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| **Case Study Title:** | **Functional Equivalence for Equipment Replacements** | **Case No.** | **RMWG-03** |
| **GMP System Impacted:** | **Facilities and Engineering** | | |
| **Introduction / Background** | Pharmaceutical manufacturers have an obligation to ensure that their manufacturing equipment is properly designed, installed, tested, operated, and maintained throughout their service lifetimes. During these service lifetimes manufacturing equipment will likely require both preventive and corrective maintenance activities that may involve the replacement of parts within the systems. Parts replacements must be performed under the appropriate change controls to ensure that manufacturing equipment remains in a validated state with respect to installation, operation, and performance. Change control considerations are greatly facilitated when replacement parts are exactly identical to the original parts. However, it is not uncommon for pharmaceutical manufacturers to resort to procuring and installing replacement parts that are not identical to the original parts due to changes affected by parts suppliers (product redesigns, discontinuations, etc.). In these instances, a risk management approach may be utilized to systematically assess whether replacement parts are functionally equivalent (also referred to as like-for-like) with original parts in order to ensure proper change control while also preventing unnecessary revalidation activities.<br><br>In this case study, a risk management approach was taken by the firm to identify the following:<br>• Risks associated with equipment parts changes that might adversely impact the validated state of manufacturing equipment<br>• Risks associated with the process of determining whether original and replacement parts are functionally equivalent<br>• Proper roles and responsibilities of the functional areas involved in the process of determining whether original and replacement parts are functionally equivalent<br><br>The outputs of the risk management approach utilized by the firm included a generic, robust, and repeatable process for performing functional equivalence assessments as well as definition of organizational roles and responsibilities supporting the process. | | |
| **Defining the Risk Question** | The risk question developed for the subject case study is:<br><br>***What process and associated functional area roles and responsibilities are required in order to assess whether replacement parts are functionally equivalent with original parts in order to ensure proper manufacturing equipment change control while also preventing unnecessary revalidation activities?*** | | |

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| **Selecting a Risk Assessment Method** | In this case study, the firm elected to craft one risk assessment for the overall (generic) functional equivalence assessment process in order to achieve two objectives:<br><br>• Identify potential gaps, inconsistencies, and redundancies within the process that had historically been used for replacement parts functional equivalence determinations.<br><br>• Identify new or improved activities that would lead to robust, efficient, and consistent functional equivalence assessments moving forward<br><br>In order to support selection of a risk assessment method, the risk assessment team examined the risk question (above) and also identified the core activities supporting the historical functional equivalence assessment process as the basis for the risk assessment. The core activities that the team examined included the equipment change control process and the maintenance systems inventory process control flow. Upon these examinations, the team noted the following observations regarding the process that had historically been used for replacement parts functional equivalence determinations:<br><br>• The functional equivalence assessment process was historically dependent upon human judgment, expertise, and experience<br><br>• Process risks (potential breakdowns of the process) were qualitative in nature, and were difficult to quantify with specificity<br><br>Given these observations, the risk assessment team selected Fault Tree Analysis (FTA) as the risk assessment method since it is well suited for analysis of qualitative fault conditions that may be related to human performance factors.<br><br>The risk methodology selected for the subject case study is:<br><br>**Fault Tree Analysis (FTA)** |
| **Risk Assessment (Risk Identification, Analysis and Evaluation)** | The risk assessment process began with a review and analysis of the change control system to determine how equipment parts replacements could potentially cause an unwanted or undetected change to the equipment's validated state. The analysis was organized into the fault tree structure depicted below in Figure 1. This fault tree illustrates the potential means by which equipment changes such as parts replacements could pose risk to the validated state of the equipment. The team concluded that many of the potential fault pathways were already being appropriately mitigated by robust quality systems (such as training, validation, and change control) that were performing as intended and are routinely audited. However, significant gaps and improvement opportunities were noted around the process utilized for the functional equivalence assessments (indicated by the yellow pathway in Figure 1). |

