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1.0 Purpose

The purpose of this procedure is to define the processes within the Quality Management System related to Issue Review. This system is an investigational tool used to document an investigation of a quality event (internal or external).

2.0 Scope

This procedure applies to the Biopharmaceutical Development Program (BDP) at the Frederick National Laboratory for Cancer Research.

3.0 Authority and Responsibility

3.1 Director of Regulatory Compliance

- Defines this procedure.
- Reviews Issues
- Reviews / Final Approval of the Risk Review Step during Issue Review

3.2 Quality Assurance (QA)

- Reviews trends associated with quality systems
- Initiates an Issue Review
- Investigates issues
- Modifies the route to include appropriate personnel in the correct steps
- Determines the risk associated with the quality event
- Identifies containment actions
- Determines the need for CAPA resulting from issue review
- Initiates a CAPA

3.3 BDP Management or other Subject Matter Experts (SME)

- Provides information in support of the investigation
- Provides input in support of risk assessments
- Approves completed action items

3.4 BDP Staff

- Provides information in support of the investigation
- Provides input in support of risk assessments
- Performs Action Items as assigned

4.0 Definitions

Contain/Correction: An action taken to immediately control or correct a detected deviation or issue. These items are identified on the Actions tab in Master Control.

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 correction actions. CAPA actions, also identified as action items can be containment actions, corrections, corrective actions or preventative actions.

Deviation: An event that deviates from the established controls for methods, facilities, manufacturing, testing, processing, packing, or holding of a drug substance or drug product. A deviation may have a negative or positive impact, or no impact.

Issues: Quality events or incidents that require investigation. Issues may or may not require a deviation and/or become a CAPA.

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).

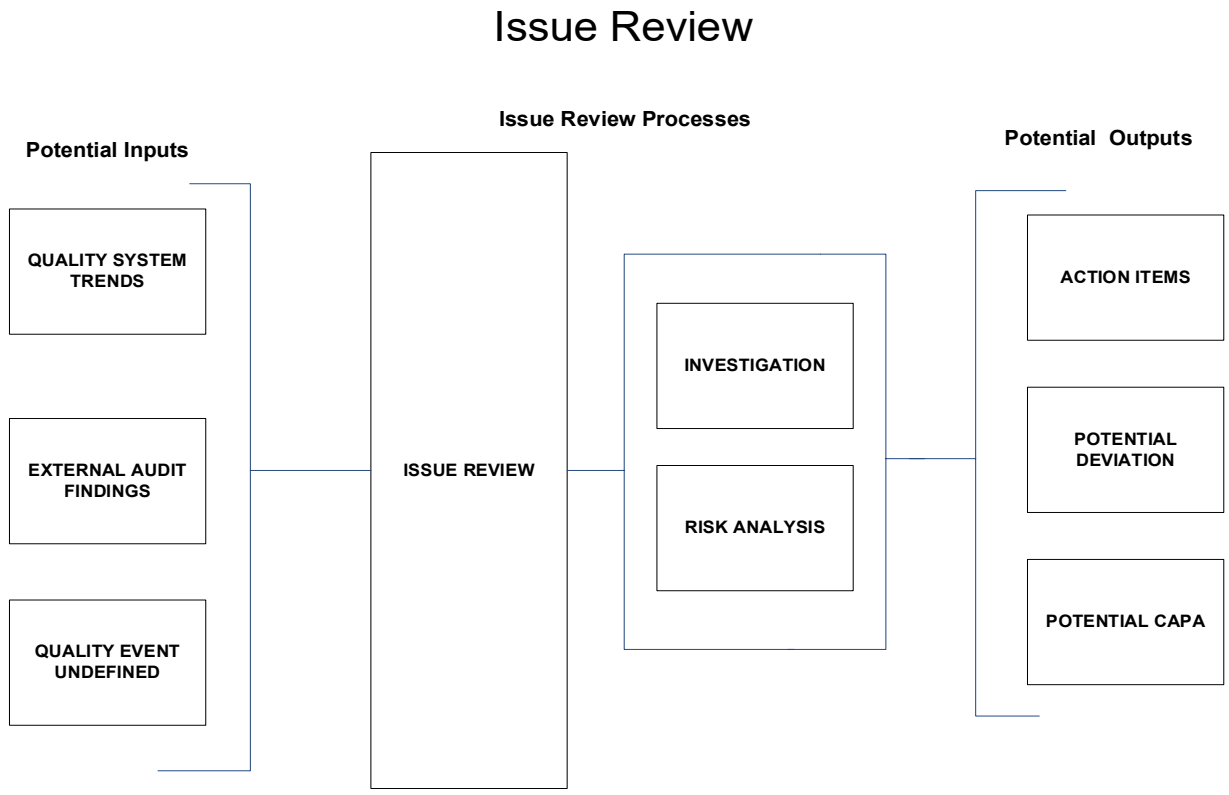
Preventative Action: An action identified to eliminate the cause of a potential undesirable situation.

