Frederick National Laboratory for
Cancer Research, Frederick, MD

BDP

Biopharmaceutical Development Program

Standard Operating Procedure

Title: Engineering Event Management

SOP Number: 21526 **Revision Number: 04**

Supersedes: Revision 03 **Effective Date:** JUN 30 2016

Originator/Date: [redacted]

Approval/Date:

Approval/Date:

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1.0 Purpose

This Standard Operating Procedure (SOP) describes the procedure for managing "engineering events" which have the potential to impact the Good Manufacturing Practice (GMP) state of systems, equipment, and areas. Events include, but are not limited to failures, changes (components, use, engineering, etc.), Status Change, and Out-of-Tolerance (OOT) events.

2.0 Scope

This SOP applies to software systems, utility systems (and their points of use), facilities, production areas that support Current Good Manufacturing Practice(CGMP) activities for the Biopharmaceutical Development Program (BDP), GMP process and analytical equipment, and the resolution of OOT (out of tolerance) events with a potential for product impact. In some instances this procedure could be applied to R&D or non-GMP equipment.

This procedure is made available through federal funds from the National Cancer Institute, NIH, under contract HHSN261200800001E.

3.0 Overview and Process

Engineering Event (EE) is a collective term for any change to a system, area, or piece of equipment. The change can come in many forms such as a failure, status change, or a modification where the system is upgraded or components are changed. EEs are a critical aspect of maintaining control on GMP systems. Like for like changes to components do not require an EE. For example, a pressure gauge fails and a direct replacement make and model is not available so a unit of identical material of construction, range, and tolerance is installed. If the gauge was different even if it is considered "better" for example it has a tighter tolerance, this would no longer be like-for-like and an EE shall be generated. Consult with Biopharmaceutical Quality Assurance Engineering (BQAE) if you need assistance in determining if a change requires an EE. See the definition section for additional guidance.

All planned EEs must have the change authorized by QA electronically before the change is implemented.

Process and analytical equipment, software systems, utility systems, facilities, and areas that support CGMP activities for the BDP are generally maintained in an In-Service status (either active or inactive) making them readily available for GMP applications. Areas that are not required may be made "Inactive" refer to ***SOP 21554 - GMP Area Status Management***. Engineering "events" that may affect the usability of a system include, but are not limited to, engineering changes, failures, Status Changes to shut down or allow only limited use to a system or area, or OOT situations.

Engineering events are documented from discovery through resolution including investigation, root cause determination (of failures), change justification (if applicable), assessment of impact, defining return to service requirements and completion of return to service activities using the electronic form on the public drive [redacted]

Affected parties are automatically notified when an engineering event is submitted or changed. The Owner, BDP Engineering, and Quality Assurance (QA) Engineering coordinate efforts to investigate and resolve the event.

When completed, data from the electronic form is reviewed and approved electronically it is then printed as Form 21526-01 either Part 1 or Part 2 and routed for signature.

4.0 Authority and Responsibility

4.1 The Director of Biopharmaceutical Quality Assurance (BQA), Biopharmaceutical Development Program (BDP) has the authority to define this procedure.

4.2 BDP Personnel are responsible for:

4.2.1 Initiating documentation for an engineering event in a timely manner.

4.2.2 Participating in root cause determinations (for failures).

4.2.3 Providing relevant input to justify changes and possible impact.

4.2.4 Participating in the completion and resolution of engineering events, as required.

4.2.5 Ensuring that information related to changes in status of equipment, utilities, and areas are referenced in appropriate equipment logs.

This procedure is made available through federal funds from the National Cancer Institute, NIH, under contract HHSN261200800001E.

4.2.6 Documenting the action taken (as applicable) in response to the event (this includes referencing the trouble call reference number on the engineering event form).

4.2.7 Coordinating or completing follow-up activities and tracking the progress of these activities.

4.3 BDP Engineering is responsible for:

4.3.1 Monitoring the Engineering Event system for equipment failures, assisting with troubleshooting, evaluating the failure or change situation, contacting appropriate resources to investigate a failure event, and initiating repair or service.

4.3.2 Documenting the action taken (as applicable) in response to the event (this includes referencing the trouble call reference number on the engineering event form).

