Safeguarding our right to serve our patients

Quality Risk Management - Applications

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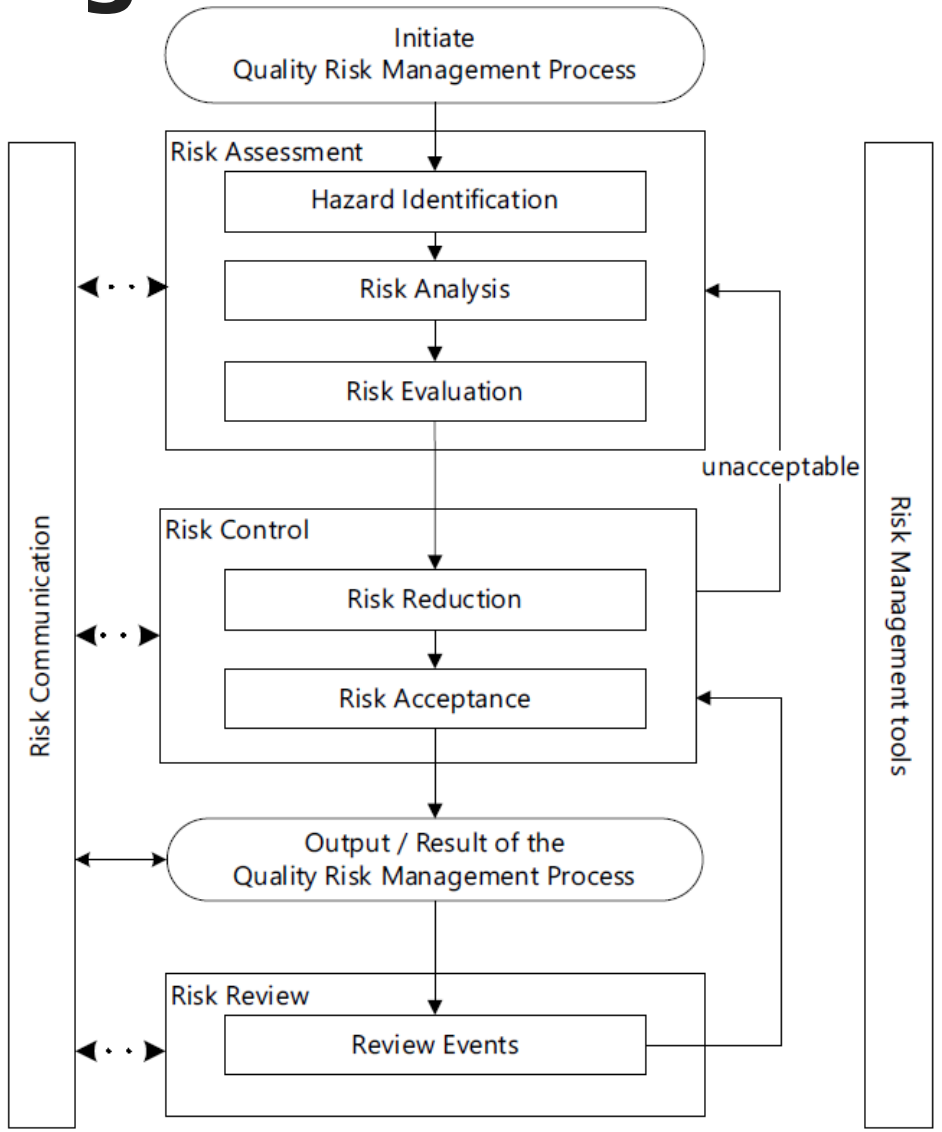
Barbara, *Verbloemen* (to gloss over)
Diagnosed with severe ulcerative colitis at age 18, Barbara tries to find peace of mind through painting and creating ceramics.

ICH Q9 (R1) Quality Risk Management

- Revision was published Jan 18, 2023
- The primary principles remain consistent

Important concept clarified:
“The level of effort, formality and documentation of the quality risk management process should be commensurate with the level of risk.”



