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Review Article

Quality Risk Management: Degree of formality, Formal and Informal QRM

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Abstract

The International Council for Harmonization's (ICH) Q9 (R1): Quality Risk Management (QRM) guideline made effective from May, 2023. ICH Q9's revision provides guidance on QRM for the pharmaceutical industry and regulatory environment. It aims to improve decision-making by offering a systematic approach that complements existing quality practices and guidelines. The document emphasizes that understanding formality in quality risk management can optimize resource usage and support risk-based decision-making by reflecting the level of importance, uncertainty, and complexity of the decision.[5] QRM is the process of appropriately managing risks to product quality throughout the product's life cycle in order to optimize its benefit–risk balance. It is a systematic process for the assessment, control, communication and review of risks to the quality of the medicinal product. The level of effort, formality and documentation of the quality risk management process should be commensurate with the level of risk. The overall approach for determining how much formality to apply during QRM activities should be described within the quality system. In addition, subjectivity can directly affect the effectiveness of risk management activities and the decisions made. Therefore, it is important that subjectivity is managed and minimized.[1,6]

Keywords: Quality Risk Management (QRM), Degree of Formality, Uncertainty, Importance, Complexity, Formal risk assessment, Informal risk assessment, QRM Techniques, QRM Tools, ICH

Introduction

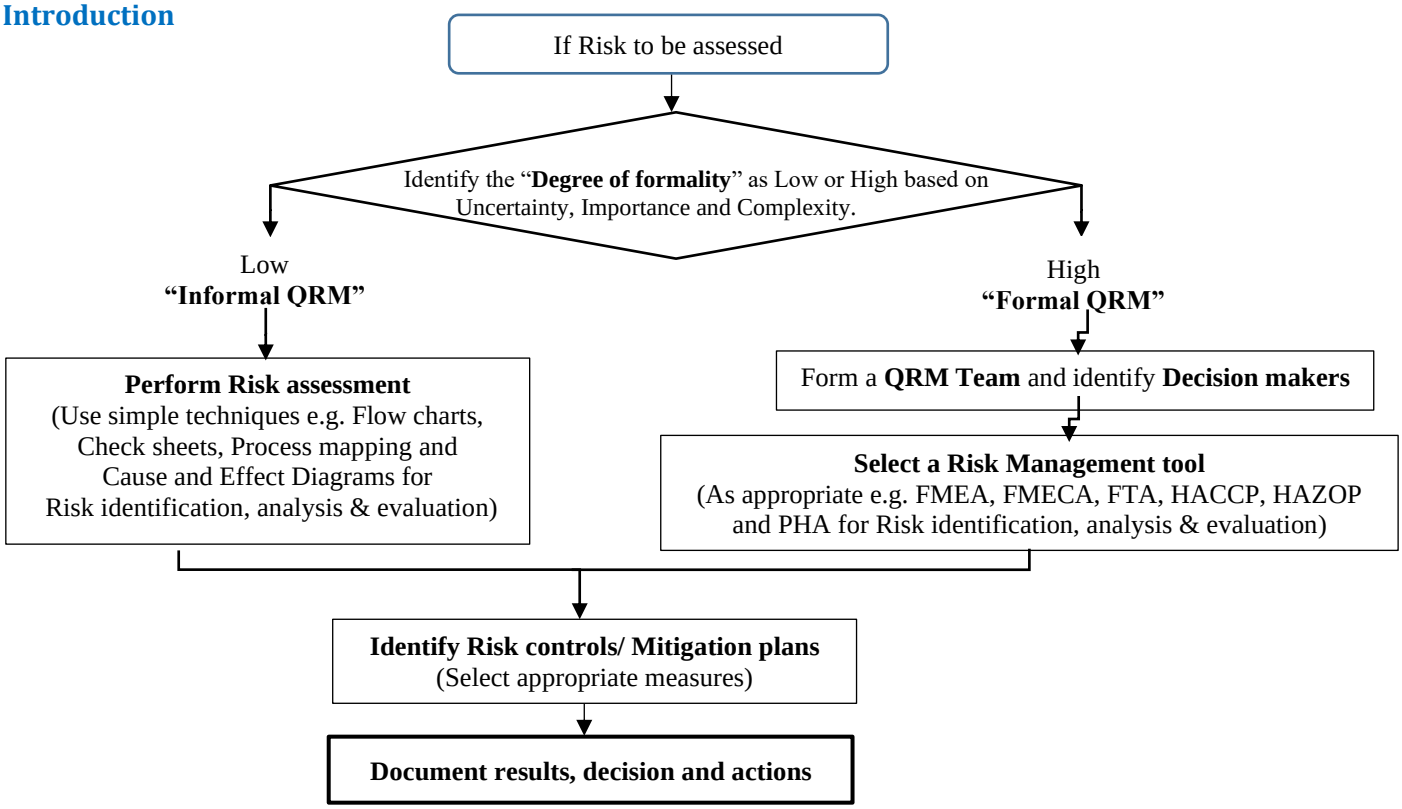

Figure I: Decision path to select the type of QRM

The Degree of formality[4] of QRM i.e. Low or High should be decided based on available knowledge and level of uncertainty, importance and complexity of the issue to be addressed. The selection of types of QRM i.e. Informal and Formal should be decided based on the degree of formality. [1,2,3]