4.3.3 Participating in root cause determinations (for failures).

4.3.4 Assisting with return-to-service activities as required.

4.4 BQA Quality Engineering Manager (or designee) is responsible for:

4.4.1 Overseeing and monitoring this process from initiation to closure to assure that EEs are appropriately managed.

4.4.2 Completing the “BQAE” tab that documents the evaluation of impact, return-to-service requirements and approval for engineering changes.

4.4.2.1 For events that may adversely impact product, BQA Engineering is responsible for ensuring that a deviation report is filed (SOP 21301 - Deviations from Written Documents).

4.4.2.2 Managing root cause determinations (for failures).

4.4.2.3 Identifying applicable return-to-service activities (including calibration/validation) that will be required as a result of the EE.

4.4.2.4 Specifying gowning requirements and schedules for environmental monitoring and/or cleaning that will apply during the period that an area/utility is in a Limited Use status.

4.4.2.5 Authorizing the change to allow the EE to proceed.

4.4.3 Completing the “Follow-up” tab (as applicable), reviewing relevant supporting documentation and approving engineering changes upon completion of the change.

4.4.3.1 Verifying that related tasks are completed.

4.4.3.2 Verifying the completion and documenting review of return-to-service activities.

4.4.3.3 Verifying that owner follow up, as applicable, is completed.

4.4.3.4 Determining the final disposition of the EE.

4.5 BQA is responsible for:

4.5.1 Managing and filing the Engineering Event documentation.

This procedure is made available through federal funds from the National Cancer Institute, NIH, under contract HHSN261200800001E.

4.5.2 At the direction of BQA Engineering, assisting in routing printed forms for authorizing signatures.

5.0 Status Designations

NOTE: Use of an area for GMP activity requires a pre-production clearance by BQA per ***SOP 21104 - Pre-Production Clearance*.**

5.1 Limited Use

This designation denotes that the equipment, utility, building, or area is functional but that the system or unit is operating at less than its usual state. Examples include:

- Putting a use point out-of-service in a system where the validated state includes the use point.
- Using a piece of equipment for a reduced operating range, reduced format, or reduced number of cycles.

NOTE: Some Limited Use conditions may be suitable to support GMP activities. Placards documenting a Limited Use designation will specify the condition causing the limited use and include associated use limitations and restrictions.

5.2 Out-of-Service/Shutdown

This designation denotes that the equipment, utility, or area is not functional. This status can result from a failure, but can also result from changes, upgrades, or preventive maintenance. Depending on the event, some requirements for use (for example, gowning or cleaning) may be significantly reduced or eliminated during periods of Shutdown.

5.3 Return-to-Service

This designation denotes that the equipment, utility, building, or area is undergoing activities to return it to an “In-Service” status. For example, these activities may include enabling the utility (if it was disabled), cleaning activities, calibration or validation activities, re-establishment of gowning requirements, and monitoring activities to confirm environmental control.

5.4 Placarding

5.4.1 Required to assess the modified status of Equipment or Utility Use Points.

5.4.1.1 Equipment or utility use points that are out-of-service must be placarded or tagged to prevent inadvertent use. At a minimum, tag/ placards need to include the date the unit or use point went out of service, who is tagging the unit or use point out of service, and the event tracking number.

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5.4.1.2 The following tag/placard is recommended.

(Side 1)

(Side 2)

6.0 Managing Engineering Events

Engineering Events are accessed through an electronic system at [redacted]. Selections are available under the EE tab. From here, users may create, update, approve, search, or generate reports regarding EEs. Prompts to the text fields may be modified by the system administrator to provide better instruction. (If the five tabs under EE are not visible click the restore down and then the maximize button on the window to make them visible.) Separate EEs need to be submitted for each distinct event.

6.1 General Navigation of EE menu.

6.1.1 Entry/Info – Allows for entry of a new event by clicking New under the Event# or recalling an entered event using the drop down.

6.1.2 List By State – Allows for listing and sorting of EEs by their status state of Awaiting Owner Approval, Awaiting BQAE Approval, Awaiting Part 1 Printing, Awaiting Part 2 Completion, Awaiting Part 2 Printing, Complete. Any EE may then be opened by double clicking.

6.1.3 Search – Allows for EEs to be searched based on a combination of date, keywords, item name, owner, event type, MEF#, or Event Status.

6.1.4 Reports – Allows for Part 1 or Part 2 printing, a listing report of all EEs not in a closed state, or a summary report providing EEs from a specified date range.

6.1.5 Record Receipt – Allows for recording the receipt of the signed printed copies to be archived in the document control area.

