Understand and Know How to Effectively Use Key Risk Tools

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The objective of this workshop is to provide a guidance of how to use different risk analysis tools. This workshop will describe different scenarios and tools that can be use in risk based approach life cycle projects.
Understand and Know How to Effectively Use Key Risk Tools

Agenda:

- Concepts and Definitions
- Why risk based approach
- Risk Tools
- Interactive Exercise: Using real life examples, participants will decide what are the best risk tools and why
- Bonus Material
- Q&A
Concept and Definitions

What is a Risk Based Approach or Risk Management Approach?

Risk Management is defined by Business dictionary.com as the identification, analysis, assessment, control, and avoidance, minimization, or elimination of unacceptable risks. [http://www.businessdictionary.com/definition/risk-management.html#ixzz3BVbyA7DN](http://www.businessdictionary.com/definition/risk-management.html#ixzz3BVbyA7DN)

ISPE on GAMP 5 Guidance define Quality Risk Management Approach as a systematic process for the assessment, control, communication, and review of risks.
Concept and Definitions

What is a Risk Based Approach or Risk Management Approach?


Concept and Definitions

- What is a Risk Based Approach or Risk Management Approach?

- In summary risk based approach require:
  - Identification of the risk
  - Analysis of the risk
  - Evaluation or assessment of the risk
  - Control the risk by avoid the risk, minimize the risk under acceptable levels, or eliminate the risk
  - Review the risk and continue monitoring the process
Concept and Definitions

- Impact Assessment (IA) is the document that defines the system/equipment criticality (Direct, Indirect, or No Impact). This document is the key to develop the risk-based approach for the entire project.

- Risk Assessment (RA) is the document that identifies the potential risk associated with the system/equipment, process, and/or project constraints. Multiple risk assessments can be performed to cover different aspects of the project. Risk assessments should define the following items:
  - System/Equipment description
  - Potential failure/risk
  - Severity
  - Probability
  - Detectability
  - Risk level
Why Risk Based Approach?

- Benefits
- Requirement
- Model
Benefits:

- Help to classify the system / equipment as GMP or Business Critical.
- Provide a clear justification of the decision made based on risk criticality.
- Identify and evaluate every single risk of the system / equipment.
- Identify areas that will require more evaluation, adjustments, or re-design prior to the implementation.
- Provide controls to reduce risk to an acceptable level.
- Provide a solid rational of the project plan, schedule, and project due date.
- Put more effort in the design stage of the process but minimize the qualification effort which means less down time.
- Avoid waste effort and duplication while minimize down time.
Effective quality risk management can facilitate better and more informed decisions, can provide regulators with greater assurance of a company’s ability to deal with potential risks, and can beneficially affect the extent and level of direct regulatory oversight.


Quality Risk Management Approach are based on clear process understanding and potential impact on patient safety. In other words, Quality Risk Management is based on GMPs systems/ equipment and how the patient safety could be impacted.
Requirements:

What are the requirements of Risk-Based Approach?

- Determine the overall impact of the project in the patient safety, product quality, and data integrity
- Analyze the risk to the business
- Identify risk to specific process
- Identify risk to specific functions
- Design to eliminate risk
- Define controls to mitigate risk that cannot be eliminated
- Define validation strategy
- Revise the risk assessments as require during the project life
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- **Model: Quality Risk Management Process**
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Model: Project Life Cycle Risk Based Approach

- System / Equipment URS
- Impact Assessment GMP or Business Critical
- Business
- Request for Proposal (RFP) GEP
- FAT (Equipment Only)
- Commissioning (Non GMP)
- Risk Assessment PFMEA/FTA/HAZOP/Risk Priority/ etc...
- GMP
- Val. Strategy (as applicable)
- Functional Req. Spec (FRS)
- Design Spec (DS) / Design qualification (DQ)
- Qualification Test Risk based Approach Evaluation
- Abbreviated Qualification
- Risk Assessment and Traceability Matrix Review
- FAT/SAT
- WS Final Report
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- **Risk Tools**
  - Type of risk assessment
  - Most Common Risk Assessments Types
  - The Use
  - How to Implement Risk Tools
Type of risk assessment

Impact Assessments:
- Impact Assessment to New Equipment/Facility/Software/Process (EFSP) – Direct, Indirect, No Impact
- Impact Assessment to changes in EFSP – installation, operational functions, Performance, or process or CPP.

