ICH Q9 Quality Risk Management – An Industry Perspective

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Overview of Presentation

- What is Quality Risk Management (QRM)?
  - Background
  - Principles
  - Relationship to ICH Q8 and Q10

- Why Quality Risk Management?
  - Benefits for Industry

- When and where can QRM be applied?
  - Example: QRM in tablet development
  - Example: QRM in facility design

- How can we implement QRM and who do we need?
  - Organization

- Summary
Background

- QRM is not new
  - Quality Risk Management used by companies and authorities informally or more formally
  - Used in other related regulated industries e.g. medical devices, food

- QRM is increasingly important
  - QRM now enshrined in EU GMPs for Human and Veterinary Medicinal Products (Eudralex Vol.4 Part I, Chapter 1, Part II (API) & Annex 20)
  - Global Boards of Health (BOH) and PIC/S are actively promoting QRM – e.g. FDA’s GMPs for the 21st Century initiative, IMB training initiatives, etc.
  - BOH inspection and submission review requests regarding quality risk management are increasing
Definitions

**Quality**

Degree to which a set of inherent properties of a product, system or process fulfills requirements

**Risk**

combination of the probability of occurrence of harm and the severity of that harm

**Management**

Systematic process for the assessment, control, communication and review of risks to the quality of the drug (medicinal) product across the product lifecycle

**QRM**
Principles of Quality Risk Management

- The evaluation of risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient.

- The level of effort, formality and documentation of the quality risk management process should be commensurate with the level of risk.
ICH Q9 Content

ICH Q9 Explains:
- A common language and process with feedback loops
- Potential methodologies for QRM
- Where QRM can add value
- How to facilitate communication

ICH Q9

Risk Communication

Initiate Quality Risk Management Process

Risk Assessment
- Risk Identification
- Risk Analysis
- Risk Evaluation

Risk Control
- Risk Reduction
- Risk Acceptance

Output / Result of the Quality Risk Management Process

Risk Review
- Review Events

Risk Management Tools
Risk Management Methods and Tools

- Facilitation Tools
  - Flowcharts
  - Checksheets
  - Process mapping
  - Cause & Effect diagrams (Ishikawa or Fishbone diagrams)

- Supporting statistical tools
  - Acceptance Control Charts (see ISO 7966)
  - Control Charts
  - Design of Experiments (DOE)
    - Pareto Charts
  - Process Capability Analysis
  - Histograms
Popular Risk Management Tools

- Failure Mode Effects Analysis (FMEA)
  - Break down large complex processes into manageable steps
- Failure Mode, Effects and Criticality Analysis (FMECA)
  - FMEA & links severity, probability & detectability to criticality
- Fault Tree Analysis (FTA)
  - Tree of failure modes combinations with logical operators
- Hazard Analysis and Critical Control Points (HACCP)
  - Systematic, proactive, and preventive method on criticality
- Hazard Operability Analysis (HAZOP)
  - Brainstorming technique
- Preliminary Hazard Analysis (PHA)
  - Possibilities that the risk event happens
- Risk ranking and filtering
  - Compare and prioritize risks with factors for each risk
How Q9 works with Q8 and Q10

Using Q9 Quality Risk Management principles

Credit: J. Ramsbotham, Solvay Pharm. NL / EFPIA
Advantages of QRM as a Technique

- **Improves decision making**
  - Identifies what gives most benefit to the patient

- **Is scientific & data-driven**
  - Facilitate communication

- **Ranks risk - allows prioritization**
  - Better use of resources

- **Improves transparency & trust**
  - Enables regulatory flexibility
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QRM Benefits our Company Operations

- Improves decision making
  - Identifies what gives most benefit to the patient
  - QRM is scientific and data-driven
  - Reduces subjectivity
- Uses resources better
  - Ranks risk - allows prioritization of effort
  - Means of building in Quality
  - Benefits apply throughout product lifecycle
- Facilitates communication
  - Matrix team approach
  - Outputs enhance product and process understanding
  - Better understanding of risk-based decisions
  - Acceptance of residual risks
- Encourages a preventive approach
  - Proactive control of risks and uncertainty
  - Benefit of knowledge transfer by team approach

“Quality risk management can facilitate better use of resources by all parties.” (ICH Q9 Section 6)
QRM Benefits our Relationships with Global Boards of Health

- Improves transparency and builds trust with competent authorities
  - Enables regulatory flexibility
- Recognise risks at a desired level
  - Zero risk not possible
- Provide assurance
  - Risks are adequately managed
  - Compliance to external and internal requirements

“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.” (ICH Q9 Section 1)
QRM Benefits our Patients

- Quality products
  - Patient focus
  - Enhanced assurance of safety & effectiveness
- Consistent supply
  - Enhanced product, process and systems robustness
- Better value
  - Focusing our efforts and resources

"An effective quality risk management approach can further ensure the high quality of the drug product to the patient by providing a proactive means to identify and control potential quality issues during development and manufacturing."