Source: www.ich.org

What is new?

- 4 new subsections
  - Section 5 – Methodology has 3 new topics
    - Formality (5.1)
    - Risk-based decision (5.2)
    - Subjectivity (5.3)
  - Section 6 – Integration of QRM into industry and regulatory operations
    - Product availability risks (Annex II.9)

There were four areas for improvement identified with the application of QRM:

- High levels of subjectivity in risk assessments and in QRM outputs
- Failing to adequately manage supply and product availability risks
- Lack of understanding as to what constitutes formality in QRM work
- Lack of clarity on risk-based decision-making

Formality

- ICH Q9(R1) describes the concept of formality within QRM as a spectrum (not binary) and the factors that may influence the level of formality for a given QRM activity.

- Having the appropriate and right number of cross-functional subject matter experts involved, resulting in more efficient resourcing and freeing up senior management to manage higher levels of risk.

- Applying **fit-for-use methodology and tool selection** in conjunction with supporting scientific data, creating more **effective and efficient risk assessments and risk control decisions**, and aligning with the principle for formality to be commensurate with the level of risk, curtailing the application of a one-size-fits-all solution.

- ICH Q9 still stresses the importance of robust QRM as a key objective (less formal does not mean less robust!) and specifies that lack of resources is not an appropriate rationale for using a lower degree of formality.

Factor	Higher levels of formality should be used when…	Links to…
Uncertainty *"lack of knowledge about hazards, harms, and consequently, their associated risk"*	There is a higher level of uncertainty, e.g., unable to easily answer: • "What might go wrong?" • "What is the likelihood (probability) it will go wrong?" • "What are the consequences (severity)?"	Effective knowledge management
Importance	The level of importance associated with a risk-based decision with respect to product quality	Reducing level of uncertainty
Complexity	The process or subject is more complex	Product quality assurance

Subjectivity

- The revised Guideline indicates how subjectivity can impact every stage of a QRM process, especially the identification of hazards and estimates of their probabilities of occurrence, the estimation of risk reduction and the effectiveness of decisions made from QRM activities.
- Subjectivity can be introduced through differences in how risks are assessed and in how hazards, harms and risks are perceived.
- Subjectivity can also be introduced through the use of tools with poorly designed risk scoring scales.
- **While subjectivity cannot be completely eliminated from QRM activities**, it **may be controlled** by **addressing bias**, the **proper use of QRM tools** and maximizing the use of **relevant data** and **sources of knowledge**.
- All participants involved with QRM activities should acknowledge, anticipate, and address the potential for subjectivity.

Risk-based decision-making

Example for Determining the Level of Formality to Apply for Risk-Based Decision-Making

Scenario	Formality	Approach
Initiation of a risk assessment *Often this is the first decision point in a QRM process, where the formality of the QRM activity is determined.*	On the spectrum of decision-making, this is somewhere in the middle. There may be a high level of importance associated with the decision, but there is often a lower level of uncertainty, and the process of determining the type of QRM activity is not complex. Some structure is required, and the output should be documented, but an in-depth evaluation of the circumstances is unnecessary.	Capture these decisions through a series of questions, documented on a standard form. A decision tree can also be used to determine the level of formality of the QRM engagement. Record the output/decision in a log or database.
Taking action based on the output of a formal risk assessment: *Consider mitigating actions from a formal risk assessment like an FMEA for a formulation process or a HACCP to determine a risk-based environmental monitoring program.*	Decisions associated with a formal assessment and the resulting actions should be more structured and formal. This should align with the formality and importance of the assessment. The process for making decisions from formal risk assessment outputs should state: • how to determine what is acceptable and what is not • who should be involved in the decision-making process • actions to take for risk that is not acceptable • how acceptability of the risk should be communicated	Use an "Action Table" in a governing QRM policy, in the procedure for using an individual tool, or both. An Action Table lays out what is required for the output of the risk assessment. For example: • mitigation actions must be identified for high risks, • mitigation actions should be considered for medium risks, but may be accepted by the team with sound rationale, • low risks are acceptable. Associated with the Action Table, the procedure describes who can make decisions to accept risks of various levels and how to escalate risks that are not acceptable.