Before initiating QRM, risk-based decision-making approach should be applied to select the type of QRM. Refer Figure-I Decision path should be followed to select the type of QRM.

Uncertainty: Uncertainty refers to the lack of knowledge about hazards, harms, and associated risks. The level of uncertainty associated with a particular area being assessed for risk determines the level of formality required to manage potential risks. [1,2,3] Effective knowledge management can reduce uncertainty, allowing accumulated and new information to be used to support risk-based decisions throughout the product lifecycle. Evaluation of Uncertainty should be done as below Table – I.

Table I: Uncertainty Rating

Uncertainty Rating	Criteria
High	Lack of knowledge about hazards, harms, and associated risks Unable to easily answer the below QRM fundamental questions - What can go wrong? What are the consequences (Severity)? What is the likelihood (Probability of occurrence) it will go wrong and how easy is it to detect them (Detectability)? Example – New dosage form/ plant/ site introduction, Critical/ Major deviation/ non-conformity, OOS etc.
Medium	Limited knowledge about hazards, harms, and associated risks No past experience about the hazards, harms, and associated risk Example - New product/ site introduction in existing facility, similar kind of critical/ major deviation/ non-conformity observed but in different dosage form/ product etc.
Low	Good knowledge about hazards, harms, and associated risks Easily answer the below QRM fundamental questions - What can go wrong? What are the consequences (Severity)? What is the likelihood (Probability of occurrence) it will go wrong and how easy is it to detect them (Detectability)? Example – Repetitive minor deviation/ non-conformity/ OOS etc.

Importance: Importance refers to the significance of the risk-based decision in relation to product quality. The higher the importance of the decision, the more formality should be applied, and the greater the need to reduce the level of uncertainty associated with it. [1,2,3] Evaluation of Importance should be done as below Table II.

Table - II: Importance Rating

Importance Rating	Criteria
High	High degree of importance in relation to product quality Example – Critical deviation/ non-conformity/ Market complaint, OOS, Major change control etc.
Medium	Medium degree of importance in relation to product quality Example - Major deviation/ non-conformity/ Market complaint etc.
Low	Low degree of importance in relation to product quality Example - Minor deviation/ non-conformity/ Market complaint, Minor change control etc.

Complexity: Complexity refers to the level of intricacy of a process or subject area involved in QRM. The higher the complexity, the more formality should be applied to ensure product quality. [1,2,3] Evaluation of Complexity should be done as below Table – III.

Table III: Complexity Rating

Complexity Rating	Criteria
High	Highly complex process or subject to understand Example – Introduction of new product with complex manufacturing process, Major change control with impacting multiple cross-functional procedure/ systems, Critical deviation/ non-conformity/ Market complaint, OOS impacting multiple cross-functional procedure/ systems etc.
Medium	Medium complex process or subject to understand Example - Change control with impacting cross-functional procedure/ systems, introduction of new product with known manufacturing process, Major deviation/ non-conformity/ Market complaint impacting multiple cross-functional procedure/ systems etc.
Low	Low complex process or subject to understand Example - Minor deviation/ non-conformity/ Market complaint, Minor change control etc.

Higher levels of uncertainty, importance, or complexity may require more formal QRM approaches to manage potential risks and support effective risk-based decision-making. [4] However, regardless of how much formality is applied, the robust management of risk is the goal of the process. The quantitative Degree of Formality can be determined with multiplication of Uncertainty, Importance and Complexity.[4]

Based on the above assessment of uncertainty, importance and complexity of the issue/ subject to be addressed and to support effective risk-based decision-making, the Formal QRM should be performed when there is a high degree of importance associated with the decision, and when the level of uncertainty and/ or complexity is high.[1,2,3] Example of situations defined below to initiate the Formal QRM (not limited to) –

- QRM to be performed for all Major Change controls that has impact on product quality or safety[4]
- QRM to be performed for all Critical and Major Deviations that significantly impact on product quality, safety, or efficacy[4]
- QRM to be performed for all Critical and Major Market complaint and ADE that significantly impact on product quality or patient safety[4]
- QRM for OOS investigation
- QRM for any Critical and Major noncompliance identified during internal and external inspection.
- QRM for introduction of new product/ equipment/ facility.
- QRM for product recall
- QRM for contamination and cross-contamination
- QRM for Data integrity breaches
- QRM for evaluation of material suppliers and contract manufacturers

