Basics of Quality Risk Management

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Module Topics

- Current Regulatory Expectations
- Some Important Definitions
- Risk Management Process
- Examples and modified FMEA
Module Objectives
On completion of this module you should be able to:

- State how Pharmaceutical Quality System (ICHQ10) and Quality Risk Management (ICH Q9) are integrated
- Conduct basic risk assessments
- Apply some basic QRM tools to industry examples
- Develop a simple FMEA for an example pharmaceutical product

Some Key Definitions

**Risk**
- Combination of the probability of occurrence of harm and the severity of that harm (ISO/IEC Guide 51:1999, definition 3.2)

**Residual Risk**
- Risk remaining after protective measures have been taken (ISO/IEC Guide 51:1999, definition 3.9)

**Tolerable Risk**
- Risk which is accepted in a given context based on the current values of society (ISO/IEC Guide 51:1999, definition 3.7)

**Risk Management File**
- The set of records and other documents, not necessarily contiguous, that are produced by a risk management process (ANSI/AAMI/ISO 14971: definition 2.19)
Some Key Definitions
(from AS4360 and ISO14971)

Risk analysis
- systematic use of available information to identify hazards and to estimate the risk. Risk analysis includes examination of different sequences of events that can produce hazardous situations and harm

Risk evaluation
- process of comparing the estimated risk against given risk criteria to determine the acceptability of the risk

Risk criteria
- terms of reference by which the significance of risk is assessed

Risk reduction
- actions taken to lessen the likelihood, negate consequences, or both, associated with a risk.

Hazard
- potential source of HARM (ISO/IEC Guide 51:1999, definition 3.5)

Hazardous situation
- circumstance in which people, property, or the environment are exposed to one or more hazard(s)

Harm
- physical injury or damage to health of people, or damage to property or the environment (ISO/IEC Guide 51:1999, definition 3.1)

Severity
- measure of the possible consequences of a hazard
Managing Risk

- We manage risk continuously, sometimes without realizing it.
- We mostly consider risk implicitly in our decision making.
- The alternative to risk management is “risky management” or reckless decision making.
- Important to maintain a balance between responsibility for risk and ability to control that risk.
- Perception of risk is increased when we have no control over circumstances.

Some definitions to keep in mind
(ICH Q9 – Guidance - Quality Risk Management)

“It is commonly understood that risk is defined as the combination of the probability of occurrence of harm and the severity of that harm.”

PRINCIPLES OF QUALITY RISK MANAGEMENT

The evaluation of the risk to quality should ultimately link back to the protection of the patient;
ICH Q9 and ANSI/AAMI/ISO 14971 Risk Model

Risk Identification
Risk Analysis
Risk Evaluation
Risk Acceptability Decisions
Risk Control

- Post-production experience
- Review of risk management experience

Risk Identification
Risk Analysis
Risk Evaluation
Risk Acceptability Decisions
Risk Control

- Option analysis
- Implementation
- Residual risk evaluation
- Overall risk acceptance

Risk Assessment
Risk Management
Risk Control

Post Production Information

PIC/S GMPs – 2009 and Risk
(the part that’s auditable)

- The basic concepts of Quality Assurance, Good Manufacturing Practice, Quality Control and Quality Risk Management are interrelated. (Ch. 1 Principles)

- Quality Risk Management can be applied both proactively and retrospectively. (Clause 1.5)

- A risk assessment approach should be used to determine the scope and extent of validation. (Annex 15 Principles)

- The likely impact of the change of facilities, systems and equipment on the product should be evaluated, including risk analysis. (Annex 15 Change Control)
PICS GMPs – 2009 and Risk

The quality risk management system should ensure that:

- the evaluation of the risk to quality is based on scientific knowledge, experience with the process and ultimately links to the protection of the patient;

- the level of effort, formality and documentation of the quality risk management process is commensurate with the level of risk.

Clause 1.6

PIC/S GMPs - Annex 20 provides voluntary methodology for applying risk management to Pharmaceuticals.

