

Final Concept Paper

ICH Q9(R1) - Quality Risk Management

Endorsed by the Management Committee on 13 November 2020

Type of Harmonisation Action Proposed

The following harmonization actions are proposed:

1. Limited and specific adjustments would be made to specific chapters and annexes of the current ICH Q9 Guideline on Quality Risk Management (QRM). The adjustments would address four areas for improvement, as outlined below.
2. Specific official ICH training materials (with examples) would be developed to supplement the existing ICH briefing pack on ICH Q9 ([link](#)), as well as to explain and facilitate the implementation and application of the proposed revisions. Harmonized training material and its comprehensive roll out is a key component of this revision.

Statement of the Perceived Problem

ICH Q9 QRM principles and framework were instrumental in introducing QRM approaches to both industry and regulators. However, the benefits of QRM, as envisaged by ICH Q9, have not yet been fully realized. There are four areas for improvement with the current application of QRM:

- a) **High levels of subjectivity in risk assessments and in QRM outputs** – the reasons for this can include highly subjective risk scoring methods and differences in how risks are assessed and how hazards, risk, and harms are perceived by different stakeholders. This can lead to varying levels of effectiveness in the management of risks. While subjectivity cannot be completely eliminated from risk assessment and QRM activities, it may be controlled using well recognised strategies, including addressing bias and behavioural factors. (This could be addressed via specific revisions to Chapter 1 and 4.1 of the guideline, as well as by the development of specific training materials that discuss strategies and tools for controlling subjectivity.).
- b) **Product availability risks** – ICH Q9 is not a supply chain guideline, but quality/manufacturing issues that impact the supply chain and product availability can present risks to patients, and management of these risks is important. ICH Q9 already addresses product availability issues, as its definition of harm includes damage ‘from a loss of product availability’. Addressing lifecycle risks to manufacturing reliability and quality assurance is the foundation for supply predictability. An increased emphasis on this would be beneficial, whilst recognising the need for flexibility in how much formality is applied in relation to risk-based drug shortage prevention and mitigation activities. (This could be addressed via specific revisions to Chapter 6, adding a new section (II.9) into Annex II on the use of QRM in the quality aspects of supply chain control, by adding a definition for “Product Availability” in Chapter 7, as well as by the development of training materials).
- c) **Lack of understanding as to what constitutes formality in QRM work** - this area has the potential to be further developed for deeper understanding to lead to a more effective application of QRM principles and better execution of QRM activities. There has been significant confusion and

uncertainty in the industry and among regulators as to what constitutes formality in QRM work, and how generally to interpret this principle. It would be useful to clarify what is expected in terms of formality and that there is flexibility in how much formality may be applied in relation to QRM activities, while emphasizing that robust risk management should always be the overarching goal of QRM. (This could be addressed by referencing Annex 1 at the end of Chapter 1 or Chapter 5, adding guidance in the introduction section of Annex I on what constitutes different degrees of ‘formality’ and the factors that might be considered when determining how much formality to apply to a given QRM activity. Training materials will also be developed to address this area.).

- d) **Lack of clarity on risk-based decision-making** - while there are references in ICH Q9 to decision-making, there is a lack of clarity on what good risk-based decision making actually means, how QRM may improve decision-making, or how risk-based decisions might be achieved. There is a breadth of peer-reviewed research in this area, but the level of visibility (and uptake) of that research within the pharmaceutical industry may be improved. It would also be useful to address the expected benefits of investing in risk-based decision-making activities. (This could be addressed via a specific revision to Chapter 1, adding a new section (II.10) into Annex II on risk-based decision-making, adding a reference to risk-based decision-making in Chapter 6, and the development of training materials).

A targeted revision to ICH Q9, supported by additional training materials, could provide important additional guidance in these areas, whilst also recognising the role of other ICH quality guidelines.

Other suggested points to be addressed were proposed by the ICH Quality Discussion Group (QDG), namely:

- This work could provide 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. Risk review ties in with the concept of continuous improvement as expressed in ICH Q10 and in the lifecycle management guidelines (ICH Q12/Q14), and it could be addressed by developing additional training materials on this topic.
- A targeted revision should be considered to Chapter 4.3 to change ‘risk identification’ to ‘**hazard identification**’, and to update Figure 1 of the guideline to reflect this. This change will align with the expectation to identify hazards relevant to patients when evaluating risks; moreover, it may improve how hazards are perceived and assessed.