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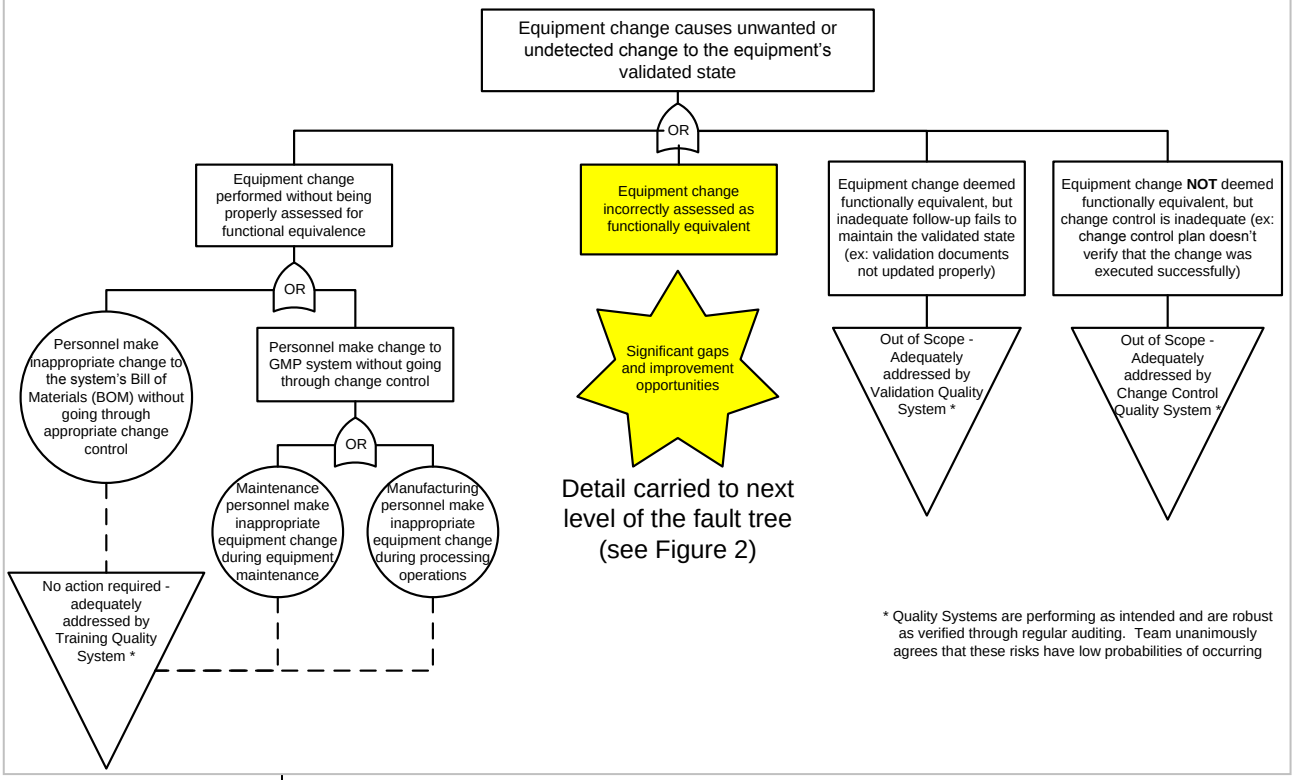
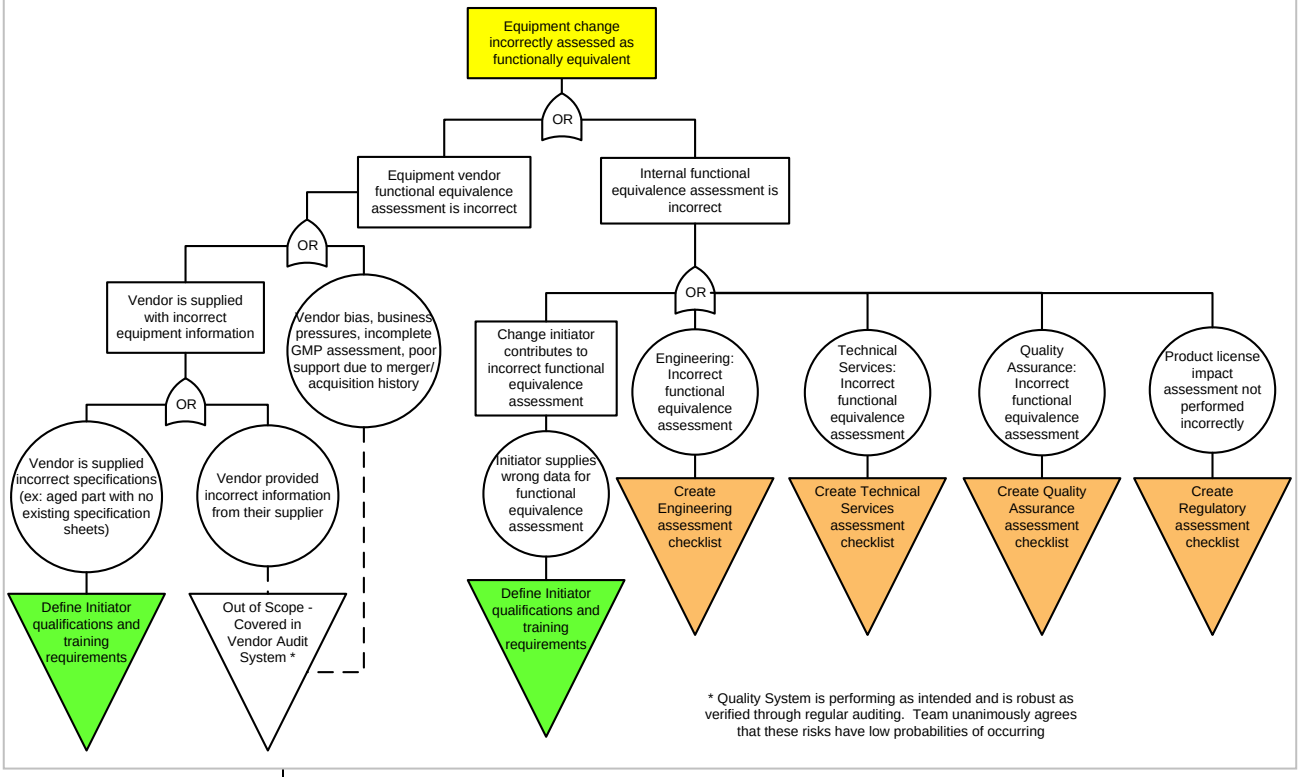
Figure 1 - Fault Tree Analysis of Equipment Changes and Associated Validation Impact