Applying QRM to the PQS Quality System

<table>
<thead>
<tr>
<th>QS Element</th>
<th>Rationale for Application</th>
</tr>
</thead>
<tbody>
<tr>
<td>Auditing Programs</td>
<td>Assign non-conformance criticality ratings based on risk to GMP compliance or product safety.</td>
</tr>
<tr>
<td>Complaints and Recalls</td>
<td>Assign initial risk evaluations to incoming incidents and again after post investigation.</td>
</tr>
<tr>
<td>CAPA System</td>
<td>Generally incidents or potential risks are qualified into the CAPA system from other QMS elements. The CAPA system manages the company higher level risk issues. Rational for Application</td>
</tr>
<tr>
<td>Deviations</td>
<td>Initial informal potential risks are assessed whenever a deviation occurs. If the risk is assessed as potentially significant then a formal deviations report is raised and risk is assessed within that document.</td>
</tr>
<tr>
<td>Quality Defects (Non-conformances)</td>
<td>Whenever a product or material does not meet specifications or in-house control limits a non-conformance report is raised. The final disposition of the Lot is not based on risk assessment however the potential for other related Lots to also be defective may be warranted based on a risk assessment.</td>
</tr>
</tbody>
</table>
Applying QRM to the PQS Quality System

<table>
<thead>
<tr>
<th>QS Element</th>
<th>Rationale for Application</th>
</tr>
</thead>
<tbody>
<tr>
<td>Computerised Systems</td>
<td>Computerised systems are assessed for risk levels based on GxP criticality and system complexity. This will drive the validation programs and the extent of formal controls.</td>
</tr>
<tr>
<td>Validation Programs</td>
<td>The cGMP requires that validation programs be driven by risk assessment (Annex 15 – 1 Principle. This is addressed in the VMP.</td>
</tr>
<tr>
<td>Change Control</td>
<td>Change control requires an impact assessment based on potential risks to marketing authorisation, compliance, maintenance of the validated state and patient safety.</td>
</tr>
<tr>
<td>Training and Documentation</td>
<td>The depth and extent of training and documentation should be directly related to the criticality of that operation to product quality. For example intensive competency training and documentation is required for aseptic operators but may not be warranted for non GMP related activities.</td>
</tr>
</tbody>
</table>

Risk Management System

- Risk Reports
- Risk Manager
- QA Manager
- Risk Gap Analysis
- Risk Register

Executive
   - Risk Policy
   - Organisation
     - Position Descriptions
     - SOP(s)
       - CAPA
       - Deviations
       - Complaints
       - Non-Conformances
       - Validation
       - Audits

RM Training

RM Tools
RM Templates
Risk Forms and Templates

- Risk Reports Register
- Quality Records - Risk Analysis Qualitative Summary Record
- Quality Record - Risk Analysis Simplified FMEA Template
- Quality Record - Risk Analysis Full FMEA Template

Formal and Informal Risk Techniques (ICH Q9)

- It is neither always appropriate nor always necessary to use a formal risk management process (using recognized tools and/or internal procedures, e.g., standard operating procedures).
- The use of informal risk management processes (using empirical tools and/or internal procedures) can also be considered acceptable
- The level of effort, formality, and documentation of the quality risk management process should be commensurate with the level of risk.
When should Risk Assessment be initiated?

<table>
<thead>
<tr>
<th>Event Occurs</th>
<th>Then ..........</th>
</tr>
</thead>
<tbody>
<tr>
<td>the event is judged to be insignificant or has negligible potential to impact a patient ..........</td>
<td>do not initiate a formal risk assessment. Record the event as required by SOPs and GMP records. The reason for the decision to not to conduct a formal risk assessment is not needed.</td>
</tr>
<tr>
<td>the event may or may not be significant or may have some potential to impact a patient ...............</td>
<td>consider moving to a formal risk assessment. Seek the advice of the QA Manager and other company management before proceeding. The reason for any decision to not to conduct a formal risk assessment is required.</td>
</tr>
<tr>
<td>the event has reasonable foreseeable potential to be significant or impact a patient ..........</td>
<td>initiate a formal risk assessment.</td>
</tr>
</tbody>
</table>

Who should be involved in risk identification, analysis & assessment?