A revised ICH Q9 that addresses the above four areas of improvement could help conserve regulatory and industry resources, e.g., by addressing the above areas more explicitly, it could lead to more effective and science-based control strategies (ICH Q8/Q11) among manufacturers, improving manufacturing consistency, lowering costs and reducing the likelihood of quality defects, recalls, and medicine shortages. If manufacturing and supply chain processes are designed and validated in a manner that adequately reflects the QRM principles, it is reasonable to expect that such problems could decrease.

For a discussion of other potential benefits of the proposed revision of ICH Q9, please see Annex 1.

Issues to be Resolved

The main technical and scientific issues that would be addressed in the revision are outlined above, and will improve the understanding and consistent application of QRM by addressing subjectivity in risk

assessment/QRM outputs, supply and product availability risks, formality in QRM and risk-based decision making, as well as the hazard identification and risk review.

Background to the Proposal

When ICH Q9 was finalised in November 2005, ICH Q10 was not yet in place. ICH Q10 introduced the concept of QRM serving as an enabler to the Pharmaceutical Quality System (PQS) and as a means of driving continual improvement and innovation. A need to shift the QRM focus from reactive to proactive will enable continual improvement to become a key aspect of the PQS. Thus, this revision of ICH Q9 is of strategic importance.

Type of Expert Working Group and Resources

The EWG should comprise experts with a strong working and application knowledge of QRM spanning small molecule, new chemical entities, and biological products.

Timing

It is anticipated that the revised guideline and its associated training materials will take until June 2022 to reach Step 4 of the ICH Process.

Annex 1: The anticipated benefits of the proposed revision of ICH Q9

The revisions proposed here have the potential to lead to many benefits via increased harmonisation in the use and implementation of QRM, which helps ensure the protection of the patient:

- Less subjective risk assessments to support manufacturing processes should lead to fewer quality defects that could present risks to patients. Recalls are required every year to protect patients from the real and/or potential risks presented by defects in medicines, leading in some cases to shortages of important medicines. Less subjective risk assessments should also lead to more science-based manufacturing operations, control strategies, and validation activities, resulting in the potential for reduced costs and the possibility to free up resources for other necessary activities. ICH Q8, Q10, and Q11 expect science- and risk-based applications, and revising ICH Q9 to address subjectivity in QRM more explicitly will help enable/accelerate the continued implementation of Q8, Q10, Q11 (and Q12), because of the foundational relevance of QRM.
- An increased emphasis on managing product availability risks related to manufacturing problems/issues and the need for risk-based drug shortage prevention and mitigations will serve the interests of patients. This is especially important given the extent of globalization of the medicines supply chain, its complexity, and its fragmentation (high number of actors).
- Additional clarity on the concept of formality in QRM may help ensure that the extent of scientific and methodological rigour applied during QRM is commensurate with the level of risk. It may also lead to resources for QRM being used more efficiently – where lower risk issues are dealt with more efficiently via less formal means, freeing up resources for managing higher risk issues and more complex problems, which usually require increased levels of rigour and effort. It is considered that a greater understanding of formality in QRM has the potential to lead to more appropriate and beneficial uses of QRM, leading to improved outcomes in terms of pharmaceutical quality, medicine availability, and patient protection.
- Additional guidance in the area of risk-based decision making could help improve the quality of decisions across a multitude of areas and activities, as well as facilitating access to new medicines for patients, especially for fast-tracked applications, which require robust risk-based decision making.

Experience from the recent quality defects (e.g. nitrosamines, contamination/cross-contamination when introducing new products or making process changes) illustrates the need for a more scientific approach by manufacturers to risk assessment and QRM activities when moving from process development, through technology transfer, supplier approval, facility design, commercial manufacturing, well-managed changes, and lifecycle management.

There are other potential issues that might benefit from the revision of this guideline, such as:

- **Digitisation** (e.g., new manufacturing technologies, automation, and use of big data): as digitisation is implemented into manufacturing facilities, the application of QRM to the design and validation of production processes, technology transfer, and the introduction, validation, and use of computerized systems and data analysis methods into manufacturing facilities may become increasingly important.
- **Emerging technologies:** the anticipated increase in emerging technologies, e.g., continuous manufacturing and process analytical technologies (PAT), may also benefit from an increased use of science-based QRM activities.

All parts of the pharmaceutical industry (branded, generics, biologicals, small molecule, manufacturers, Marketing Authorisation Holders, wholesalers, and Contract Research Organisations, etc.) and regulators (such as Assessors, GxP Inspectors, and Official Testing Laboratories) could benefit from the additional guidance proposed here.