SOP Title:	**Deviations**
SOP Number:	**21301**
Revision:	**07**

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1. PURPOSE

This procedure defines the process for reporting, evaluating, dispositioning, and documenting deviations from approved written procedures, such as Standard Operating Procedures (SOP), Batch Production Records (BPR), and GMP regulations. The CAPA system, including root cause analysis, is discussed in **SOP 21918.**

2. SCOPE

This SOP applies to individuals in the Biopharmaceutical Development Program (BDP) who perform GMP and GLP operations.

This procedure applies to the differences in operations from documented procedures or processes.

This procedure applies to deviations that occur during the execution of validation protocols.

3. RESPONSIBILITIES

3.1 BDP Personnel

- Recognizes deviations (and potential deviations) from approved written documents and GMP regulations.
- Alerts management and/or BQA to the presence of deviations.
- Performs immediate containment/corrections.

3.2 BDP Management

- Assists employees in the recognition, evaluation, documentation, and submission of deviations.
- Investigates deviations.
- Facilitates the completion of correction or containments actions, as needed.
- Approves deviations.

3.3 Project Scientist

- Participates in the identification and execution of correction or containment actions, as needed.
- Investigates deviations.

3.4 Deviation Originators (Writers)

- Describes the deviation, completing the deviation and immediate actions tabs.
- Provides sufficient information to clearly document the event.
- Provides initial assessment of possible product impact. Providing suggested plans, as needed, for corrective and preventative action.
- Completes the deviation initiation step.
- Investigates deviations.

3.5 Reviewers / Approvers

- Reviews and approves deviations, and actions in a timely manner.
- Approves actions in a timely manner.
- Assists in the implementation of actions, as needed.

3.6 Actions Owners

- Completes actions and provide supporting documentation and records as needed.

3.7 Quality Assurance Management

- Assesses the sufficiency of descriptions, product impact assessments, and actions.
- Assesses the risk and mitigation measures.
- Determines if CAPA is required.
- Launches required CAPA.
- Trends and reports to Management.
- Schedules Deviation review meetings, as needed.
- Modifies the steps to ensure project scientist or area supervisor is included in the deviation review and approval process.

3.8 Director of Regulatory Compliance (Head of Quality Assurance)

- Approves Major or Critical Deviations.

4. DEFINITIONS

- **Containment/Correction:** An action taken to immediately control or correct a detected deviation or issue. These items are identified on the Immediate 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:** A quality system that includes a structured approach to an investigation to determine the root cause of a deviation and implements corrective and/or preventive action.
- **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.
- **Deviation Category:** The degree of adverse impact on the product by the deviation. These categories include Minor, Major and Critical (see Step 5.1 for definitions).
- **Issues:** Quality events or incidents that require investigation. Issues may or may not require a deviation and/or become a CAPA.
- **Planned Deviation**: Changes to established procedures that are identified and approved before they happen.
- **Preventive Actions:** An action that is performed to eliminate the potential deviation, issue, or undesirable situation. This is a proactive action resulting from risk analysis, trend analysis, or other analysis.
- **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).
- **Product Related Deviations:** A deviation to the process that impacts the product. Examples of a product deviation would include, but would not be limited to, those that occur during production, raw material receipt, or during testing.
- **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. Corrective Actions address and eliminate this factor eliminating recurrence.

- **System Related Deviation:** A deviation to an established process. This would include any program established to ensure product quality. (e.g., Environmental Monitoring System)
- **Unplanned Deviations:** Changes to established procedures that occur without prior knowledge or changes that are executed without prior approval.

5. PROCEDURE

5.1 Deviation Categories

The degree of adverse impact on the product by the deviation. Critical, Major or Minor Deviations require the completion of a deviation form.

5.1.1 Critical Deviations

An event that is likely to cause a product to fail established final product test specifications or general expectations and that makes the product unfit for its intended use. The deviation results in a substantial impact on a quality attribute, process parameter, equipment or instrument used for process or control for which impact to patients, personnel, or environment is highly likely.

5.1.2 Major Deviations

An event that could possibly cause a product to fail established final product test specifications or general expectations but that may still allow the product to be used as intended with an approved corrective action. The deviation results in a moderate impact on a quality attribute, process parameter, equipment or instrument used for process or control.