6.1.6 Revoke – Allows for users with required privileges in BQAE to revoke electronically applied approvals.

6.1.7 Cancel – Allows for users with required privileges in BQAE or system administrator to cancel an EE.

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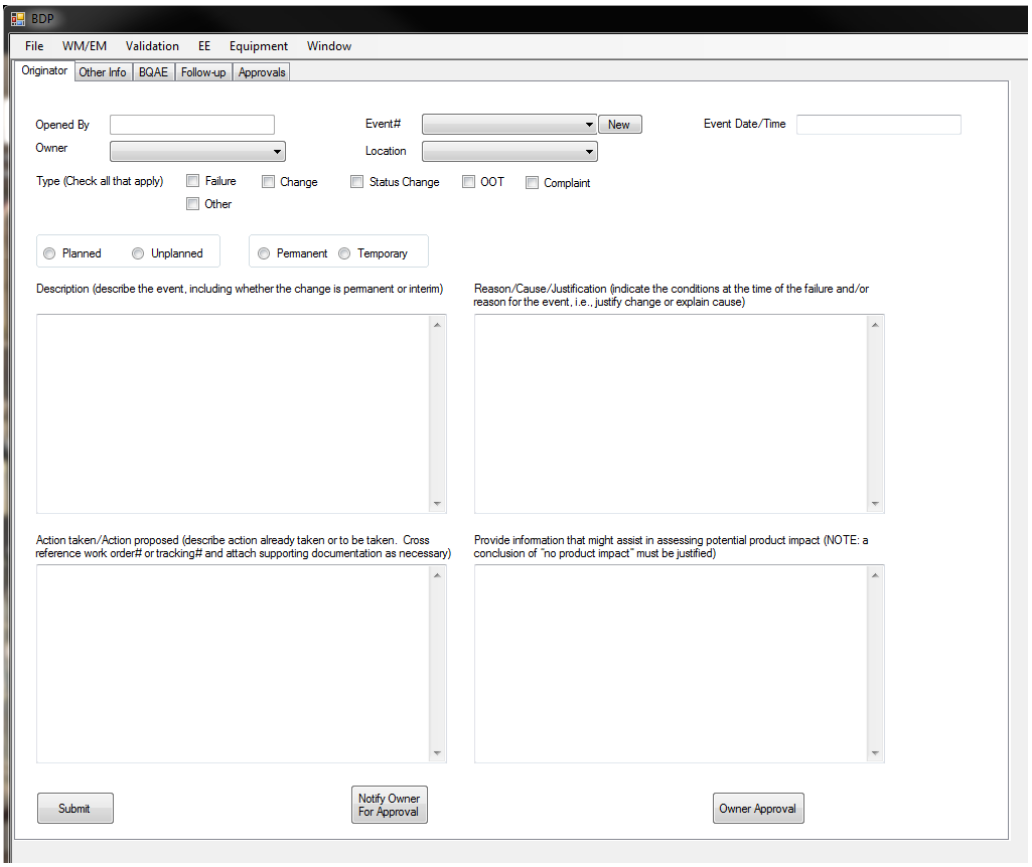
6.2 Generating Engineering Events

6.2.1 The “Originator” tab initiates the engineering event and collects initial data. It is accessed under the Entry/Info tab of EE in the application.



6.2.2 BDP staff initiates the EE selecting Entry/Info and using the “Originator” tab, and providing as much information as is known about the event.

6.2.2.1 Click *New* and the *Opened By* tab is automatically populated.

6.2.2.2 At a minimum, a new EE requires a description to generate an EE number. An error message alerting the user is displayed if insufficient information is provided. This feature prevents the unintentional creation of blank EEs.

6.2.2.3 Enter the Date/Time that the event occurred for unplanned events or the date and time the EE is initiated for planned events.

6.2.2.4 Enter the owner of the event. The individual selected is not required to be the owner of the equipment as more than one equipment owner may be involved in an EE.

6.2.2.5 Enter the location of the event. The location selected is not necessarily the location of the equipment. For example the event was located in A2518 but the HVAC equipment is on the roof.

6.2.2.6 Select the EE Type, more than one selection may be chosen.

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6.2.2.7 Indicate if the EE is Planned or Unplanned.

6.2.2.7.1 A planned EE is proactively initiated before a change is made to the system. Engineering events for planned changes should be initiated and approved before being executed.

