6.16.6 **Approvers:** Select and add Department Management or the Project Scientist and QA as approvers to the extension request.

6.16.7 **Sign off** As [Data Complete] and submit the request. (Requestor)

6.16.8 The extension request is then approved by Department Manager and QA.

7.0 CAPA Reporting

CAPA are reviewed monthly by QA Management and are reported to Management quarterly during Quality Board Meetings.

8.0 References and Related Documents

SOP 21919 Issue Review from Quality Events

SOP 21301 Deviations

9.0 Change Summary