5.1.3 Minor Deviations

An event that will not obviously cause a product to fail established final product test specifications or general product expectation. The deviation does not affect the safety, identity, strength, quality, or purity of the product. The deviation has a minimal impact on a process parameter, equipment or instrument used for process or control.

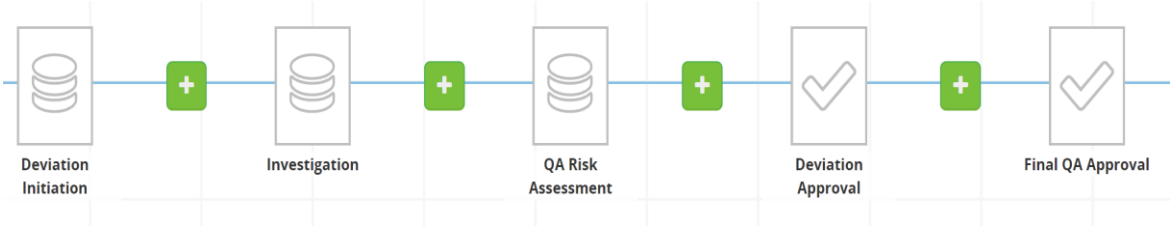
5.1.4 Insignificant Deviations

Deviations to correct typographical errors, spelling or grammatical are made using Good Documentation Practices, **SOP 21409 Good Documentation Practices.** No other action is required.

Clarifications by Project Scientists to explain and refine an insufficiently described manufacturing process or testing procedures are documented in the comments section to the MPR at the time of occurrence. Action items may be assigned to update the documents for future use, but no other actions are required.

5.2 Workflow

Below represents the deviation workflow



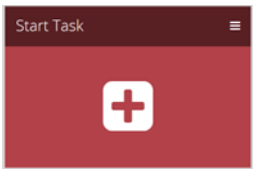
5.3 General Information

- It is preferable that the person who caused the deviation to occur, and/or took immediate actions to correct the situation, initiates the deviation to accurately describe the occurrence and circumstances.
- All required fields for each step are indicated with a *.
- During each step, the form can be saved and returned to later.
  - After initiating the deviation, users can save the deviation at any time using the [SAVE] button.
  - The signoff button has the following options:
    - **Work In Progress**: This will allow the user to save all changes and unlock the deviations to allow other users to access it.
    - **Data Complete:** This will save changes and move the deviation to the next step of the workflow if all required fields are complete.
    - **Data Rejection:** With the exception of the first step, the user will be able to send the document back to any of the previous steps for editing.
- If required information is not complete, the system will not allow the user to Sign off as Data Complete or Data Rejection. Additional required information is highlighted in red.

5.4 Launching/Starting a Deviation from Start Task

5.4.1 The deviation originator logs into MasterControl.

5.4.2 On your Dashboard go to Start Task



5.4.3 Choose [Form]

5.4.4 From the forms listed, Choose [Deviation FBS]

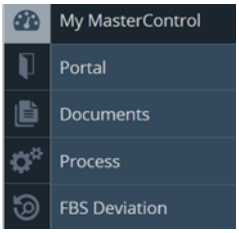
5.4.5 Under Actions choose the Icon.

5.4.6 The deviation form in MasterControl will launch.

5.5 Launching/ Starting a Deviation from a Custom Hub

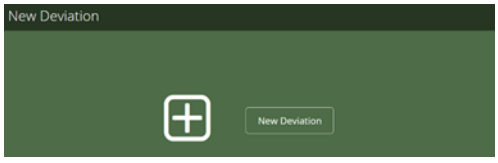
5.5.1 Log into MasterControl

5.5.2 From the Hubs



5.5.3 Go to the Field Based Solution (FBS) Deviation

5.5.4 Start a New Deviation



5.6 Form Header

The following information appears in the form header after launched.

5.6.1 Deviation Numbering

The eQMS system automatically assigns a deviation number to any deviation launched. With the following format:

DEV-YYYY-NNNN

DEV= identifies the form as a deviation
YYYY = the year the deviation was launched
NNNN= consecutive numbering starting at 0001

5.6.2 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.

5.6.3 Step Due Date

5.6.4 The due dates are calculated by the system for each step based on predefined times. Deviation Title

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

5.7 Initiation Step

5.7.1 The initiator has three (3) days to complete this step.

5.7.2 The initiation step of the workflow is completed by the originator that launches the deviation form.

5.7.3 Deviation Tab

This tab describes the relevant facts of the deviation. The form can be saved and updated.