- Lack of **clarity on risk-based decision-making** and on what good risk-based decision-making means, how QRM may improve decision-making, and how risk-based decisions might be achieved
- More **effective, efficient, and science-based control strategies** among manufacturers, improving manufacturing consistency, lowering costs and reducing the likelihood of quality defects, recalls, and medicine shortages
- Additional clarity on the expectations relating to keeping risk assessments current and on the implementation of risk review activities based on **lifecycle** manufacturing performance and quality feedback.

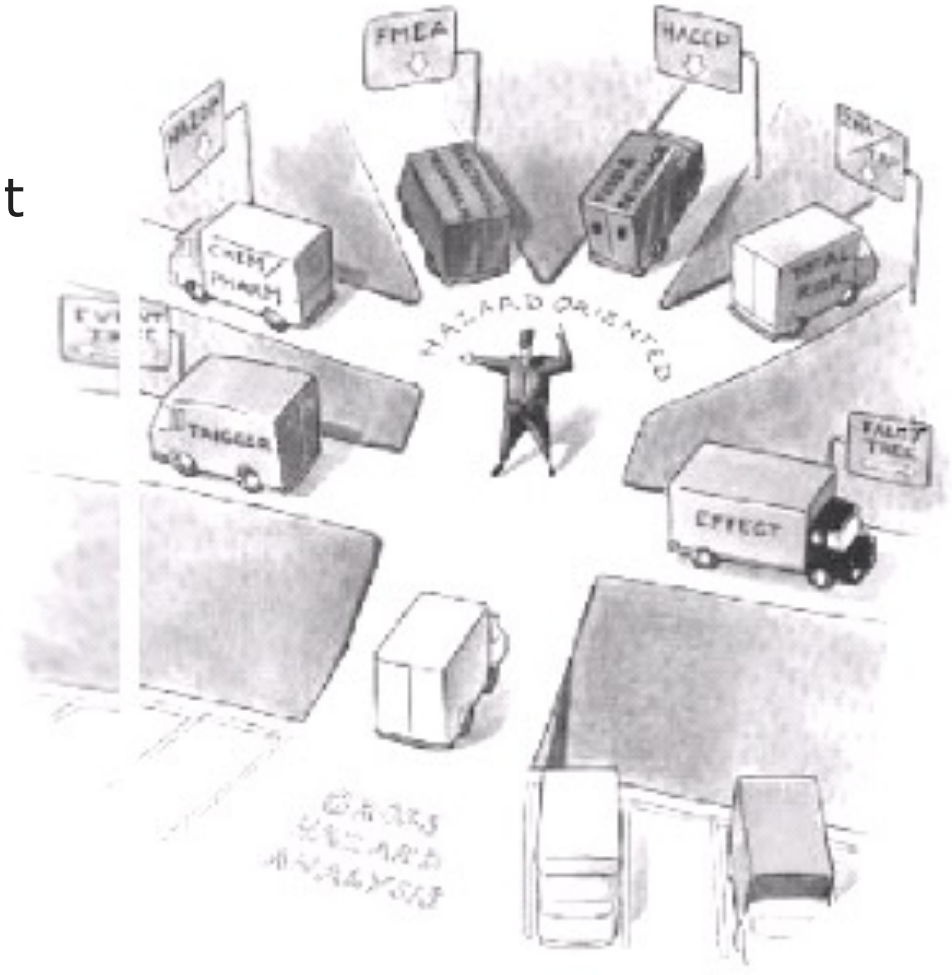
Potential applications for QRM

- Considering all the elements discussed so far…
- Considering new and emerging technologies (such as cell and gene therapies) where compliance needs to be built in and risk-based decisions carry a critical load of direct patient impact (many in rare-diseases, always close to compassionate use situations)
- Considering the importance of digitalization and emerging technologies, as they can lead to improved control strategies and risk reduction, but at the same time could also present certain challenges
  - Data governance is an important enabler to this process

➢ The application of quality risk management to the design, validation and technology transfer of advanced production processes and analytical methods, advanced data analysis methods and computerized systems is paramount in building robust Quality management systems that are fit-for-the-future.

