Quality Risk Management – The Pharmaceutical Experience

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Overview

- Regulatory Requirements
- Overview of elements of Quality Risk Management (ICHQ9)
- Challenges
- Questions/Discussion
Regulatory Requirements - Summary

- International Conference Harmonization (ICH) Q9 – Quality Risk Management
- European Medicines Agency (EMA)
  - Eudralex – Volume 4, Good Manufacturing Practice (GMP) Guidelines
  - Guide presented in 3 parts
    - Part I covers GMP Principles for the manufacture of medicinal products
    - Part II covers GMP for active substances used as starting materials
    - Part III is intended to host a collection of GMP related documents, which are not detailed guidelines on the principles of GMP laid down in the directives (EU Commission Directive 2003/94/EC and 91/412/EC))

  The aim of Part III is to clarify regulatory expectations & should be viewed as a source of information on current good practice.
  ICH Q9 and ICH Q10 have recently been adopted as Part III of the EU GMP Guide

- FDA
  - Guidance for Industry – Q9 Quality Risk Management
    - Represents FDA’s current thinking
QRM & the EU GMP Guide – some examples

- **Chapter 1 - Quality System**
  - To achieve the quality objective reliably there must be a comprehensively designed & correctly implemented system of Quality Assurance incorporating GMP, QC & QRM
  - The QRM system should ensure that the evaluation of risk to quality is based on scientific knowledge, experience of the process & ultimately links to the protection of the patient
  - The level of effort, formality & documentation of QRM is commensurate with the level of risk

- **Chapters 3 & 5 - Premises & Equipment and Production**
  - Proposed update to chapters 3 & 5 of the GMP Guide “Dedicated Facilities” states that principles & concepts of QRM should be taken into consideration

- **Chapter 8 - Complaints & Product Recall (concept paper issued)**
  - Implementation of QRM principles when investigating defects/complaints and when making decisions in relation to product recalls/other risk-mitigating marketplace actions
How ICH Q8, Q9 and Q10 guidelines are working together throughout the product lifecycle

- High level guidances (not prescriptive)
- Science and risk-based
- Encourages systematic approaches
- Applicable over entire product lifecycle
- Intended to work together to enhance pharmaceutical product quality

Reference  ICH November 2010
How Q8, Q9, Q10 are working together throughout the product lifecycle

The greatest benefits come from using the principles described in ICH Q8, Q9 & Q10 together to provide an integrated approach to reducing risk, based on science.

We can think of risks to product quality arising from site operations - which will range from high to low -

And also from the product, its manufacturing process & associated measurement and testing methods - which will also range from high to low.

Courtesy of ICH
ICH Q9 - Overview

- Quality Risk Management (QRM) is a systematic process for the assessment, control, communication & review of risks to quality of the drug product across the product lifecycle

▶ Primary Principles

- The evaluation of the risk to quality should be based on scientific knowledge & ultimately link to the protection of the patient and
- The level of effort, formality & documentation of the quality risk management process should be commensurate with the level of risk
Integration of Quality Risk Management

• QRM is a process that supports science-based & practical decisions when integrated into quality systems

• **Examples:**
  - Development
  - Validation
  - Quality defects – Investigations
  - Auditing & Inspection
  - Change Management
  - Documentation
  - Training

**Regulatory Feedback – example of some industry observations**

- The QRM procedure was not referenced in the Complaint procedure or the Recall procedure and the procedures did not detail how risk assessment was to be applied in those areas.

- The change management operating procedure included a change impact assessment but no risk assessment was conducted or considered.

- Inadequate assessment of cross-contamination risk posed by the manufacture of potentially hazardous compounds in shared manufacturing areas using multi-product equipment.

- Deviation XYZ related to glass damage to a vessel identified during routine preventative maintenance. Quality risk assessment outcome - risk presented was low based on a high rating for detection of glass particles but this was inadequately justified.
The Components of the Quality Risk Management Process (ICH Q9)

- **Initiate Quality Risk Management**
- **Risk Assessment**
  - Risk Identification
  - Risk Analysis
  - Risk Evaluation
- **Risk Control**
  - Risk Reduction
  - Risk Acceptance
- **Output / Results of the QRM Process**
- **Risk Review**
  - Review Events

Risk Management Tools: Unacceptable
Pfizer 10 Step Approach

1. Collect and Organize Info
2. Formulate Risk Question
3. Choose Tool
4. Identify Risk Factors, Hazards
5. Define Risk Components & Scales
6. Create Matrix
7. Determine Action Threshold
8. Apply Tool
9. Define Risk Mitigation
10. Document and Approve

The Components of the Quality Risk Management Process (ICHQ9)

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Some risk terminology

- **Risk** - the combination of the probability of occurrence of harm and the severity of that harm (ICH Q9)
- **Consequence** - A result of an action, process, etc.; an outcome; effect; a logical result or conclusion; inference; the relation of effect to cause
- **Mitigation** - Actions taken to manage risk
- **Hazard** - the potential source of harm
- **Harm** – damage to health, including the damage that can occur from loss of product quality or availability
- **Severity** – a measure of the possible consequences of a hazard
- **Residual Risk** - Risks remaining after protective measures have been taken
Some Risk Terminology

Risk Factors consist of
- Hazards, or potential sources of harm, and
- Consequences, or the potential outcomes resulting from the Hazard

Risk components
- Severity of harm - a measure of the possible consequences or degree of harm
- Probability that harm will occur - frequency or likelihood of occurrence of the hazard
- Detection of risk - the ability to discover or determine the existence, or presence of the hazard
**Pfizer 10 Step Process**