- **Originating Department** – Choose from the populated list of departments.
- **Source** – Choose from the list of what was the documented source of the deviation (e.g., Production Record, QC record, SOP, Complaint etc.).
- **Date Created** – is autogenerated by the system defaults to the date the form was launched.

- **Date of Event** – Include the date the event occurred, or the date it most likely occurred if unknown. Form planned deviations, use the current date.
- **Date of Awareness** – This may be the same as the date of the event or can be a later date if the event was not identified when it happened. For planned deviations tuse the current date.
- **Deviation Type** – (Planned vs Unplanned) Choose between planned or unplanned deviation.
    - **Planned Deviations** In addition to the information required for every deviation, planned deviations also require:
        - A justification providing the reason why the deviation has to be done. The justification must be clear and provide strong support for the deviation.
        - The originator determines if this is a one time, temporary, or permanent change. One Time planned deviation is limited to an isolated circumstance. The approximate date of the deviation should be included in the justification. Temporary planned deviations require either the dates from and to or other controls that make the deviation temporary. Permanent planned deviations require a change control reference. This includes Engineering Change numbers or Document Change Record (DCR) numbers, as applicable. Document changes can be created and launched directly from the deviation.
        - For planned deviations, an Investigation and QA Risk Assessment is not required. These steps will be skipped in the workflow.
        - A planned deviation must be approved prior to the implementation of the actions / deviations. **If the actions are implemented before approval, the deviation is an unplanned deviation**.
    - **Unplanned Deviations**
- **Reference** - Link to the SOP or MPR deviated from. If the reference is not included in MasterControl, the reference can be typed into the field.
- **What, Where, When, Weight (Scope of Impact), Who.** Complete these fields to briefly describe the deviation.

- **Deviation Impacting QC?** Choose from Impacting QC or not Impacting QC. One **must** be chosen.
- **Room Number Reference** Choose from the rooms listed.
- **Patient /Donor ID** This is only required if this specifically impacts a particular patient. (e.g., cell therapy products).
- **Unit / DIN** This is only required if this specifically impacts a particular patient. (e.g., autologous cell therapy products).
- **Questions Yes or No required**
  - Does the deviation 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.
  - Does the deviation involve or impact a project? If **YES**, then choose from the list of projects.
  - Does the deviation 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 deviation involve or impact in-use equipment? If **YES,** then include the Equipment ID Number (MEF Number), and the equipment description.
  - Does the deviation involve or impact a supplier or vendor? If **YES**, then select the vendor or vendors that are involved or impacted.
- **Category (Major, Minor or Critical)** Choose the correct category using the definitions in Step 5.1.

5.7.4 **Immediate Actions Tab**

5.7.4.1 **Immediate Action Description** - This is a required field. Choose from the list of immediate actions that could contain or correct the issue. If none of the choices apply, this is also a free text field. Include on that same line who performed the action and the date completed. Additional lines can be added for more immediate actions by using the  icon.

5.7.4.2 **How did the immediate actions contain the scope of the deviation and/or mitigate the risk?** This section describes how any actions to contain or correct the issue mitigated the risk to the product. Example: For a deviation written due to a power failure, additional cleaning was requested and completed to mitigate the risk of an environmental excursion before the product was introduced into the area.

5.7.4.3 **Change Control Reference**- Include any Engineering Event reference or Document Change Control (DCR) reference.

5.7.4.4 **Supporting Materials** – Links - Include any links to MasterControl infocards that would support the deviation and/ or provide additional information for the approvers.

5.7.4.5 **Supporting Materials** - Attachments Include any supporting information not found in MasterControl. Examples of this includes but is not limited to supplier specifications, photographs, pictures, diagrams, communications with suppliers.

5.8 Investigation

5.8.1 The investigator(s) have five (5) days to complete this step.

5.8.2 The step defaults to QA who adds others to participate in the investigation. Investigators include but are not limited to the project scientists and department management from impacted departments.

5.8.3 The investigation prompts the investigator a number of Yes/No Discrepancy /Error questions. For every Yes answer, describe the error or discrepancy in the Comments section.

- User Error Involved
- Material Discrepancy
- Method / Procedure or SOP Discrepancy
- Specification Discrepancy
- Environmental Discrepancy

5.8.4 **Issue Statement** The investigator provides brief explanation of the problem and why it is an issue. This brief explanation is provided by the impacted department and reviewed by all the investigators in the step.

