

Final Concept Paper

ICH Q9(R1) - Quality Risk Management

24 March 2023

Endorsed by the Management Committee on 4 April 2023

Type of Harmonisation Action Proposed

Establishment of an Implementation Working Group (IWG) to review and update the existing training materials that are on the ICH website in relation to Quality Risk Management (QRM). These materials, which are comprised of 36 PowerPoint presentations and 1 Q&A document, were developed in 2006-2010 and they include a) the *ICH Q9 Briefing Pack* and b) the *ICH Q8/Q9/Q10 Training Material*. The objective of this IWG would be to address the discrepancies and conflicts that exist between these training materials and the revised guidance that is presented in ICH Q9(R1) following the recent revision of ICH Q9. There are also discrepancies and conflicts between the 2006-2010 training materials and the new training materials that were finalized by the ICH Q9(R1) Expert Working Group (EWG) in 2023 to support the changes that were made to the Guideline, and these issues would also be addressed.

The 2006-2010 materials also need to be reformatted to bring them into compliance with the formatting requirements of official ICH training materials. Currently, the materials are not in the required ICH format, they have varying structures, styles and visual features, they carry a disclaimer indicating that they are not official ICH materials, and they do not show the ICH logo.

Statement of the Perceived Problem

A revised version of the ICH Q9 Guideline was published by ICH in January 2023. This provided detailed guidance in relation to the following four main areas:

- Subjectivity in QRM
- Product Availability Risks
- Formality in QRM
- Risk-based Decision-making

A number of other changes were also made to the Guideline. For example, the term ‘Risk Identification’ was changed to the term ‘Hazard Identification’; and a clearer distinction was made between hazards, harms, and their associated risks. The revision also addressed the potential role of detection controls in reducing the probability of occurrence of harm.

A suite of new training materials was developed by the ICH Q9(R1) EWG during 2022/2023 to support the revisions to the Q9 Guideline. This focused not only on the aforementioned four topic areas (Subjectivity in QRM, Product Availability Risks, Formality in QRM, and Risk-based Decision-making), it also contained training material on Hazard Identification and Risk Review, two topics that had been identified in the 2020 Concept Paper on ICH Q9(R1) as needing new training materials.

The 2006-2010 training materials that are on the ICH website in relation to QRM and ICH Q9 are, in some places, not in line with the revised ICH Q9(R1) Guideline and with the new 2023 training materials that were developed to support the revisions to the Guideline. In some areas, the 2006-2010 training materials are in conflict with the revised Guideline and its associated training materials. Examples of such discrepancies and conflicts are shown in Appendix 1.

The IWG would focus on addressing such discrepancies and conflicts. This would be achieved by reviewing, revising and updating, where necessary, the 2006-2010 training materials to bring them in line with the revised ICH Q9(R1) Guideline and its associated 2023 training materials.

Despite the above, it is important to recognise that the 2006-2010 training materials provide invaluable content across a large number of areas, and many of those areas were not addressed in the new 2023 training materials that were developed to support the new guidance in ICH Q9(R1). Thus, the majority of the content in the 2006-2010 training materials should be retained.

In order to maximize the benefits that may be derived from the ICH Q9(R1) Guideline and its associated training materials, it is considered that all of the training materials, old and new, that are on the ICH website in relation to QRM should be harmonised and free from discrepancies and conflicting content. The IWG would work towards this goal.

Issues to be Resolved

The following issues will be resolved:

- Certain elements of the 2006-2010 training materials need to be revised or deleted to address discrepancies and conflicts with the revised Guideline and its associated 2023 training materials.
- In relation to terminology, in addition to the need to change ‘Risk Identification’ to ‘Hazard Identification’, there are other certain terminology changes that will need to be considered to bring the 2006-2010 training materials in line with the revised Guideline and its associated new training materials. An example of this is the use of the words ‘hazard’, ‘harm’ and ‘risk’ in the 2006-2010 materials.
- In light of the age of the 2006-2010 materials, edits will need to be made to bring the materials up-to-date in terms of their visual appearance.

Other issues to be resolved are listed in Appendix 2.

The main technical and scientific issues that would be addressed in the work of the IWG are outlined above, and in doing so, the industry and its regulators will benefit from a more harmonized set of QRM training materials which supports the overall contents of ICH Q9(R1).

Background to the Proposal

In 2005, the ICH Q9 Guideline was instrumental in introducing QRM approaches to both industry and regulators. A suite of training materials was developed between 2006 and 2010 to support the Guideline; these materials explained the key concepts set out in the Guideline, and they provided examples and case studies which illustrated the practical application of QRM and its methods and tools. However, as acknowledged in the 2020 Concept Paper on the revision of the Guideline, the full benefits of QRM, as envisaged by ICH Q9, were not fully realized. There were four areas pertaining to the application of QRM identified for improvement when the revision work was proposed and agreed.