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

The Issue Review tool is used in the Quality Management System to assess the impact of the event or multiple related events or trends. The assessment includes an investigation that examines the facts, the frequency of occurrence, and evaluates the risk. Results of the investigation may trigger additional Quality System investigations (e.g., CAPA or Deviations). Below shows ***potential*** inputs and outputs to an issue review. Issue review is not required if enough data exists to create a CAPA, Deviation, or Action Items directly from the Inputs.



6.0 Initiation of an Issue Review

6.1 QA initiates an Issue Review in the event of a quality event that is not defined by any other quality system, and/or if an event occurs that requires investigation before determining the scope of the issue.

6.2 Launching an Issue Review Form

6.2.1 Go to FBS Issue Review on the left navigation bar

6.2.2 Choose [New Issue Review]

6.2.3 A new Issue Review form is launched and is currently at the Initiation Step.

7.0 Issue Review Form

7.1 Issue Numbering

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

ISSUE-YYYY-NNNN

ISSUE= identifies the form as an issue review

YYYY = the year the deviation was launched

NNNN= consecutive numbering starting at 0001

7.2 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.

7.3 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 7.13 for details regarding extension requests.

7.4 Event Title / Summary

Enter an Event title /Summary that is relevant to the issue. This field is editable at other steps.

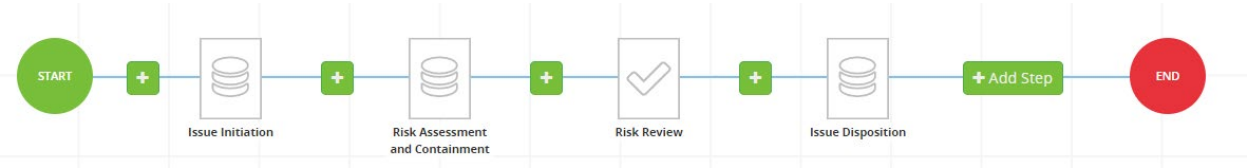
7.5 General Information

- 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.
- At anytime during the process before the final approvals, action items and communications can be added to their respective tabs. Follow section 7.11 for action items and section 7.12 for the communications log

- QA modifies the steps of the workflow to include the required personnel at each step that are required to provide information, review or approve each step.

7.6 Workflow

Below represents the issue workflow



See section 7.7 Issue Initiation, Section 7.8 Risk Assessment and Containment, Section 7.9 Risk Review and Section 7.10 Issue Disposition for specifics about the information contained in each of the sections.

7.7 Issue Initation Tab

7.7.1 Issue Details

Upon initiation of an issue review by QA, the Event Information is completed.

- **Originating Department**: This identifies the department in which the issue originates. If the issue is a systemic 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
  - 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.)
- **Date of the Event:** is a single calendar date of when the issue occurred. In the even the issue occurred over time, the first date it was identified to have occurred is te date of Event.

7.7.2 Provide Event Specifics

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

Complete the questions regarding the issue

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 to 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.

7.7.3 Concern

Complete the following information under the header ***Concern.***

- **Preliminary Issue Statement:** As the investigation on the issue may lead to further investigation in a CAPA, the preliminary issue statement concisely defines the event or events so that the significance can be understood by those reviewing the issue.

  NOTE: This field is limited to 2000 spaces/characters and should be a ***brief summary*** of the issue. Anything above the 2000-character limit must be added as an attachment to the Issue.

- **Issue Category:** The issue 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)

- **Preliminary Investigation Summary:** Clearly and concisely summarizes the facts of the investigation.

- **Preliminary Investigation Results:** This section should detail the final 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 issue. 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 attachment, 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 data analysis.

7.8 Risk Assessment and Containment Tab

7.8.1 Risk Assessment

- **Refined Issue Statement:** This section defaults to the preliminary issue statement. As the investigation proceeds, and as the root cause is further investigated, the preliminary issue statement can be refined and updated.

- **Refined Issue Category:** This section defaults to the preliminary issue category and can be changed as the investigation proceeds and as the root cause is further investigated.

7.8.2 The risk assessment is based off a simple risk matrix of Impact vs Detectability. Choose from the following:

- **Impact –** How much impact this has on the product or project

  - Negligible Impact
  - Minor Impact
  - Moderate Impact

- Critical Impact

- **Detectability** – The ability to discover or determine the existence of a failure or hazard. Detection may be through in-process testing, final product testing, or other means.