5.8.5 I**ssue Category** The issue category is a pre-defined drop-down list created to group related issue types.

5.8.6 I**nvestigation Summary** This section should clearly and concisely demonstrate that the root cause has been identified and that the corrective actions have been taken to ensure the safety, identity, strength, purity, and quality of the product. This is an executive summary of the deviation.

5.8.7 **Investigation Results** This section should detail the final results of the investigation and can include more details that the summary. Conclusions reached should be included. Root cause identified should be detailed in this section.

5.8.8 **Identifiable Cause** This is a predetermined list identifying the cause of the deviation. This is used for trending purposes. Choose from Machine, Man, Materials, Measurement, Method or Mother Nature (Environment) as what is the cause of the deviation. Identifiable cause must match the root cause identified in the investigation results.

5.8.9 **Impacted Departments** Select the departments that are impacted by the deviation.

5.8.10 **Reportable Deviation** (YES/NO) This is limited to r**eportable to Regulatory Authorities** (e.g., FDA, EU). If Yes, include a tracking number, date reported and details of the report.

5.8.11 **Notification Required** (YES/NO). This is limited to the notification to the sponsor or principal investigator. If Yes, include notification details, date notified and notification details. If notification is required, notifications can be done through the Communications Log Tab. See section 5.13 Communications Logon completion of the communications log. Email notification can be sent directly from the deviation to keep a good account of the notifications. Notifications can only be sent prior to approval.

5.8.12 **Systems Affected** Include from the list of systems what system is impacted. In none are impacted, choose N/A.

5.8.13 **Additional Containment / Corrections The** investigator determines if additional immediate actions are required a result of the investigation and risk assessment are required.

5.8.14 **Risk Assessment and Escalation** During the investigation step the investigators can do a preliminary risk assessment. This will be editable by QA at the QA Risk Assessment Step.

5.8.15 All the investigators need to sign off on the step as Data Complete for the deviation to move to the next step. Below are choices for sign off status to choose from:

- **Work in Progress-** Data is saved in the investigation but the investigation is not complete. This is used when this step is a shared step between the originators and QA.
- **Data Complete-** After all the investigation is complete, the investigator(s) sign off as data complete.
- **Data Rejection-** If one investigator does not agree with either the investigation or the information in the initiation, the data is rejected

5.9 QA Risk Assessment

5.9.1 The step defaults to QA and QA Management. The user has two (2) days to complete this step. QA may add others to participate as necessary. Based on the results of the risk assessment, a CAPA may need to be initiated.

5.9.2 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 deviation 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 deviation is likely to be detected by a direct or indirect measurement of the product .
    - **Fair Detectability** – Failure resulting from the deviation 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 deviation.

  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.

5.9.3 **Risk Statement /Rationale** is a summary in support of the risk score. Describe the logic of ratings chosen for impact and detectability.

5.9.4 **Required Issue Review or CAPA** is determined by the risk score. Risk score of:

- Scores of 1-9 does not require an Issue Review or CAPA to be launched.
- Scores of 10-15 may or may not require an Issue Review or CAPA to be launched. QA **must** include rationale for the decision within the Risk Statement / Rationale.
- Scores above 15 require an Issue Review or CAPA launch. If none is launched from the deviation, the rationale for not launching one must be included in the Risk Statement / Rationale.

5.9.5 **CAPA Reference** This is the cross reference to any CAPA launched. A CAPA can be automatically launched by choosing the icon. Information from the deviation will automatically populate the CAPA form. These CAPAs are reserved for items of large scope and implementation. Use action items tab of all other corrections, corrective, and preventative actions.

5.9.6 **Track & Trend Notes** includes any tracking or trending information, how the deviation will be trended and includes but is not limited to information :

- Primary and secondary/contributing root cause. (if applicable)
  - If the root cause is identified as Man, include the factor contributing to human error (e.g, attention gap, memory gap, training gap, decision gap, procedure gap, organization gap or, application gap) and the technician initials.
- Indication of what assay/program the deviation is against. (e.g. Flow Cytometry, Stability, Environmental Monitoring, Outsourced testing)
- If outsourced testing, indicate the vendor used for testing.
- Which SOP, Form, or MPR the deviation is against.