In order to further explore the risks associated with the functional equivalence assessment process for equipment replacement parts, the risk assessment team continued development of the fault tree as depicted below in Figure 2. The team focused on two key areas of risk: functional equivalence assessments performed by parts vendors, and functional equivalence assessments performed internally by the firm's different functional areas.

Figure 2 - Fault Tree Analysis of Functional Equivalence Assessments




The detailed fault tree analysis executed by the risk assessment team revealed two areas of significant risk where improvement was required:

- The Initiator (petitioner and preliminary data collector) for functional equivalence evaluations should be a Subject Matter Expert (SME) that is appropriately trained and qualified to craft accurate initial assessments (see green triangles in Figure 2).
- Specific roles and responsibilities for each functional area participating in functional equivalence assessments should be clearly defined (see beige triangles in Figure 2).

## Risk Control

For each of the two areas of significant risk identified in the FTAs and summarized above, associated risk control plans were established.

- Training curricula were established to define the training and qualification criteria for personnel initiating functional equivalence assessments. These controls were designed to ensure that Initiators would be able to identify, compile, and/or generate the data and rationale required to support thorough and accurate functional equivalence assessments.
- Roles and responsibilities for each functional area participating in functional equivalence assessments were delineated in the form of executable checklists designed to ensure that every functional equivalence assessment will be performed in a thorough and reproducible

fashion. Each organization identified in Figure 2 (Engineering, Technical Services, Quality Assurance, and Regulatory) created a checklist tailored to their specific roles and responsibilities that the team had collectively defined. This approach minimized both gaps and redundancies in the assessment efforts, while providing a common assessment record format to facilitate overall review of the assessment package. Each functional area checklist details unique areas of consideration for the assessment and provides spaces for the assessment conclusions and the signatures of the assessor(s). An example checklist from the Engineering functional area is shown below in Figure 3

Figure 3 – Engineering Functional Equivalence Determination Checklist

| Areas of Consideration | Typical Characteristics of Functionally Equivalent Parts | Assessment | Performed By |
|---|---|---|---|
| Materials of construction and ratings | | | |
| • Composition of process-contact parts | Comparable materials of construction for wetted surfaces | | |
| • Compatibility with process | Parts designed to operate at expected process extremes (heat, pressure, chemistry, etc.) | | |
| • Surface finishes | Comparable surface finishes that support continued effective cleaning and/or sterilization | | |
| Inputs, outputs, capacity and performance characteristics | | | |
| • Materials / flows | Similar mass-transfer characteristics (volume, pumping, friction loss, pressure drop, etc.) | | |
| • Electrical | Similar electrical service requirements and electrical performance characteristics (resistance, frequency, voltage) | | |
| • Data | Data receipt and/or transmission in the same format (units, file types, etc.) and with similar performance characteristics (reporting frequency, speed, etc.) | | |
| • Sizes | Comparable sizes (ex: inlet size, nominal hold capacity, outlet size) | | |
| • Metrology | Measurement tolerances, scales, and units that meet process specifications and are comparable | | |
| System connections | | | |
| • Units (for instruments, control systems) | Part connections that allow for receipt and/or transmission of data in the same format (units, file types, etc.) and with the similar performance characteristics | | |
| • Orientation (for hardware) and configurations | Parts are physically configured (as constructed and as installed) in a comparable manner so as to continue to meet process specifications and support process performance (ex: flow, drainability, cleanability, sterilization, etc.) | | |
| • Sizes / locations | Parts utilize the same system connections in the facility | | |
| Specifications (general) | | | |
| • Mechanisms of action | Parts have comparable mechanisms of action (ex: sequence of operations, purported usage, design and operating principles, etc.) | | |
| • Operational ranges | Parts feature comparable operational ranges across all process parameters | | |

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| **Risk Documentation and Communication** | The outputs of this risk management effort comprise the documented justification for controlled revisions to:<br>• Training and qualification curricula for personnel initiating change controls where functional equivalence will be assessed<br>• Equipment change control SOPs that direct the functional equivalence assessment process for parts replacements<br>• Maintenance systems inventory process control flow<br>Training is required to be performed on these updated documents and training records are periodically audited for compliance. |
| **Risk Review** | As part of the firm's standard practice for the ongoing maintenance of quality systems, routine audits and document reviews are performed throughout each of the quality systems impacted by this risk assessment (in this case training, change control, and equipment maintenance). Adverse findings or trends identified during these reviews would provide indication whether the risk assessment needs to be revised. |