  - ***High Detectability-*** Failure resulting from the issue is easily detected. Detection means may include but are not limited to validated automatic detection systems (e.g. SCADA) that are a direct measurement of the product.
  - ***Good Detectability*** – Failure resulting from the issue is likely to be detected by a direct or indirect measurement of the product**.**
  - ***Fair Detectability*** – Failure resulting from the issue is probable. Detection is from a non-validated or a subjective detection process or system. Examples of this include but are not limited to a visual product check.
  - ***Low or No Ability to Detect*** – There are no means to detect a failure resulting from the issue.

  A risk score populates with the calculated risk score. The risk matrix definitions and scores can be reviewed by clicking on the Risk Matrix icon.

7.8.3 Recommendation

Based on the information provided in the risk assessment, the system will recommend if CAPA is necessary. The information cannot be changed; however, QA can decide not to move forward with the system recommended action.

Complete the following checkboxes appropriate for the action required.

- Initiate Root Cause Investigation / CAPA
- Contain
- Fix and Document
- Notify- Select required notifications and include notification details. Information concerning notifications are included in the communications log. See section 7.12 for details on the communications log.
- Other Recommended Action – Describe the other recommended action

7.8.4 Immediate Containment /Correction

This section identifies the actions taken to contain or correct the issue. Include any immediate actions, performed by and the date performed. A containment/correction summary is required to describe what these actions contained or corrected. Finally, QA also includes how these immediate actions mitigated the risk to the product or process.

Attach any Supporting Materials as attachment, or if the supporting materials are part of the eQMS system, these can be linked.

7.9 Risk Review Tab

This step is a review and approval by QA Management as to the details of the investigation and issue. Nothing can be changed at this step. To make changes the workflow is rejected rather than approved back to the step to which changes are required.

7.10 Issue Disposition Tab

7.10.1 Issue Disposition /CAPA Escalation

If during the risk assessment, it was determined that a CAPA is necessary, the information is pre-populated under disposition and cannot be changed.

If during the risk assessment, anything other than CAPA was determined, choose one of the following:

- **Fix and Document, No Further Action Needed**: Include the rationale and the final resolution to the issue.

  This disposition would be used when the issue under review did not require any further action. This would also be chosen if tracking or trending would not be necessary.

  This disposition requires a rationale describing why there is no addition requirements and also requires a Final Issue Resolution;documening the fix.

- **Close, Track and Trend**: Include the rationale, the final resolution to the issue, track and trend notes.

  This disposition requires a rationale describing why there is no addition requirements and also requires a Final Issue Resolution;documening the fix. Track and trend notes are included in this disposition describing key words to use in trending and describes the plan from tracking / trending.

- **CAPA Escalation**: Use the  icon to launch the CAPA form from the issue. The CAPA launch includes the investigation and many of the same fields pre-populated from the Issue Review form.

7.11 Action Items Tab

7.11.1 Action items can be assigned at any time prior to dispositioning the issue. Launching an Action Item will launch a separate form to the person responsible for the action.

7.11.2 Complete the information as defined below

7.11.2.1 Task Type:

- Containment
- Correction
- Corrective Action
- Data Gathering / Investigation
- Preventative Action

7.11.2.2 Include a descriptive task title, assignee and due date. The due date needs to be a realistically achievable date that takes into consideration the importance of the issue.

7.11.2.3 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.

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

7.11.2.5 Upon Completion of the Task, the assignee adds completion notes and a task completion date. The assignee signs off as [Data Complete].

7.11.2.6 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.

7.11.2.7 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.

7.11.2.8 Action items do not need to be completed before the issue is dispositioned. Action items completion is tracked separately.

7.12 Communications Log

7.12.1 Communications as actions from the issue are documented in the communications log.

7.12.2 **Type:** The type of communication is defined by a drop down list and includes email, internal memo letter, project team meeting or technical report. If another type of communication is used, this is also a free-type field. (e.g., phone call)

7.12.3 **Details:** Include the details of the communication and attach a copy of the communication with the deviation. Attach a copy of responses and any resolution.

7.12.4 The communications log can be updated until the deviation is in approval.

7.12.5 Emails summarizing the details in the communications tab can be sent via the  icon.

7.13 Extension Requests

7.13.1 An extension request is generated for step extensions. The person responsible for the step is responsible for requesting extensions and submitting them.

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

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

7.13.4 **Extension Request Reason:** This 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.

7.13.5 **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.

7.13.6 **Approvers:** Select and add Department Management and QA as approvers to the extension request.

7.13.7 **Sign off:** as [Data Complete] to submit the request. It is the sent to the approvers

8.0 References and Related Documents

SOP 21918 Corrective and Preventative Actions (CAPA)

9.0 Change Summary

[redacted]