**Collect & Organize the information**
- Gathering relevant information, reviewing appropriate references & identifying assumptions
- Tools can be used to organize the information
- Define the boundaries of the QRM exercise

**Formulate the Risk Question:**
- Starting point of the QRM exercise, high level statement outlining the issue & purpose for conducting the QRM exercise including risk factors, the scope of the issue and any related limits or constraints
- **Example:** What is the supplier audit schedule that will ensure that suppliers presenting a high risk to the patient are audited in a more frequent manner?
Choose Tool

- Basic risk management facilitation methods (flowcharts, check sheets etc)
- Failure Mode Effects Analysis & Failure Mode Effects & Criticality Analysis
- Fault Tree Analysis
- Hazard Analysis & Critical Control Points
- Hazard & Operability Analysis
- Preliminary Hazard Analysis
- Risk Ranking & Filtering
- Supporting statistical tools

- Risk Management Tool adapted from *The development of a Quality Risk Management solution designed to facilitate compliance with the risk-based qualification, validation and change control GMP requirement of the EU*. Dublin: Dublin Institute of Technology, 2007. Kevin O'Donnell PhD

Identify Risks Factors and Related Hazards:

➢ What are the Risk Factors (patient safety, compliance and business) arising from all potential hazards identified?
Define the Risk Components & Scales

- What does Severity, Probability & Detection mean in terms of this Risk Question?

In terms of a QRM exercise to create a supplier audit schedule:
- **Severity** - Criticality of the product
- **Probability** - Complexity of the site (multi-product)
- **Detection** - Audit history

### Severity Scale

<table>
<thead>
<tr>
<th>Factor</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>Sterile products</td>
</tr>
<tr>
<td>6</td>
<td>Product orally administered</td>
</tr>
<tr>
<td>3</td>
<td>Topical products and compounds not directly used by patient</td>
</tr>
<tr>
<td>1</td>
<td>Compounds used during manufacturing process</td>
</tr>
</tbody>
</table>
### Pfizer 10 Step Process

1. Collect and Organize Info
2. Formulate Risk Question
3. Choose Tool
4. Identify Risk Factors, Hazards
5. Define Risk Components & scales
6. Create the matrix
7. Determine Action Threshold
8. Apply Tool
9. Define Risk Mitigation
10. Document and Approve

#### Create the Matrix

<table>
<thead>
<tr>
<th>Probability</th>
<th>Severity</th>
<th>Probability</th>
<th>Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Medium</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Medium</td>
<td>Low</td>
<td>Medium</td>
<td>High</td>
</tr>
<tr>
<td>Low</td>
<td>Low</td>
<td>Medium</td>
<td>High</td>
</tr>
</tbody>
</table>

#### Risk Evaluation Score

- Increasing Probability: High → Medium → Low
- Increasing Severity: Medium → High
- Decreasing Detection: High → Medium → Low

#### Final Risk Evaluation Score

<table>
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*Connecting People, Science and Regulation*
Determine Action Threshold
• A level or value above which an action will take place and below which it will not

Apply the tool
• Analyze the detailed risks and quantify those risks using the scales for severity, probability and detection to provide a risk score
• Determine what actions are required based on the threshold for action
Define Risk Mitigation

Consider measures/actions that could:

- Decrease the severity
  - stop failure before significant consequences, reject, recall
- Decrease the probability
  - Inspect defect out of batch
- Increase the detection
  - Move from manual to machine inspection
- Reapply the tool taking the mitigating measures into consideration
- Determine if the mitigations/actions have introduced new risks

Document and Approve

- Document and approve in a Quality Risk Assessment Report
Risk Review

Address the need to revisit the risk assessment at a point in the future to take into account any new information/experience

- Determine an appropriate frequency
- Purpose - what items will be reviewed

Risk Communication

- Communicating information with the key groups & stakeholders throughout
- Understanding our risks & conveying them to others
Level of formality - When to use a less formal approach

- 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. (ICH Q9)

Tool selection

- How to select the best tool for the risk scenario
Risk Register - What is the expectation
This is not EMA regulatory requirement

Medicines and Healthcare products Regulatory Agency (MHRA)
Good Manufacturing Practice - QRM Frequently Asked Questions

Question - Should sites have a formal risk register and management process?
Yes, a risk register (or equivalent title document) should list and track all key risks as perceived by the organisation and summarise how these have been mitigated. There should be clear reference to risk assessments and indeed a list of risk assessments conducted should be included or linked to the register.
A management process should be in place to review risk management – this may be incorporated into the quality management review process.

People having different perspective on the same risk/subjectivity
Thank You!
Back up slides
Background and Overview of ICH

Inception - 1990

Unique harmonization project bringing together the regulatory authorities & pharmaceutical industry of Europe, Japan & US to discuss scientific & technical aspects of drug registration

Mission –

to achieve greater harmonisation to ensure that safe, effective, & high quality medicines are developed & registered in the most resource-efficient manner

Well-defined Objectives –
• To improve efficiency of new drug development and registration process
• To promote public health, prevent duplication of clinical trials in humans & minimise the use of animal testing without compromising safety & effectiveness

Accomplished through the development & implementation of harmonised Guidelines & standards
How ICH Q8, Q9 and Q10 guidelines are working together throughout the product lifecycle

Pharmaceutical Quality System

- Pharmaceutical Development
- Technology Transfer
- Commercial Manufacturing
- Product Discontinuation

Investigational products

GMP

Management Responsibilities

- Process Performance & Product Quality Monitoring System
- Corrective Action / Preventive Action (CA/PA) System
- Change Management System
- Management Review

Enablers

- Knowledge Management
- Quality Risk Management

PQS elements

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