6.2.2.7.2 An unplanned EE has no advance notice and typically handles failures, OOTs, and changes associated with failures.

6.2.2.8 Indicate if the event is Permanent or Temporary. If temporary is selected a box will appear to enter the estimated or known end date.

6.2.2.9 Fill in the four larger fields.

6.2.2.9.1 Description – Describe the event including whether the change is permanent or interim.

6.2.2.9.2 Reason/Cause/Justification – Indicate the conditions at the time of a failure and/or reason for the event. Provide justification for the change or explain the root cause of the failure. If the root cause is not known, this should be stated and possible explanations for further investigation suggested.

6.2.2.9.3 Action taken/Action proposed – Describe the action taken or to be taken. Work order #s or deviation tracking #s and any supporting documents should be referenced. Include dates for taken and planned actions where possible.

6.2.2.9.4 Provide information that might assist in assessing potential product impact – The originator should provide relevant information regarding impact or potential impact as a result of the EE. This information assists BQAE in assessing risk and impact. Insufficient information may delay the approval process.

6.2.3 The “Other Info” tab is used to add other relevant info specific to the EE.

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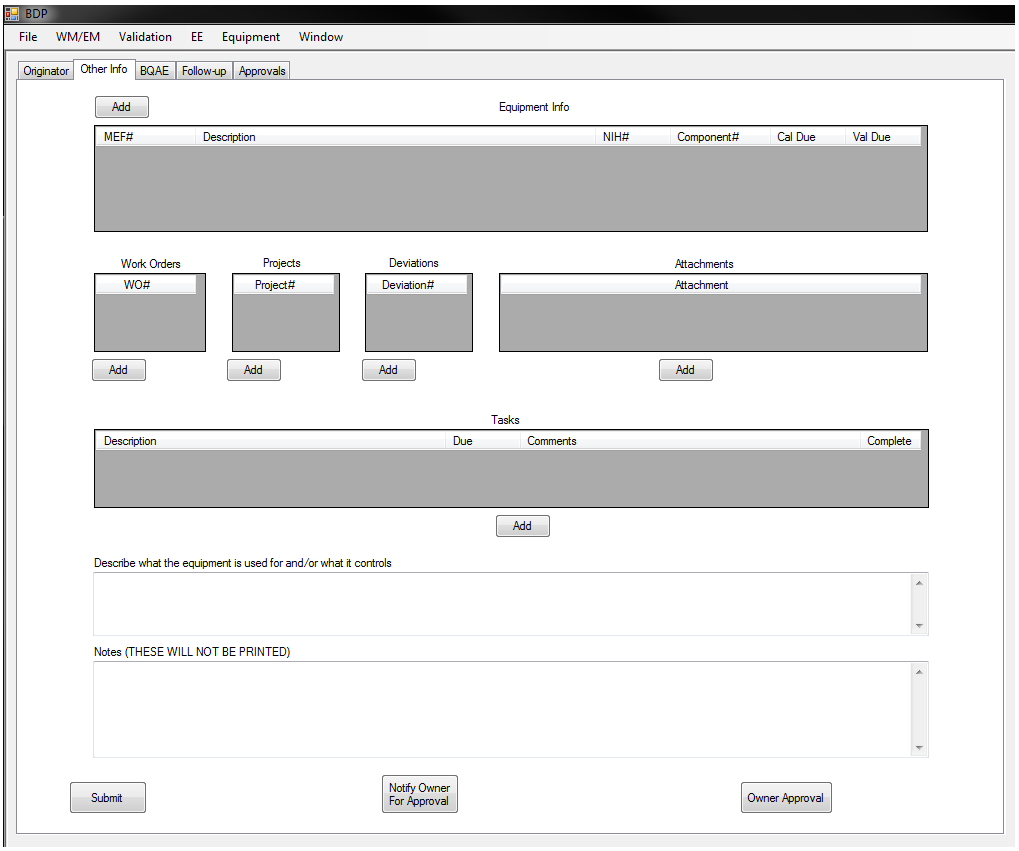

6.2.3.1 Add Equipment Info as needed by using the “Add” button and entering directly or searching for any and all equipment impacted by the EE.

6.2.3.2 Reference any applicable Work Orders, Project Numbers, Deviation Numbers by selecting the related “Add” button.

6.2.3.3 Attachments for documentation supporting the EE in PDF form should also be added.

6.2.3.4 Tasks may also be generated.

6.2.3.4.1 When used, by selecting “Add” a window will request the Description of the task, the due date, and the responsible person.