(ICH Q9 Section 1)
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QRM: a Critical Component within Product Lifecycle

Quality Risk Management (ICHQ9)
Opportunities to impact risk using quality risk management

Pharmaceutical Quality System (ICHQ10)
QRM identified as one of the two key enablers of effective quality systems

Pharmaceutical Development (ICHQ8)
QRM and scientific approaches combine to enhance process knowledge

Credit: G. Claycamp, FDA, June 2006
Application Areas – Some Examples

- **Product Development**
  - Quality by Design: QRM is a key supporting tool

- **Marketed Products**
  - Investigations and complaints
  - Packaging design and labelling controls
  - Laboratory controls
  - Materials management

- **Systems & Facilities**
  - Validation/Qualification
  - Equipment & Utilities design and maintenance
  - Documentation systems
  - Auditing programmes

QRM can provide benefit to operations within all quality systems and throughout the product lifecycle

ICH Q9 Annex II
Application Examples

- QRM in tablet development
  - EFPIA Mock P2 – ‘Examplain Tablets’
  - Drying operation

- QRM in facility design
  - Biopharmaceutical manufacturing facility
  - Risk of cross-contamination between adjacent manufacturing suites

- Examples illustrate
  - Application of common principles in different areas of industry
  - Different risks: therefore different level of effort
  - Use of different tools
‘Examplain Tablets’ Risk Identification - Manufacturing Process

Cause and Effect Diagram for Water Content

Credit: EFPIA, Mock P2, 2006
### ‘Examplain Tablets’ Initial Risk Assessment

**Initial classification of unit operations potential influence on product quality**

<table>
<thead>
<tr>
<th>Unit operations Quality attributes</th>
<th>Dispensing (Raw Material Properties)</th>
<th>Granulation</th>
<th>Drying</th>
<th>Blending (Magnesium Stearate)</th>
<th>Tableting</th>
<th>Packaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dissolution</td>
<td></td>
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<td></td>
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<td>Prior knowledge</td>
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</tr>
<tr>
<td>Appearance</td>
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<td></td>
<td></td>
<td></td>
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</tr>
<tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Prior knowledge</td>
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</table>

**Influence:**
- high
- low

Drying operation may affect product quality

Credit: EFPIA, Mock P2, 2006
Risk Control of Drying Process

First Review Risk Assessment

Failure modes understood
Risk reduction:
- Drying end-point control using NIR
- Control of drying trajectory
- Particle size monitored using laser diffraction

Third Review Risk Assessment

Experimental work to develop process understanding leads to risk reduction

Credit: EFPIA, Mock P2, 2006
## Examplain Tablets’ Updated Risk Assessment

### - Process understanding gained during development

#### Unit operation

<table>
<thead>
<tr>
<th>Unit operations / Quality attributes</th>
<th>Dispensing (Raw Material Properties)</th>
<th>Granulation</th>
<th>Drying</th>
<th>Blending (Magnesium Stearate)</th>
<th>Tableting</th>
<th>Packaging</th>
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<td>Power consumption</td>
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<td>Prior knowledge</td>
<td>Prior knowledge</td>
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<tr>
<td>Identification</td>
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<td>Prior knowledge</td>
<td>Prior knowledge</td>
<td>Prior knowledge</td>
<td>Prior knowledge</td>
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<tr>
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<td>Purified water used</td>
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<td>Prior knowledge</td>
<td>Prior knowledge</td>
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</tbody>
</table>

**Quality Attributes**

- Process understanding gained during development
- Control Strategy

Credit: EFPIA, Mock P2, 2006
Example: Cross-contamination Prevention

- Proposed ‘Non-traditional’ biopharmaceutical facility utilization:
  - Concurrent mammalian cell and bacterial (BL2) cell manufacturing processes in adjacent dedicated suites
- Facility design review identified the following concerns:
  - Potential for cross-contamination between mammalian & bacterial processes through shared Production Service areas
  - Operations for control and containment of the process within manufacturing suites

**Cross contamination hazards include:**
- Raw materials
- Product
- Cell culture & fermentation components
- Process byproducts (ex: effluents, isoforms, etc.)
- Process support (cleaning agents, etc.)
Risk Management Strategy

- Cross contamination between processes is dependent upon three events occurring:
  - Release hazard in Suite 1 + Transport hazard + Ingress hazard to Suite 2
- Approach: systematic risk assessment of the internal operations and flows for each component at each facility interface gate