Annex I of ICH Q9 (R1)

- The purpose of this annex is to provide a general overview of and references for some of the primary tools that might be used in quality risk management by industry and regulators.
- The references are included as an aid to gain more knowledge and detail about the particular tool.
- The list of tools is not exhaustive.
- It is important to note that no one tool or set of tools is applicable to every situation in which a quality risk management procedure is used.



Quality risk management methods and tools

Annex I of ICH Q9 (R1)

Failure Mode Effects Analysis (FMEA)

- Break down large complex processes into manageable steps
- Potential failure modes for processes and likely effect on outcomes and/or product performance
- Used to: equipment, facilities;
- Prioritize risks; monitor effectiveness of risk control activities
- Risks are evaluated qualitatively and quantitatively

Failure Mode, Effects and Criticality Analysis (FMECA)

- FMEA & links severity, probability & detectability to criticality
- Investigation of severity of consequences (probability, occurrence and detectability)
- Used to: product and specifications
- Additional preventative actions might be used to minimize risks
- Failure and risks associated with manufacturing processes
- Score is presented to be evaluated on a relative risk basis

Fault Tree Analysis (FTA)

- Tree of failure modes combinations with logical operators
- Failure of a functionality of a product or process
- Identification of causal chains
- Used to: risk assessments and monitoring programs
- Pathway to root cause – fix once everywhere to prevent other issues to be caused by the solutions implemented

Quality risk management methods and tools

Annex I of ICH Q9 (R1)

Hazard Analysis and Critical Control Points (HACCP)

- Systematic, proactive, and preventive method on criticality
- Assuring product quality, reliability and safety
- Used to: identify and manage risks associated with physical, chemical and bio hazards (incl. micro contamination)
- Applicable throughout the product or process lifecycle (after establishment of the control strategy)

Hazard Operability Analysis (HAZOP)

- Brainstorming technique
- Risks caused by deviations from the design or operating intentions
- Used to: manufacturing processes including outsourced manufacturing, upstream suppliers, equipment and facilities, DS and DP
- Output – list of critical operations for risk management

Risk ranking and filtering

- Compare and prioritize risks with factors for each risk
- Break down risk questions into multiple components, drill down to factors impacting the risks and combined factors get a relative score
- Used to: prioritize inspection and audit and contains quali and quanti elements

Quality risk management methods and tools

Annex I of ICH Q9 (R1)

Preliminary Hazard Analysis (PHA)

- Possibilities that the risk event happens
- Qualitative evaluation of the extent of a possible injury or damage
- Relative ranking (severity, likelihood of occurrence)
- Used to: facility design and early development

Supporting statistical tools

- Control Charts
- Design of Experiments (DOE)
- Pareto Charts
- Probabilistic Risk Assessment (PRA)
- Process Capability Analysis

Basic risk management facilitation methods

- Flow charts
- Check sheets
- Process mapping
- Cause and effect diagrams (e.g. Ishikawa, fish bone)

Quality Management Systems policies and procedures should support the standardization and application of the right tool for the right job!

Annex II – Potential applications for QRM

- II.1 Quality Risk Management as Part of Integrated Quality Management
- II.2 Quality Risk Management as Part of Regulatory Operations
- II.3 Quality Risk Management as Part of Development
- II.4 Quality Risk Management for Facilities, Equipment and Utilities
- II.5 Quality Risk Management as Part of Materials Management
- II.6 Quality Risk Management as Part of Production
- II.7 Quality Risk Management as Part of Laboratory Control and Stability Studies
- II.8 Quality Risk Management as Part of Packaging and Labeling
- II.9 Quality Risk Management as Part of Supply Chain Control