6.2.3.4.2 When the task is complete it can be opened by the responsible person and marked as such with a comment field to add any additional information.

6.2.3.4.3 If the task is not completed by the due date, email notification will be sent.

6.2.3.4.4 Tasks must be completed before Part 1 may be approved.

6.2.3.5 The Originator for Engineering Events for calibration failures must cross-reference the Engineering Event reference number in the calibration tracking system (BMRAM).

6.2.3.6 If the equipment, system or building must be left in an unusable state, placard the area or equipment “Out-of-Service”, update the equipment

log, and when possible, alert the Equipment/ System Owner. See also ***SOP 21503 - Responding to Alarms***.

6.2.3.7 The MEF numbers of all impacted equipment should be listed using the *Add* button under Equipment Info. Equipment may be entered directly or searched for.

6.2.3.8 PDF documents may be attached to the record (for example, a calibration certificate) to provide information about the event. To attach a document select the "Attach" button and follow prompts to attach the document to the Engineering Event.

6.2.3.9 Initial notification is initiated when the EE is generated.

6.2.3.10 Requests to change the status of equipment, systems, or an area are managed as planned changes.

6.2.3.11 If the proposed change is a result of a corrective or preventive action from a deviation enter the number in the Deviations field. Use the Description text box to reference fields not covered under the Other Info tab.

6.2.4 Submitting the Engineering Event

6.2.4.1 When the originator has supplied the information initially available (minimum information is "Type" of event and "Description"), selecting "submit" will save the record and send an e-mail notification to affected parties including the equipment owner.

6.2.4.2 BQAE must then review the information and will alert the originator or owner regarding additional information or will Notify Owner for Approval.

6.2.4.3 Owner Approval: The equipment owner, or responsible person, completes the originator tab and confirms that information on the tab is accurate. Selecting "Owner Approval" will move the record to review by Biopharmaceutical Quality Assurance Engineering. Owner approval should not occur until after all of the Part 1 information is complete; this means that the BQAE tab should be completed.

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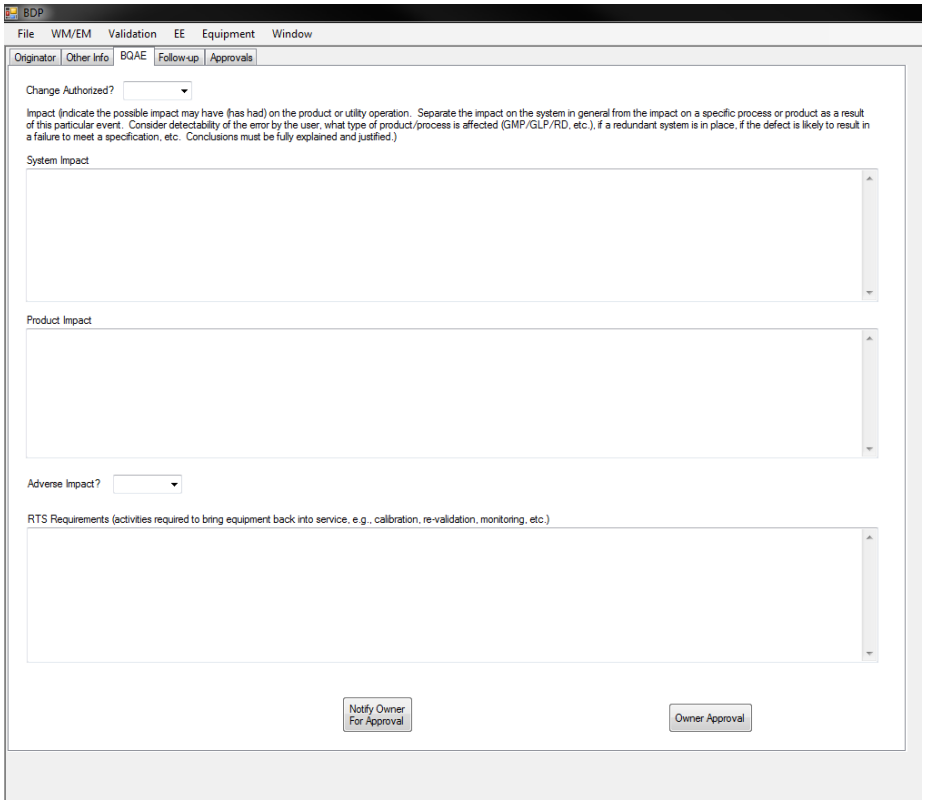
6.3 BQAE Tab

6.3.1 BQAE evaluates the event and works with the originator and/or owner to document the impact the event may have on product or utility operation, the Return-to-Service (RTS) activities that will be required to bring the equipment back into service, and the qualification activities that are required to demonstrate that the equipment is in a state of control.