Risk Assessments:
The most common:
- FMEA (Failure Modes & Effects Analysis)
- FTA (Fault Tree Analysis)
- HAZOP (Hazard Operability Analysis)
- Risk Priority
### Impact Assessment to New Equipment/Facility/Software/Process (EFSP) – Direct, Indirect, No Impact

#### Impact Assessment for Equipment/Facility/System/Process

<table>
<thead>
<tr>
<th>Equipment/Facility/System/Process (EFSP)</th>
<th>Brief Description of Use</th>
<th>Does the EFSP cause a direct physical contact with the product?</th>
<th>Does the EFSP involve a distribution of a material that has direct contact with the product?</th>
<th>In the EFSP used in manufacturing, is sterilization or decontamination required?</th>
<th>Does the EFSP produce, monitor, evaluate, store or report data used to control or reject product or CIP materials or data used to control or reject product or CIP materials or data used to monitor or evaluate product or CIP materials or data used to monitor or evaluate product or CIP materials or data used to monitor or evaluate product?</th>
<th>Does the EFSP perform a sterilization step or operation in the manufacturing, processing, packaging, or testing?</th>
<th>Direct/Indirect/No Impact</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Media Fill</strong></td>
<td></td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Direct/Indirect/No Impact</td>
<td>Notes</td>
</tr>
<tr>
<td><strong>Anализер</strong></td>
<td></td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Direct/Indirect/No Impact</td>
<td>Notes</td>
</tr>
<tr>
<td><strong>HPW and Clean Stream</strong></td>
<td></td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Direct/Indirect/No Impact</td>
<td>Notes</td>
</tr>
<tr>
<td><strong>Eq. Monitoring Systems</strong></td>
<td></td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Direct/Indirect/No Impact</td>
<td>Notes</td>
</tr>
<tr>
<td><strong>Labeler</strong></td>
<td></td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Direct/Indirect/No Impact</td>
<td>Notes</td>
</tr>
<tr>
<td><strong>Railer</strong></td>
<td></td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Direct/Indirect/No Impact</td>
<td>Notes</td>
</tr>
<tr>
<td><strong>Caseracker</strong></td>
<td></td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Direct/Indirect/No Impact</td>
<td>Notes</td>
</tr>
</tbody>
</table>

**Comments:** Write a brief rationale on removal, shelve, delete, or modify.

**Prepared By/Date:**
- QA/Validation Engineer: _________________________________

**Approved By/Date:**
- Project Engineer Manager: ________________________________
- Operations Manager: ________________________________
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Impact Assessment to changes in EFSP – *installation, operational functions, Performance, or process or CPP*

<table>
<thead>
<tr>
<th>Equipment/Facility/System/Process (EFSP)</th>
<th>Brief description of the change</th>
<th>Does change impact qualified / validated state?</th>
<th>Does change affect installation?</th>
<th>Does change affect operational functions?</th>
<th>Does change affect the performance of the EFSP?</th>
<th>Does change affect Process or CPPs?</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Env. Monitoring Systems</td>
<td>Preplacing sensors</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Change Request and Qualification Required</td>
</tr>
<tr>
<td>Labelers</td>
<td>Adding a new configuration new change parts)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Change Request and Qualification Required</td>
</tr>
<tr>
<td>Boilers</td>
<td>Boiler upgrade</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No Change Request or Validation</td>
</tr>
<tr>
<td>Casepacker</td>
<td>Replacing PLC</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No Change Request or Validation</td>
</tr>
</tbody>
</table>

**Rational:**
Write a brief rational of the qualification or verification strategy recommended for the applicable change.