Prevent or control each of these events and cross-contamination cannot occur.
Risk Assessment

- Identify the complete array of release, transport, and ingress risks within scope
- Hazard Operability Analysis (HAZOP) used as the risk assessment tool for detailed analysis
  - Suitable for facilities, equipment, and processes
  - Capable of assessing process systems and their physical and operational environments
  - Capable of assessing operational and procedural controls
## Risk Analysis: Risk Rating System

<table>
<thead>
<tr>
<th>Deviation Occurrence</th>
<th>Deviation Severity</th>
<th>No Action Required</th>
<th>One or More Controls Required</th>
<th>More Than One Control Required</th>
<th>Engineering Or Design Control Required</th>
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<tr>
<td>High</td>
<td>Low</td>
<td>None</td>
<td>One or More</td>
<td>More Than One</td>
<td>More Than One</td>
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<tr>
<td>High</td>
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<td>More Than One</td>
<td>Engineering Or Design Control Required</td>
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<td>High</td>
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</table>

Controls may be procedural, training, or engineering / facility design controls and may consider the ability to detect deviations or hazard components as part of a mitigating control.
Risk Control

Risk Reduction – based on HAZOP outputs
- Facility design changes
- Process design and control enhancements
- Facility operating procedure and control enhancements

Risk Acceptance
- Reduce residual risks to As Low As Reasonably Practicable (ALARP)
- ALARP – stop when risk reduction benefits disproportionately low for resources used
- Accept residual risks
Risk Communication & Risk Review

- **Risk Communication**
  - Continuous reporting of process outcomes and progress to key stakeholders and management
  - Regular updates prepared Senior Management for efficient decision-making on risk mitigation and regulatory submission strategies
  - Meetings with Regulatory Agency to solicit feedback and facilitate understanding

- **Risk Review**
  - Endorsed controlling actions were assessed to ensure no further negative impact
  - Ongoing assessment may be performed as necessitated by changes
Outcomes & Benefits of QRM Process

- **Summary report**
  - Extensive documentation package, basis for regulatory submissions
  - QRM process was easily replicated with less effort for a similar risk assessment at a different facility

- **Enhanced communication and transparency**
  - Quality Risk Management results showed multiple layers of control in place to prevent cross-contamination between suites
  - Regular communication facilitated efficient, objective decision-making by Senior Management
  - Enhanced understanding of facility design and controls for Regulatory Agency

- **Continual improvement**
  - Opportunities identified for continual improvement of site-wide and global facility management and operational processes
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What does Senior Management need to do?

- Ensure organisation is aware of ICH Q9 and the opportunity it affords
  - Appropriate education and training

- Encourage open, risk aware culture
  - Establish & support “QRM leaders” across organisations

- Encourage integration of Quality Risk Management with existing Quality systems
  - Do NOT set up as a separate department
  - Coordinate implementation and resource allocation
  - Prioritise; start small, learn as you go
QRM Roles and Responsibilities

- **Facilitator / Team Lead**
  - Guide the QRM process

- **Team Members**
  - Can include Subject Matter Experts / process representative or owner, Quality, Regulatory Affairs, Operators & Technicians and others as needed
  - Provide expertise, input, and perspective

- **Internal Stakeholders**
  - Can include direct line management, senior management
  - Can affect (or can be affected by) the QRM process

- **Reviewers & Approvers**
  - Review and access outcome of the QRM process
An Approach to Implementation of QRM

- Initial QRM efforts
- Replications, sharing proven practices
- QRM Policies and SOPs in place
- Sharing best practices, leading industry
- Most advanced
- Optimizing
- Managed
- Defined
- Repeatable
- Disciplined
- Standard
- Predictable
- Continually improving
- Process

Initial QRM efforts
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Summary – What QRM Is and Is Not

- Quality Risk Management is **NOT**
  - Making do with insufficient time, money, or people
  - Providing an excuse not to do the right things
  - Deciding what to do based on what might be observed during an inspection
  - Providing an excuse to be out of compliance with applicable regulations

- Quality Risk Management **IS**
  - Knowing our processes (manufacturing and business)
  - Understanding what is truly important
  - Focusing our money, time, energy, and people on the important things that provide quality assurance to our patients
  - Facilitating communication
ICH Q9 briefing pack is available

On the ICH Q9 Document

- Background
- History
- Content
- Tools
- Applications

Additional features

- Executive Summary
- Frequently Asked Questions (Q&A)

Direct link:

See www.ich.org
Acknowledgements

- European Federation of Pharmaceutical Industries and Associations (EFPIA)
  - Georges France, Topic leader of Q-Implementation Working Group
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  - email: stephan.roenninger@roche.com

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