6.3.1.1 Change Authorized: This indicates if the change proposed under the Originator tab is approved by BQAE or if this field is not applicable.

6.3.1.2 Adverse Impact: If a product has possibly been adversely impacted by an engineering event, BQA Engineering or the System Owner will file a deviation documenting this (see ***SOP 21301 - Deviations from Written Documents***).

6.3.1.3 Attachments: PDF documents may be attached to the record (for example, a calibration certificate) to provide information about the event. To attach a document select the “Attach” button and follow prompts to attach the document to the engineering event under the Other Info tab.

6.3.1.4 Return to Service Requirements: When available and appropriate, BQA Engineering will consult equipment or system-specific SOPs that describe Return-to-Service activities. Attachment 3 is provided as general guidance for Return-to-Service activities for utilities and presents suggested Return-to-Service activities based on the criticality of the event.

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6.3.2 Approval

6.3.2.1 BQAE will review the information and when information is satisfactory will Notify Owner for Approval.

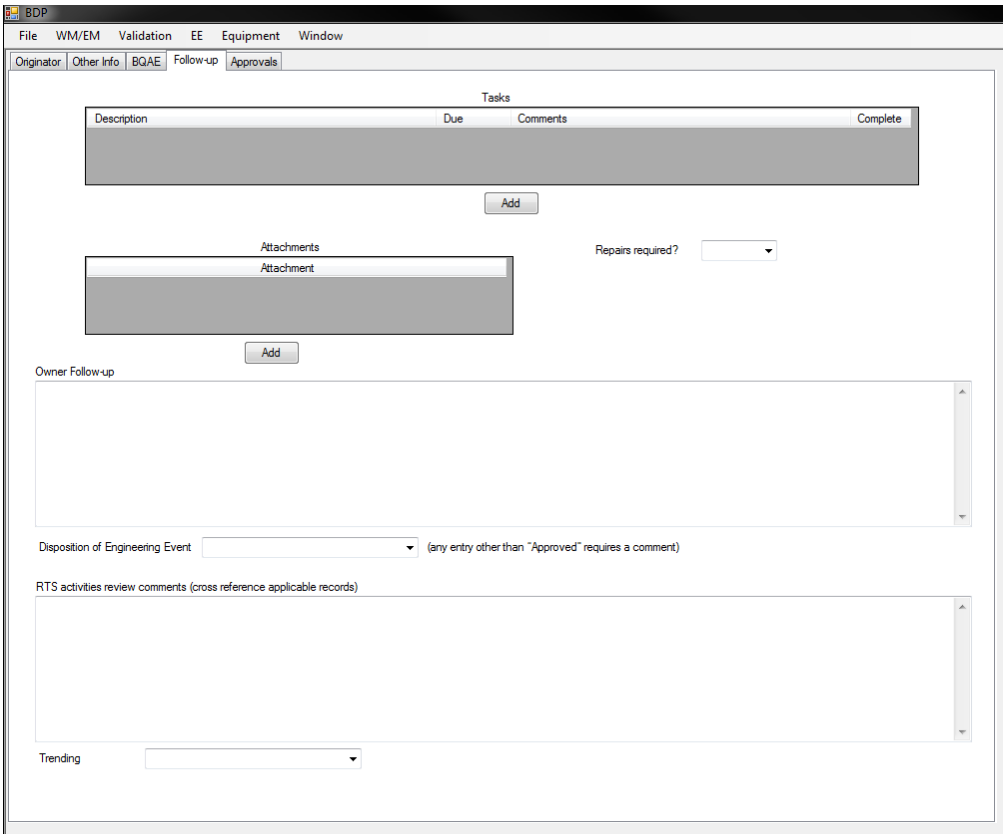
6.3.2.1.1 Owner approval for this section is to make the owner aware of the impact assessment by BQAE. It is also an opportunity for the owner to verify the accuracy of the information and any assumptions used by BQAE in assessing the impact.