5.9.7 **Additional Containment /Corrections**: Select yes or no if additional containment actions are required as a result of the investigation. This may be required if the investigation determines a broader scope for the deviation. If yes is chosen, describe the additional containment / immediate corrections required. Include how this will mitigate the risk associated with the deviation.

5.9.8 **Analyzer Number** An analyzer may be established to identify or notify QA of a threshold number being met. If an analyzer is used, action will be required if a threshold is reached.

5.9.9 **Supporting Materials** can either be linked as with MasterControl infocards or attached as other documents from outside of the MasterControl system. This is in support of the investigation and the risk assessment.

5.9.10 QA verifies any completed actions and adds the completion dates to the Action Items tab. Once approved, the completion is only tracked through the actions, and may not appear in the deviation.

5.9.11 QA must modify the next step to include all required approvers in Deviation Approval.

5.10 Deviation Approval

5.10.1 QA modifies this step to include all the required approvers and modifies themselves from the step. Approvers may include impacted department management, project scientist, QC for deviations impacting QC. The approvers have three (3) days to complete this step.

5.10.2 Assigned approvers review the information in the deviation, the immediate actions, the action items assigned.

5.10.3 All assigned approvers need to sign off on the step as Data Approval for the deviation to move to the next step. Below are choices for sign off status to choose from:

- **Data Approval-** The approvers review and evaluate all the information in the deviation and approve. By approving the deviation, the approvers agree with the investigation and any assigned actions.
- **Data Rejection-** If one of the approvers does not agree with either the investigation, risk assessment or the information in the initiation, the data is rejected. The user rejecting the deviation chooses the step to move the task back to:

- **Initiation-** this moves the deviation back to the beginning of the workflow. Information from all the tabs can be edited.
- **Investigation** this moves the deviation back to the investigation step. Where changes or additional information can be added.
- **QA Risk Assessment** this moves the deviation back to the QA Risk Assessment step. Changes to the assessment or additional actions (corrections, corrective, preventative) actions can be assigned if rejected back to this step.

Rejecting a planned deviation automatically moves the deviation back to the initiation step. Users must reject planned deviations that were executed before approval.

5.11 Final QA Approval

5.11.1 This is the final step in the workflow that closes the deviation. Action items associated with the deviation remain open and are closed independent of the deviation. Completion dates of actions do not update automatically and cannot be updated once the deviation is approved.

- **Data Approval**- QA reviews and evaluates all the information in the deviation and approves. By approving the deviation, QA agrees with the investigation and any assigned actions.
- **Data Rejection**- If QA does not agree with either the investigation, risk assessment or the information in the initiation, the data is rejected. The user rejecting the deviation chooses the step to move the task back to:
  - **Initiation-** this moves the deviation back to the beginning of the workflow. Information from all the tabs can be edited.
  - **Investigation t**his moves the deviation back to the investigation step. Where changes or additional information can be added.
  - **QA Risk Assessment** this moves the deviation back to the QA Risk Assessment step. Changes to the assessment or additional actions (corrections, corrective, preventative) actions can be assigned if rejected back to this step.

Rejecting a planned deviation automatically moves the deviation back to the initiation step. Users must reject planned deviations that were executed before approval.

5.11.2 Minor Deviations are approved by QA Management. Major or Critical deviations are approved by the Head of Quality.

5.12 Action Items

5.12.1 Action items can be assigned at any time prior to the deviation approval.

5.12.2 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.

5.12.3 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 at Action Item Completion.

5.12.4 Upon Completion of the Task, the assignee adds completion notes and a task completion date. The assignee will need to Sign off as Data Complete.

5.12.5 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.

5.12.6 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.

5.12.7 Action Items are verified by QA and the effectiveness of the actions is evaluated during internal audits.

5.13 Communications Log

5.13.1 Communications as actions from the deviation are documented in the communications log.

- **Type** The type of communication is defined by 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)

- **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.

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

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

5.14 Tracking/Trending

Deviations are tracked and trended monthly and reported in the monthly Adherence Report.

A quarterly trending is provided for Quality Board.

5.15 Effectiveness Checks of Actions

Deviations are evaluated for effectiveness checks during internal audits.

6. REFERENCES AND RELATED DOCUMENTS

Document Number	Title
21409	Good Documentation Practices
21526	Engineering Event Management
21918	Corrective and Preventative Actions (CAPA) Program