Annex II – Potential applications for QRM

QRM as part of **Integrated quality management**

Periodic review	• To select, evaluate and interpret trend results of data within the product quality review; • To interpret monitoring data (e.g., to support an assessment of the appropriateness of revalidation or changes in sampling).
Change management / change control	• To manage changes based on knowledge and information accumulated in pharmaceutical development and during manufacturing; To evaluate the impact of the changes on the availability of the final product; • To evaluate the impact on product quality of changes to the facility, equipment, material, manufacturing process or technical transfers; • To determine appropriate actions preceding the implementation of a change, e.g., additional testing, (re)qualification, (re)validation or communication with regulators.
Continual improvement	• To facilitate continual improvement in processes throughout the product lifecycle.

Considerations around the application of QRM

Quality Management Systems:

– **Quality Risk Management** approach should be detailed to cover:

- How are risk questions defined and scoped?
- Has the terminology shifted from Risk identification to Hazard identification?
- How are teams instructed and guided toward assigning ratings? (qualitative vs quantitative tools)
- What stakeholder assumptions are made in performing the risk assessment?
- How are potential sources of **bias** managed?
- How can decision makers demonstrate that they are managing and minimizing subjectivity?
- Was consideration given to drug shortage prevention and mitigation activities

– Site Risk Register – **formalization** and governance for changes
– Change control process – assessment must **inform implementation** tasks

Considerations around the application of QRM

Lifecycle approach to risk management

- Is the application of quality risk management appropriate in each area?
    - qualification and validation
    - quality investigations
    - risk-based decisions on release

- What is the **formality** applied to quality risk management to capture **risk-based decisions**?
- Is the application of **root cause analysis** to address root causes and other contributing factors along the causal chain appropriate?
- Are the **tools** utilized **appropriate** for the intended purpose, e.g., FMEA is the only tool utilized? – how are they linked to risk mitigation? How are they revised to understand remaining risks post implementation of interim actions?

➢ Do read the risk assessments? Probe the subjectivity factor, alignment of the tool to its application.

Considerations around the application of QRM

Process variability

- QRM can be leveraged to identify the areas producing **variability**, support development of **monitoring** programs for critical parameters of the **manufacturing process**, establish control charts with upper and lower-level limit expectations, and routinely assess process capability. Ideally, real-time data capture will be used to ensure the current process is within the normal processing range.
- When process drift is observed, QRM can facilitate the required **escalations** to product and process stakeholders and to take actions tracked through quality system.
- Management review meetings should be established to routinely review process capability to **enable risk communication** and ensure stakeholders understand when and how the drift is occurring.

Considerations around the application of QRM

Manufacturing, facilities and **equipment**

- QRM can be applied across the facility, ensuring utility systems are robust. Leveraging QRM at the design phase can remove inefficient designs, mitigating risks of human errors. Ideally, if financially feasible, this can be further supported via the use of automation and digitalization across the facility.
- To mitigate the effects of an aging facility, a robust maintenance program is critical. QRM risk-based decisions can be created and incorporated into calibration and maintenance procedures to guide engineers to **remove subjectivity** and create consistent determination of equipment classification and frequency of maintenance.
- Real-time automated monitoring programs must be established to ensure facility systems are performing as intended. A detailed review of facility systems can occur through QRM tools to ensure **holistic** capture of all required monitoring.

Considerations around the application of QRM

Oversight of outsourced activities and suppliers

- QRM can be leveraged to **develop a monitoring program** for product quality parameters of a supplier and contract manufacturing organization (CMO). The monitoring should have criticality scales developed by stakeholders included in procedures, along with the action to be taken if overall risk thresholds are achieved. The intent is to **remove subjectivity** by creating a criticality scale and placing risk-based decisions within a procedure to ensure stakeholders act consistently.
- A Material Review Board composed of product stakeholders should routinely review data. If product quality is drifting, communication should be established with the supplier/CMO, with clear expectations and a means of collaboration. This is highly relevant for Advanced Therapies, where risk-based decisions are frequent.
- Use of QRM can help to identify weaknesses and reduce the risk of a drug product shortage if a critical supplier cannot provide a component, API, or intermediate.