6.3.2.1.2 Any issues should be addressed at this time with BQAE.

6.3.2.2 BQAE will apply QA approval once all fields are acceptable. Only authorized BQAE staff has permission to apply this approval.

6.4 Follow-up Tab

6.4.1 This tab is related to the BQAE tab and captures actions associated with RTS activities, trending of the event, and the final disposition of the event.



6.4.2 Tasks: Can be assigned to a specific individual to execute, assist with tracking RTS, or conduct follow-up activities. Email notification will be sent to the responsible party to inform them of any tasks for which they are responsible. When a task is past due the assigned person and BQAE will be sent notification on a weekly basis until the task is addressed or the Due date revised. Tasks must be completed before Part 2 may be approved.

6.4.3 Attachments that document the RTS or follow-up may be added.

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6.4.4 Owner Follow-up: Field allows for an explanation of activities performed or results that are not part of an attachment.

6.4.5 Disposition of Engineering Event: Captures the final status of the event. The options are Approved, Conditionally Approved, Cancelled, or Rejected. Any entry other than Approved will require a comment in the RTS activities review comments section.

6.4.5.1 Conditional Approval is used in cases where factors prevent the timely resolution of the EE. Examples would be a repair or validation/data collection activity requiring funding approval or a lead time of unknown duration.

6.4.5.2 The comment for Conditional Approval should detail the associated circumstances.

6.4.5.3 If the EE is conditionally approved a follow up EE referencing the original EE is required to finalize the event.

6.4.6 RTS activities review comments: BQAE will complete this section unless RTS activities were not required in which case the section will be marked as NA or not applicable.

6.5 Printing/Signing of Part 1 (Originator, Other Info, and BQAE tabs) and Part 2 (Follow-up) Forms

6.5.1 When the tabs associated with each form are approved by the owner and QA, the form is locked (font shown in gray and no longer editable). BQAE has the ability to revoke the approval if there is a need for additional edits, if this occurs the digital approvals must be reapplied before printing is possible.

6.5.2 To print, BQAE uses Reports under the EE tab and selects either Part 1 or Part 2. Reports may only be printed officially if both digital approvals are applied; a message of an unofficial copy will be printed otherwise.

6.5.3 The report and the attachments (unless magnitude of the attachment is prohibitive) are printed and routed for signature.

6.6 Filing of Printed Signed Copies

6.6.1 Signed EEs and the associated printed attachments are given to BQA to be filed in the document control room. EEs are filed in binders by the EE number.

6.6.2 As part of the filing process Record Receipt of the hard copy under the EE menu. Enter the EE number, form Part and the date. This entry will populate the Closed Dates under the Approvals Tab.

7.0 Vendor Complaint Tracking

7.1 The Engineering Event system will be used with the considerations below to document complaints or feedback for vendors that supply equipment management services (for example calibration or maintenance services).

7.2 Considerations for Completing an EE form for a Complaint

7.2.1 Originator and Other Info Tab

- Equipment/Utility Name: input the vendor name
- Owner: input Originator's name
- Location: leave blank

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- Type: Select "Complaint", "Unplanned", and "Temporary"
- Description: Describe the complaint
- Equipment Info: leave blank if appropriate
- Action Taken: Describe the action taken. In some situations, no action will be taken:
    - For example, repeated failure of a vendor to return phone calls could be logged as a complaint. There may not be any action taken as a result of this specific complaint. An incorrect calibration certificate (miscalculation, etc.) may also be logged as a complaint and the action taken could be inputted as "requested updated calibration certificate".
        - Reason / Cause / Justification: Input any information that is known or input "N/A".
        - Assessment of potential impact: Input any information that is known or input "N/A".
        - Attachments: Input attachments where appropriate. For example, provide an example of an incorrect calibration certification.

7.2.1.1 BQAE Tab

The BQAE tab will be completed by QA Engineering (as for all other engineering events) with the following considerations:

- Impact: provide information if available.
- Adverse Impact: provide information if available. The adverse impact may be "no".
- Change Authorized: In most cases select "N/A".
- RTS Requirements: provide any appropriate information or input "N/A".
- Qualification Activities: provide any appropriate information or input "N/A".