- **Team based risk assessment is essential**
- Need the “voice of the customer” present – may refer to clinical advice?
- Need a person with expert product or process knowledge
- Need a quality assurance /regulatory representative
- Need a production/engineering representative
Components of Product Risk Assessment

1. Risk identification and analysis
   • What can go wrong? (Hazards and their Failure Modes)

2. Risk evaluation
   • What are the consequences if it did go wrong? (Hazard ....... Harm ....... Severity)
   • What is the likelihood it will go wrong? (Probability)

3. Risk acceptability decision
   • Is the risk tolerable or acceptable?
   • Or should it be mitigated or controlled?

Relating Hazards to Harm – Example

<table>
<thead>
<tr>
<th>Potential Hazard</th>
<th>Foreseeable sequence of events (Failure Mode)</th>
<th>Hazardous situation</th>
<th>Harm (Severity)</th>
</tr>
</thead>
</table>
| Chemical (cleaning residue) | 1) Incomplete cleaning of equipment used in prod’n 2) Use wrong cleaning agent | Patient receives undetected dose of impurities | • Adverse reaction  
• Acute injury  
• Complaint |
| Biological (Microbial contamination) | (1) Excessive bioburden in bulk mix due to:  
(1) poor cleaning  
(2) extended/ wet storage of equipment  
(3) Environmental | Bioburden grows through the filter and contaminates product. Lower SAL | • Fails sterility test  
• Bacterial infection  
• Death |
| Pyrogens (biological contamination) | (1) Excessive pyrogens in product due to:  
(1) HA0 cycle failure  
(2) Inadequate vial wash | Undetected pyrogens appear in finished product. | • Fails LAL test  
• Febrile reaction by patient  
• Acute / chronic injury |
### Risk Assessment Components - Risk Priority Number (RPN)

- **Severity or Consequences**: Potential hazard or harm (the consequences) to the Patient or User
- **Frequency / Likelihood**: Past History or Knowledge of the probable failure mode
- **Probability**: Would our detection systems stop the hazard before it reached patients
- **Detectability**: Refers to

\[ \text{RPN} = \text{Severity or Consequences} \times \text{Probability} \times \text{Detectability} \]

### Suggested Severity Levels

<table>
<thead>
<tr>
<th>Severity level (Quantitative)</th>
<th>Severity level (Qualitative)</th>
<th>Example description of consequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Negligible</td>
<td>Will not result in harm requiring attention.</td>
</tr>
<tr>
<td>2</td>
<td>Marginal</td>
<td>Results in customer inconvenience and/or harm requiring local first aid treatment.</td>
</tr>
<tr>
<td>3</td>
<td>Moderate</td>
<td>Results in serious harm or a customer / community health problem requiring medical treatment.</td>
</tr>
<tr>
<td>4</td>
<td>Critical</td>
<td>Results in extensive harm or a customer / community health problem requiring hospitalisation or prolonged medical treatment.</td>
</tr>
<tr>
<td>5</td>
<td>Catastrophic</td>
<td>Results in death or extensive harm; a general community health problem attracting public interest and requiring significant medical treatment or hospitalisation for those effected.</td>
</tr>
</tbody>
</table>
DoH Suggested Likelihood Levels

<table>
<thead>
<tr>
<th>Likelihood level (Quantitative)</th>
<th>Likelihood level (Qualitative)</th>
<th>Example description of probability (based on events/time)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Rare</td>
<td>Unlikely</td>
<td>May occur every 10–30 years</td>
</tr>
<tr>
<td>2 Unlikely</td>
<td>Possible</td>
<td>May occur every 5-10 years</td>
</tr>
<tr>
<td>3 Possible</td>
<td>Likely</td>
<td>May occur every 1-5 years</td>
</tr>
<tr>
<td>4 Likely</td>
<td>Almost Certain</td>
<td>May occur more than once per year</td>
</tr>
<tr>
<td>5 Almost Certain</td>
<td></td>
<td>May occur several times per year</td>
</tr>
</tbody>
</table>