Informal QRM can be performed when there is a high degree of importance associated with the decision, but the degree of uncertainty and/or complexity is lower.[1,2,3] Example of situations defined below where Informal QRM can be initiated wherever required (not limited to) –

- QRM to be performed in case of Minor Change control that has no impact on product quality or safety but may impact on regulatory compliance, non-critical manufacturing process, complex to understand etc.[4]
- QRM to be performed in case of Minor deviations that do not significantly impact on product quality, safety, or efficacy.[4]
- QRM to be performed in case of Minor market complaint that has no impact on product quality or patient safety.[4]
- QRM for any Minor noncompliance identified during internal and external inspection.
- QRM for introduction of new SOP/ Guideline which will provide more control on system and better compliance with regulatory
- QRM for introduction of new CSV system that has no role in product manufacturing
- QRM for periodic review of non-critical process

Informal QRM is less structured process as compared to Formal QRM process. The structure and requirement of documentation for both type of QRM is defined as below Table - IV .

Table IV: Structure and requirement of Informal QRM and Formal QRM process[1,2,3,5]

Informal QRM	Formal QRM
QRM to be performed embedded with risk assessment and risk control activities. Use simple techniques e.g. Brainstorming, Flow charts, Check sheets, Process mapping and Cause and Effect Diagrams for Risk identification, analysis & evaluation[4] No QRM tools used in some or all parts of the process. No cross-functional team necessary. No standalone QRM reports generated. The outcome of the quality risk management process i.e. risk controls/ mitigation plans is usually documented in the relevant parts of the quality system.	All parts of the quality risk management process (risk assessment, risk control, risk review and risk communication) are explicitly performed, and stand-alone quality risk management reports or related documents which address all aspects of the process to be generated and are documented. A cross-functional team and Decision makers should be assembled with experienced and knowledgeable personnel. QRM tools to be used (as appropriate) e.g. FMEA, FMECA, FTA, HACCP, HAZOP and PHA for Risk identification, analysis & evaluation, are used in some or all parts of the process. Document identified risk controls/ mitigation plans and risk evaluation post implementation of mitigation plans.

The cross-functional team should be formed in case of Formal QRM which includes experts from appropriate areas (e.g. product development, business development, engineering, regulatory affairs, production, sales, marketing, supply chain, legal, statistics and clinical) in addition to individuals who are knowledgeable about the QRM process.

One or Two members of QRM team should be identified as Decision makers. The Decision makers should have the responsibility to:

- Coordinate with various functions and departments of the organization for QRM;
- assure that a QRM process is defined, deployed and reviewed and that adequate resources and knowledge are available; and
- assure that subjectivity in quality risk management activities is managed and minimized, to facilitate scientifically robust risk-based decision-making. [1,2,3,6]

The output of a risk assessment is either a quantitative estimate of risk (Formal QRM) or a qualitative description (Informal QRM) of a range of risk.

During Informal QRM, risk can be expressed using qualitative descriptors, such as “high”, “medium”, or “low”, which should be defined in as much detail as possible. Simple techniques (as defined in Table IV) such as Brainstorming, Flow charts, Check sheets, Process mapping and Cause and Effect Diagrams can be used either individually or in combination for Risk identification, analysis & evaluation. The selection of a techniques should be commensurate with the level of risk and applicable area/ situation.

During Formal QRM, quantitative risk management tools (as defined in Table IV) such as FMEA, FMECA, FTA, HACCP, HAZOP, PHA are used either individually or in combination to measure the risk combining multiple levels of severity, detectability and probability into an overall estimate of relative risk. A "risk score" is used to further define descriptors in risk ranking. The QRM techniques used in Informal QRM can also combine with QRM tool for effective Formal QRM. The selection of a tool should be commensurate with the level of risk and applicable area/ situation.

Statistical tools can also support and facilitate quality risk management. They can enable effective data assessment, aid in determining the significance of the data set(s), and facilitate more reliable decision-making.

Summary

The degree of formality in QRM is a crucial as it promotes consistency, transparency, and documentation of risk assessments and decision-making processes. It also supports accountability and traceability, which are vital in regulated pharmaceuticals industries, where regulatory compliance is utmost priority. In addition, formal QRM approach can enhance collaboration among various stakeholders, such as quality, production, and regulatory affairs. Ultimately, formality in QRM can improve the quality and safety of pharmaceutical products by ensuring that the process is conducted in a rigorous and systematic manner.

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