**Performed By/Date:**
Validations Engineer:

**Approved By/Date:**
Packaging Engineer:
Process Excellence:
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FMEA (Failure Modes & Effects Analysis)

http://www.six-sigma-material.com/FMEA.html
FTA (Fault Tree Analysis)

http://archaqx.blogspot.com/2010_07_01_archive.html
HAZOP (Hazard Operability Analysis)

<table>
<thead>
<tr>
<th>Area:</th>
<th>Unit:</th>
<th>Node:</th>
<th>Drawings:</th>
<th>Design intent:</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>No.</th>
<th>Guideword</th>
<th>Deviation</th>
<th>Causes</th>
<th>Consequences</th>
<th>Safeguards</th>
<th>Recommendation</th>
<th>Action by</th>
</tr>
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</tbody>
</table>

http://www.enggencyclopedia.com/2012/05/hazop-study/
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Risk Priority

<table>
<thead>
<tr>
<th>Probability</th>
<th>Low</th>
<th>Medium</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td></td>
<td></td>
<td>Risk Class 1</td>
</tr>
<tr>
<td>Medium</td>
<td></td>
<td></td>
<td>Risk Class 2</td>
</tr>
<tr>
<td>Low</td>
<td></td>
<td></td>
<td>Risk Class 3</td>
</tr>
</tbody>
</table>

Severity = Impact on Patient Safety, Product Quality, and Data Integrity (or other harm)
Probability = Likelihood of the fault occurring
Risk Class = Severity × Probability

<table>
<thead>
<tr>
<th>Detectability</th>
<th>High</th>
<th>Medium</th>
<th>Low</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk Class</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

High Risk Priority
Medium Risk Priority
Low Risk Priority

Detectability = Likelihood that the fault will be noted before harm occurs
Risk Priority = Risk Class × Detectability

Source: Figure M3.5, GAMP 5: A Risk-Based Approach to Compliant GxP Computerized Systems, © Copyright ISPE 2008. All rights reserved. www.ISPE.org.
The Use:

- Impact Assessment to New Equipment/ Facility/ Software/ Process (EFSP): Used to classify the new EFSP between Direct, Indirect, or No Impact to the product/device quality related with patient safety.

- Impact Assessment to changes in EFSP: Used to determined if the changes have impact to the installation, operational functions, performance, process or CPP of Direct impact EFSP.

- FMEA (Failure Modes & Effects Analysis): Mostly used to identify failure mode in processes like manufacturing process (PFMEA) and design process (DFMEA). FMEA is based on severity, occurrence and detection. (e.g. Possible failure modes in a manufacturing line, product development, device design, etc…)
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The Use:

FTA (Fault Tree Analysis): Typically used to determine cause of a failure and path of an event as part of an investigation. (e.g. Media Fill positive, poor performance in a system/device) However, it can be use to determine how to mitigate a possible risk.

HAZOP (Hazard Operability Analysis): Used for safety risk evaluation. It is focus in an issue, cause of the issue and it consequences. (e.g. Packaging Work area safety assessment, Employee position safety assessment like chemist, line operator, etc…)

Risk Priority: Used to categorize the risk of a possible failure. It takes in consideration the severity probability and detectability, like FMEA, but focus in specific events. (e.g. Reduce quantity of lots to be run in a validation, categorize changes in existing EFSP between Low/Medium/High)
How to implement risk tools

When we use risk assessments, we need to have a rational that justify the risk assessment and the tools to be used. In other words, we need to define the assumptions and rules of the game. Some of the justifications are:

- **Vendor documentation** – Certificates, White Papers, systems validations
- **Industry Guidance** – ISPE, ASTM, PDA, EU, CFRs, etc…
- **Knowledge and Statistical Historical Data in our process:**
  - Anova: Analyze difference in performance - % of missing caps in capper machines and determine cold spot in a autoclave
  - Control Chart: Demonstrate that the parameters are within the acceptable range - fill volume, temperature range, critical process parameters, etc…
  - Cpk: Demonstrate that a process is in control and centered - cap torque, concentration, part or component measure, etc…
Example:

Introduction of a product to a new line:

- Develop a FMEA describing the following failure modes:
  - Raw material interaction, solubility, etc…
  - Manufacturing equipment (tanks, pipe, etc…) compatibility, if new equipment is required, dedicated or non-dedicated parts.
  - Component configuration and product compatibility
  - Micro and Chemistry test method impact
  - Storage, handling, and distribution impact
  - Environmental considerations
- Use HAZOP for safety analysis (if applicable)
- Use Fault Tree Analysis for high failure modes that don’t have obvious solution (e.g. Product not homogeneous)
- Use Priority risk to justify why some testing will not be performed.
# PFMEA

## PFMEA Description/Scope:

<table>
<thead>
<tr>
<th>Process step</th>
<th>Potential failure</th>
<th>Potential Effect</th>
<th>SEV</th>
<th>Potential Cause</th>
<th>OCC</th>
<th>Current Controls</th>
<th>DET</th>
<th>RPN</th>
<th>Actions</th>
<th>SEV</th>
<th>OCC</th>
<th>DET</th>
<th>RPN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Storage</td>
<td>Spill</td>
<td>Explosion due to contact with other material</td>
<td>10</td>
<td>Damage drum</td>
<td>3</td>
<td>SOPs, segregation</td>
<td>10</td>
<td>300</td>
<td>Add spill container</td>
<td>10</td>
<td>3</td>
<td>1</td>
<td>30</td>
</tr>
<tr>
<td>Bulk</td>
<td>Prod. not homogeneous</td>
<td>Out of Spec Product</td>
<td>10</td>
<td>Wrong Agitator design</td>
<td>2</td>
<td>Existing agitator</td>
<td>1</td>
<td>20</td>
<td>N/A</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Wrong Mixing time</td>
<td>2</td>
<td>New product and process</td>
<td>10</td>
<td>200</td>
<td>Performance Process Qualification</td>
<td>10</td>
<td>2</td>
<td>2</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Wrong Soln Temp</td>
<td>4</td>
<td>New product and process</td>
<td>10</td>
<td>400</td>
<td>Performance Process Qualification</td>
<td>10</td>
<td>4</td>
<td>2</td>
<td>80</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Raw Mat. Not dissolved</td>
<td>3</td>
<td>Performance Process Qualification</td>
<td>10</td>
<td>300</td>
<td>Performance Process Qualification</td>
<td>10</td>
<td>3</td>
<td>2</td>
<td>60</td>
</tr>
</tbody>
</table>
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- HAZOP

<table>
<thead>
<tr>
<th>Area</th>
<th>Warehouse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unit</td>
<td>Incoming Raw Material</td>
</tr>
<tr>
<td>Drawing</td>
<td>BL-12345</td>
</tr>
<tr>
<td>Design Intent</td>
<td>Storage incoming raw material</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>No.</th>
<th>Deviation</th>
<th>Cause</th>
<th>Risk</th>
<th>Protection</th>
<th>Recommendation</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Spill</td>
<td>Defective drum</td>
<td>High corrosive material</td>
<td>Area segregation, Safety signs</td>
<td>Add spill containers with 50% more of total drum capacity.</td>
<td>Spill container added.</td>
</tr>
</tbody>
</table>
Fault Three Analysis:

- Product not homogeneous
  - Inadequate mixing
    - Wrong agitator design
    - Wrong mixing time
  - Material not in solution
    - Wrong Soln. Temp
    - Raw Material needs to be dissolved prior to add it to the batch
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- Risk Priority
Interactive Exercise:

Using real life examples, participants will decide what are the best risk tools and why

- **Systems:**
  - Upgrade to manufacturing equipment PLC/HMI

- **Equipment:**
  - Autoclave
Bonus Material

- Impact Assessment Determination and Qualification Requirements Charts
- Risk Priority
Questions and Answers

?