Considerations around the application of QRM

Supply Chain control

- Regarding product availability risks related to quality and manufacturing issues, product lifecycle oversight of the supply chain includes maintaining current knowledge of quality and manufacturing hazards and prioritizing efforts to manage such risks.
- Understanding hazards to quality and manufacturing is critical to maintaining supply predictability.
- When risks are well understood and controlled, a higher confidence in product availability can be attained.

Thank you for your attention!

Back up

Annex II – Potential applications for QRM

QRM as part of **Integrated quality management**

Training and education	• To determine the appropriateness of initial and/or ongoing training sessions based on education, experience and working habits of staff, as well as on a periodic assessment of previous training (e.g., its effectiveness); • To identify the training, experience, qualifications and physical abilities that allow personnel to perform an operation reliably and with no adverse impact on the quality of the product.
Quality defects	• To provide the basis for identifying, evaluating, and communicating the potential quality impact of a suspected quality defect, complaint, trend, deviation, investigation, out of specification result, etc; • To facilitate risk communications and determine appropriate action to address significant product defects, in conjunction with regulatory authorities (e.g., recall).
Auditing / Inspection	• To define the frequency and scope of audits, both internal and external, taking into account factors such as: • Existing legal requirements; • Overall compliance status and history of the company or facility (including inspections); • Robustness of a company's quality risk management activities; • Complexity of the site, the manufacturing process, the product and its therapeutic significance; • Number and significance of quality defects (e.g., recall); • Major changes of building, equipment, processes, key personnel; • Experience with manufacturing of a product; Test results of official control laboratories.

Annex II – Potential applications for QRM

QRM as part of **Regulatory Operations Inspection and assessment activities**

- To assist with resource allocation including, for example, inspection planning and frequency, and inspection and assessment intensity (see "Auditing" section in Annex II.1);
- To evaluate the significance of, for example, quality defects, potential recalls and inspectional findings;
- To determine the appropriateness and type of post-inspection regulatory follow-up;
- To evaluate information submitted by industry including pharmaceutical development information;
- To evaluate impact of proposed variations or changes;
- To identify risks which should be communicated between inspectors and assessors to facilitate better understanding of how risks can be or are controlled (e.g., parametric release, Process Analytical Technology (PAT)).

Annex II – Potential applications for QRM

QRM as part of **Development**

- To design a quality product and its manufacturing process to consistently deliver the intended performance of the product (see ICH Q8);
- To enhance knowledge of product performance over a wide range of material attributes (e.g., particle size distribution, moisture content, flow properties), processing options and process parameters;
- To assess the critical attributes of raw materials, solvents, Active Pharmaceutical Ingredient (API) starting materials, APIs, excipients, or packaging materials;
- To establish appropriate specifications, identify critical process parameters and establish manufacturing controls (e.g., using information from pharmaceutical development studies regarding the clinical significance of quality attributes and the ability to control them during processing);
- To decrease variability of quality attributes: reduce product and material defects; reduce manufacturing defects.
- To assess the need for additional studies (e.g., bioequivalence, stability) relating to scale up and technology transfer;
- To make use of the "design space" concept (see ICH Q8).

Annex II – Potential applications for QRM

QRM as part of **Equipment and Utilities Design of facility / equipment**

- To determine appropriate zones when designing buildings and facilities, e.g., flow of material and personnel; minimize contamination; pest control measures; prevention of mix-ups; open versus closed equipment; clean rooms versus isolator technologies; dedicated or segregated facilities / equipment.
- To determine appropriate product contact materials for equipment and containers (e.g., selection of stainless steel grade, gaskets, lubricants);
- To determine appropriate utilities (e.g., steam, gases, power source, compressed air, heating, ventilation and air conditioning (HVAC), water);
- To determine appropriate preventive maintenance for associated equipment (e.g., inventory of necessary spare parts)

Annex II – Potential applications for QRM

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