Example Risk Evaluation Table

<table>
<thead>
<tr>
<th>Probability</th>
<th>Negligible (1)</th>
<th>Marginal (2)</th>
<th>Moderate (3)</th>
<th>Critical (4)</th>
<th>Catastrophic (5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Almost certain</td>
<td>Medium (5)</td>
<td>High (10)</td>
<td>High (15)</td>
<td>High (20)</td>
<td>High (25)</td>
</tr>
<tr>
<td>Likely</td>
<td>Low (4)</td>
<td>Medium (8)</td>
<td>High (12)</td>
<td>High (16)</td>
<td>High (20)</td>
</tr>
<tr>
<td>Possible</td>
<td>Low (3)</td>
<td>Medium (6)</td>
<td>Medium (9)</td>
<td>High (12)</td>
<td>High (15)</td>
</tr>
<tr>
<td>Unlikely</td>
<td>Low (2)</td>
<td>Low (4)</td>
<td>Medium (6)</td>
<td>Medium (8)</td>
<td>High (10)</td>
</tr>
<tr>
<td>Rare</td>
<td>Low (1)</td>
<td>Low (2)</td>
<td>Low (3)</td>
<td>Low (4)</td>
<td>Medium (5)</td>
</tr>
</tbody>
</table>
Example Analysis

The company manufactures microdose, narrow therapeutic prescription tablets. **The mixing process is not validated**

<table>
<thead>
<tr>
<th>Hz #</th>
<th>Hazard Statement</th>
<th>Potential or Foreseeable Failure Modes:</th>
<th>Potential Harm:</th>
<th>Score</th>
</tr>
</thead>
</table>
| 1    | The patient receives a dose that is outside the therapeutic window | The mixing process is not validated for the new blender. The bulk product is not mixed to acceptable homogeneity (less than 3% rsd) | (a) the patient receives **excess dose** - leads to patient acute discomfort and a complaint  
(b) the patient receives **insufficient dose** – which could lead to inadequate treatment and complaint / adverse event but no chronic harm. | 8  
|      |                  |                                        |                 | 6     |

Example Likelihood (Frequency) Analysis

- These records were examined
  - In-process testing records for last 12 months (23 batches)
  - Non-conforming (failed) batches history - last 2 years
  - Complaints history
  - Maintenance history of the blending equipment
  - Adverse events profile
  - Internal audit reports for the process line
  - Tested multiple samples from the current manufactured Lot

The risk team concluded that the process potentially that it was possible that 1 in 10 batches would produce defects.
Example
Detectability (Frequency) Analysis

<table>
<thead>
<tr>
<th>Hz#</th>
<th>Detectability</th>
<th>Score</th>
<th>Frequency Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>The risk team identified, via examination of batch records and process instructions:</td>
<td>8</td>
<td>The Frequency was calculated as: [ Pr(\text{occur}) \times \text{Detect.} ] 8.6 = 8</td>
</tr>
<tr>
<td></td>
<td>• There was no in-process testing for bulk blend uniformity.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• The QC laboratory tested 20 tablets for content uniformity from an average batch size of 200,000 tablets</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Occasional units are checked for defects</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Risk Rank = Severity (8) x Likelihood (8) x Detectability (8) = 512 ..., Unacceptable

Typical Risk Acceptance Criteria (based on analysis)

- **Unacceptable Risk**: Cannot accept the risk - must re-design product/processes or not proceed
- **High/Major Risk**: Cannot accept the risk - must mitigate or control the risk eg via validation of processes
- **Medium Risk**: Should or may mitigate or control the risk eg. increase verification/testing or other controls
- **Low (ALARP) Risk**: As Low As Reasonably Practical Risk - broadly acceptance - action is optional. Document procedures and Train personnel
- **Negligible Risk**: The risk is inconsequential and no action is warranted - business as usual.
Risk Control/ Risk Mitigation

1. Risk Control - Option Analysis
   • What can be done to mitigate risks?
   • What options are available?
   • What are the trade-offs in terms of risks, benefits and costs?