7.2.1.2 Follow-up Tab

The Follow-up Tab will be completed by QA Engineering (as for all other engineering events) with the following considerations:

- RTS Activities Review Comments: provide any appropriate information. For example, in the example for an incorrect calibration certificate, document that a corrected certification was received. Otherwise, input "noted".
- Disposition of Engineering Event: select "approved" if appropriate.
- RTS Authorization Comments: provide any appropriate information or input "N/A".
- Trending: select appropriate trending category from drop-down list.

8.0 Assignment of Event Tracking Number

8.1 The electronic form automatically assigns a tracking number to the event using the following format.

EEYYMM###

Where EE designates an "Engineering Event"

YY are the last two digits of the year

MM are the digits of the month

is a sequential number assigned to the event, starting at 001 on the first of each month.

8.2 Therefore, EE1601003 is the 3rd engineering event registered in January 2016.

9.0 Documentation

9.1 Once electronically completed and printed, Form 21526-01. Parts 1 and 2, and any associated attachments are filed by BQA.

10.0 Definitions

10.1 **Engineering Event –** a planned or unplanned engineering change, equipment/system failure, shutdown or limited use request, or a calibration OOT where OOT equipment was used in the range impacted by the OOT.

10.1.1 **Engineering Change –** a planned modification to a piece of equipment/system/ building or area as part of a change or repair. Engineering changes also include changes to the intended use of equipment (such as a change from GMP to R&D status), and changes in location of non-portable equipment. Engineering changes are approved by BQA Engineering before being executed. Use the following guidelines but consult with BQAE if there are any questions as to whether an EE is needed.

10.1.1.1 **When Required -** the following are cases where an EE is needed. If the range, tolerance, or materials of construction (MOC) for key parts of the component vital to operation have changed an EE is needed. Firmware or software updates as revision control and an evaluation of changes is needed. Changes to systems used for aseptic processing of product such as filling equipment as such equipment is higher risk due to the stage of product it handles. If the role of the component is critical to operation and the risk associated with its failure is high. Changes to lubricants where there is potential for product contact.

10.1.1.2 **Like-For-Like –** this is a change to a system component considered similar enough that an EE is not required to document the change. Repairing a component with the same make and model or an equivalent with matching specifications are examples.

10.1.1.3 **Considerations –** the following should be considered in making a determination of like for like and the need for an EE. If the system component is product contact and the make and model were updated by the vendor to an equivalent part, an EE is still the best way to document the vendor substitution. Use an EE if there is no other approved mechanism, even if the requirements do not fall into the established categories of an EE, to capture the event.

10.1.1.4 **Exclusions –** an EE is not required for relocation of portable equipment, simply have the MEF database updated to reflect the change. Changes described and governed by other systems such as SOPs, Preventive maintenance, or calibration programs are themselves not considered EEs.

10.1.2 **Engineering Failure –** for the purposes of this SOP, an engineering failure is defined as an interruption in service, alarming, or operation outside accepted

parameters of a piece of equipment/system/building or area. Unplanned engineering changes are managed as engineering failures.

10.1.3 **Limited Use Request –** a request to place an active building, area, equipment, or system into a limited use status by reducing or eliminating monitoring, gowning, or cleaning requirements, eliminating use of specific use points for water, air, etc.

NOTE: A status of "Shut-down/Out-of-Service" denotes a non-functioning building, area, equipment, or system. "Limited Use" denotes that the building, area, equipment or system continues to be conditionally functional. In either status, cleaning, monitoring, and gowning requirements may be reduced or eliminated.

10.1.4 **Shut Down Requests/Out-of-Service –** a request to place a building, area, equipment, or system out-of-service. A Shut-down request may be made to take a building, area, equipment, or system to a non-functioning status to accommodate building/system renovation, repair, upgrades, preventive maintenance, and periods of non-use.

NOTE: Non-functioning equipment is assigned a status of "out-of-service" and placarded according to ***SOP 21508 - Equipment Calibration Program***.

10.1.5 **Out of Tolerance Event –** a situation where equipment is found not to meet specified calibration parameters established by the BDP. Refer to **SOP 21508** for additional detail.

10.2 **GMP Systems/Equipment** - a System/Equipment which operates in support of CGMP processes. This includes a system with a direct or indirect impact on product quality.

11.0 References and Related Documents

11.1 **SOP 21104** *Pre-Production Clearance*

11.2 **SOP 21301** *Deviations from Written Documents*

11.3 **SOP 21503** *Responding to Alarms*

11.4 **SOP 21508** *Equipment Calibration Program*

11.5 **SOP 21554** *GMP Area Status Management*

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