

Final Business Plan

ICH Q9(R1) - Quality Risk Management

Endorsed by the Management Committee on 26 October 2020

1. The issue and its costs

- *What problem/issue is the proposal expected to tackle?*

ICH Q9 has provided the pharmaceutical industry and regulators alike with a common framework for applying Quality Risk Management (QRM) principles in their work. However, despite the guideline being in place for almost 15 years, the benefits of QRM, as envisaged by ICH Q9, have not yet been fully realised. There are indications that current approaches to QRM have not been sufficiently effective, and this has also limited the value-realization of the other ICH Guidelines, such as ICH Q8 and Q10, which expect science- and risk-based approaches. The interpretation of ICH Guidelines addressing QRM has not been consistent across regulators and regulated industry. Revisions to ICH Q9 will help provide consistency and clarity, helping to improve quality manufacturing. Thereby it may contribute to reduce the number of shortages and/or recalls.

Manufacturing and supply processes that are designed and validated using more robust and efficient QRM may decrease concerns such as recalls and shortages. In addition, experience from recent quality defects (e.g., nitrosamines) illustrates the need for more effective management of risk when moving from process development through technology transfer, into supplier approval and commercial manufacturing.

There are four areas of concern with the current application of QRM, and the problems and issues that would be addressed in a proposed targeted revision of ICH Q9 (supported by new training materials) relate to those. These are as follows:

- *High levels of subjectivity in risk assessments and QRM outputs, leading to a lack of good science;*
- *Challenges in the management of product availability risks, resulting in continued shortages of important medicines for patients;*
- *A lack of understanding of what constitutes formality in QRM, and how to apply varying degrees of formality in QRM activities so that a better use of resources can be made;*
- *A lack of clarity on what constitutes good risk-based decision-making.*

This targeted revision of ICH Q9 could also provide clarity in relation to risk review activities, as well as hazard identification.

Addressing the above four key areas has the potential to lead to more effective, robust, integrated, and science-based QRM activities within the pharmaceutical environment.

- *What are the costs (social/health and financial) to our stakeholders associated with the current situation or associated with “non-action”?*

The health and social costs associated with ineffective QRM activities include the harms that can be caused by serious quality defects (such as a lack of sterility assurance, contamination incidents, and product labelling errors), as well as product shortages. Additionally, more effective QRM strategies would promote cost savings by reducing costs associated with quality defects and product recalls and the actions needed to address those. Additionally, financial efficiencies would be gained

from better-designed manufacturing processes, and more effective control strategies and validation activities, which may not address the correct risks at present. There are also various social/health and financial costs associated with ineffective QRM activities that may be significantly reduced if action is taken.

All of these issues can have a significant impact not only on patients, but also on the health systems in many countries. They can also impact pharmaceutical companies in various ways, including a company's ability to invest in optimising/modernising its manufacturing processes and technologies.

2. Planning

- *What are the main deliverables?*

The main deliverable of this proposal is a revised ICH Q9 Guideline in which targeted revisions to specific chapters and annexes are implemented to address four key areas for improvement include: subjectivity in risk assessment/QRM outputs, supply and product availability risks, formality in QRM, and risk-based decision making. The revised guideline will also provide additional guidance on hazard identification and risk review. Per the Concept Paper, the second deliverable is specific training material addressing the revised sections of the ICH Q9 Guideline. This material will supplement the existing ICH briefing pack on ICH Q9 and facilitate the implementation of the proposed revisions.

- *What resources (financial and human) would be required?*

An Expert Working Group (EWG) will be required. The team would primarily work virtually, via teleconferences and email. To complete the revision and the training material, there will be a need for two face-to-face meetings per year (pending MC approval as per the Working Group's Work Plan and ICH procedures), subject to COVID-19 travel restrictions.

- *What is the time frame of the project?*

It is anticipated that the revised guideline and its associated training materials will take until June 2022 to reach Step 4. However, the ongoing COVID-19 pandemic introduces significant uncertainty regarding the timeframe of the project. Limited ability to meet due to travel restriction as well as potential unforeseen increase in workload of working group members may require the extension of the milestones below by approximately up to 6 months.

- *What will be the key milestones?*

- Final Concept Paper and Business Plan endorsed: **November 2020**
- Step 2b (Adoption of the draft guideline): **September – October 2021**
- Step 3 (Regulatory Consultation): **November 2021 – January 2022**
- Development of Training Materials: **November 2021 – May 2022**
- Finalisation and WG endorsement of the ICH training materials: **May 2022**
- Step 4 (Adoption of final ICH Guideline): **June 2022**

- *What special actions to advance the topic through ICH, e.g. stakeholder engagement or training, can be anticipated either in the development of the guideline or for its implementation?*

A training package concerning the guideline revisions will be required to facilitate implementation of the proposed revisions. This will consider and supplement the already existing ICH Q9 briefing pack. QRM Case Studies will be developed to help both the discussions at the EWG meetings as well as the development of the proposed training materials.

3. The impacts of the project

- *What are the likely benefits (social, health, and financial) to our key stakeholders of the fulfilment of the objective?*

It is anticipated that the updated guideline and its associated training material may result in the following benefits:

- More scientific and robust applications of QRM principles, tools, and activities, where subjectivity in QRM outputs is better controlled. This could lead to more science-based manufacturing operations, control strategies, and validation activities, which may result in fewer quality defects and recalls for patients, and potentially in reduced costs for the pharmaceutical industry and healthcare systems.
 - Increased competencies in how risks, hazards, and harms are identified, assessed, perceived, and communicated.
 - Increased assurance that shortage indicators related to quality can be identified and supply disruptions can be minimized, where possible as a result of an increased emphasis on risk-based drug shortage prevention and mitigation activities. Resources for QRM being used more efficiently – where lower risk issues are dealt with via less formal means, freeing up resources for managing higher risk issues and more complex problems with increased levels of formality.
 - Improved decision-making on risk issues across a multitude of areas and activities relevant to both regulators and the pharmaceutical industry.
 - A more robust application of QRM through the use of analytics as digitisation, automation, and new technologies are implemented in manufacturing facilities. This could lead to more scientific and robust control strategies and validation activities that may result in increased quality and fewer production failures.
- *What are the regulatory implications of the proposed work – is the topic feasible (implementable) from a regulatory standpoint?*

The proposed work concerns a revision to an existing ICH Guideline coupled with the development of supporting training materials. There are no legal issues anticipated, and there should be no impact on existing regional regulatory procedures. It is anticipated that the revised version of ICH Q9 will be easily implementable from a regulatory perspective. The proposed work will assist the pharmaceutical industry and regulatory bodies alike, as it will result in additional guidance in relation to QRM topic areas and manufacturing issues that have evolved since the initial publication, which can be challenging.

- *Will the guideline have implications for the submission of content in the CTD/eCTD? If so, how will the working group address submission of content in the dossier? Will a consult be requested with the ICH M8 Working Group?*

No. The revised guideline will have no implications for the submission of content in the CTD/eCTD, and a consult with the ICH M8 Working Group will not be required.

4. Post-hoc evaluation

- *How and when will the results of the work be evaluated?*

At the conclusion of each stage of the work, it will be determined whether the deliverables and their timelines were met, by comparison against the Concept Paper and Business Plan.