2. Existing Controls
   • What controls are already in place?

3. Monitoring and Control Plans
   • Can we detect the failure mode?
   • What monitoring and reporting feedback are in place?

ICH Q9 - Some Risk Tools

- Below is a non exhaustive list of some of these tools:
  - Basic risk management facilitation methods (flowcharts, check sheets, etc.)
  - Failure Mode Effects Analysis (FMEA)
  - Failure Mode, Effects, and Criticality Analysis (FMECA)
  - Fault Tree Analysis (FTA)
  - Hazard Analysis and Critical Control Points (HACCP)
  - Hazard Operability Analysis (HAZOP)
  - Preliminary Hazard Analysis (PHA)
  - Risk ranking and filtering
  - Supporting statistical tools
Types of tools

<table>
<thead>
<tr>
<th>Facilitation (Qualitative) Tools</th>
<th>Analytical (Semi) Quantitative Tools</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brainstorming</td>
<td>Failure Mode Effects Analysis (FMEA);</td>
</tr>
<tr>
<td>Cause and Effect Diagrams</td>
<td>Hazard Analysis and Critical Control Points (HACCP);</td>
</tr>
<tr>
<td>Flowcharts</td>
<td>Preliminary Hazard Analysis (PHA);</td>
</tr>
<tr>
<td>Risk ranking and filtering</td>
<td>Supporting statistical tools</td>
</tr>
</tbody>
</table>

Summary of Main (Semi) Quantitative Risk Tools

<table>
<thead>
<tr>
<th>Feature</th>
<th>PHA</th>
<th>FTA</th>
<th>HACCP</th>
<th>FME(CA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Purpose</td>
<td>Preliminary risk identification</td>
<td>Identify probable fault paths</td>
<td>Identify process risks and controls</td>
<td>Assess product / process failure modes and quantitative risk</td>
</tr>
<tr>
<td>Focus</td>
<td>Simple version of FMEA</td>
<td>Root cause(s) of process faults</td>
<td>Process hazards eg contaminants</td>
<td>Identify and risk rate failure modes</td>
</tr>
<tr>
<td>Strengths</td>
<td>Easy application with limited data</td>
<td>Shows multiple factors effect on one fault</td>
<td>Identify CPPs for a unit process</td>
<td>Rank and prioritize risks</td>
</tr>
<tr>
<td>Limitations</td>
<td>Limited value for complex systems</td>
<td>No risk ranking or prioritisation</td>
<td>Must understand the process – relies on SME</td>
<td>Analysis complex and tedious</td>
</tr>
<tr>
<td>Severity ?</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Likelihood ?</td>
<td>Yes</td>
<td>Optional</td>
<td>Yes, SME needed</td>
<td>Yes</td>
</tr>
<tr>
<td>Detectability ?</td>
<td>No</td>
<td>Optional</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Output</td>
<td>Tables</td>
<td>Charts / graphics</td>
<td>Tables</td>
<td>Tables</td>
</tr>
</tbody>
</table>
How is an “FMEA Risk Analysis” done?

Characterize and profile product potential hazards

Is failure mode detectable?

Define a Control Plan

Identify Potential Failure Modes

Identify Potential Failure Mode Causes

Possible effects of Failure Modes

Consequences of the Effects (Harm)

Likelihood or Probability Rate

Severity Rating

Detectability Rating

Verification and QC Methods

Past History or Knowledge

Potential harm / risk to the Patient or User

Simplified FMEA Template

Quality Record – Simplified FMEA Record

Product/Process Name:

Classification/Briefing:

Process/Design/Audit/Compliance/Deviation/Non-Conformance:

Source Reference:

Present Risk

Remaining or Residual Risk

Hazard/Effect Consequence

Likelihood of Failure Mode Occurrence

Pr (OF) and Detection

Prevent (P)

Recommended Action / Mitigation

Remedial Action

**Frequency combination of the Likelihood of the failure mode occurring X the Detectability. **

***Where there is no detectability, just use Likelihood.***