These were:

1. High levels of subjectivity in risk assessments and in QRM outputs;
2. Product availability risks;
3. A lack of understanding as to what constituted formality in QRM work;
4. A lack of clarity on risk-based decision-making.

Guidance was developed on each of these four areas during the revision of ICH Q9, and the revised Guideline containing that new guidance was published as a *Step 4* document in January 2023. In order to support the application of the new guidance, a specific set of training materials on each of those four

topics was developed by the ICH Q9(R1) EWG, and these new materials were published on the ICH website during 2023. Training materials were also developed on two additional topics - Hazard Identification and Risk Review; the need for those materials had been identified in the 2020 Concept Paper on the Guideline revision work, and they were likewise published by ICH in January 2023.

In 2021 and 2022, the EWG for the revision of the Guideline identified the potential need to review and update the existing training materials that were on the ICH website in relation to Quality Risk Management (QRM). This was because those materials, which had been developed in 2006-2010, are in some places not in line with the revised Guideline or its associated 2023 training materials. In other places, the 2006-2010 training materials are actually in conflict with the new guidance presented in ICH Q9(R1) and with the 2023 training materials that support the revised Guideline. This issue was brought to the attention of the ICH Management Committee and Assembly during 2022, and it was decided that an IWG should be convened in order to revise and update the 2006-2010 training materials to address these discrepancies and conflicts.

Type of Expert Working Group and Resources

Given the expertise of the current EWG members in relation to Quality Risk Management and the ICH Q9(R1) Guideline, it is recommended that the IWG membership be the same as the current ICH Q9(R1) EWG. Subgroups of the EWG would be formed to work on various elements of the training materials from 2006-2010, to revise and update them, where necessary, to bring them in line with the revised version of the Guideline and its associated 2023 training materials. It is envisaged that the IWG would work through teleconferences, email, and occasionally, via in-person meetings. The subgroups would obtain input from the entire IWG through discussions, mainly via email and teleconferences.

Timing

Given that there are 36 PowerPoint presentations and 1 Q&A document in the ICH Q9 Briefing Pack and the Q8/Q9/Q10 Training Material from 2006-2010 that will need to be reviewed and revised as part of this work, it is anticipated that the review and revision work on those materials would take approximately 12 months to complete.

The following are the suggested timelines for the work:

Agreement of IWG Concept Paper by the ICH Q9(R1) EWG.	March 2023
Adoption of Concept Paper by the ICH Management Committee.	To be determined
Review of the 36 PowerPoint presentations and 1 Q&A document in the 2006-2010 training materials, and generation/finalization of the revised/updated versions.	September 2023-September 2024 (12 months)

Appendix 1: Examples of discrepancies and conflicts between the 2006-2010 training materials and the ICH Q9(R1) Guideline or its supportive 2023 training materials

- The 2006-2010 training materials refer to formality in QRM in *binary* terms (i.e. formal/informal), and there are many references to this in the materials. The training materials also contain a decision tree for determining when QRM should be applied, and this explicitly refers to ‘formal risk management’ and ‘informal risk management’ as outputs of the decision tree. These concepts of formal and informal risk management conflict with the guidance on formality that is included in ICH Q9(R1), which states that formality in QRM is not a binary concept (i.e., formal/informal); it states that formality can be considered to be a continuum (or spectrum), ranging from low to high. The revised Guideline also states that varying degrees of formality may be applied during QRM activities, including when making risk-based decisions.
- The 2006-2010 training materials refer to the term ‘risk identification’, whilst the ICH Q9(R1) Guideline and its associated training materials refer to ‘hazard identification’, and the latter indicates why the term ‘risk identification’ is problematic.
- The 2006-2010 training materials state that QRM is not mandatory; while this was true at that time, and while ICH Q9, as a Guideline, was and remains a non-mandatory one, it is no longer correct to state that *QRM* is not mandatory. Applying QRM principles and concepts is now a well-established regulatory requirement in many areas, not least in the manufacture of drug substances and drug products, as indicated by ICH Q7 and the various other GMP guidelines that exist.
- The ICH Q9(R1) Guideline provides a clarification in relation to one of the two principles of QRM that were listed in ICH Q9. This was the principle that the evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient. In the revised version of the Guideline, this principle has been extended to clarify that the term ‘*risk to quality*’ includes situations where product availability may be impacted, leading to potential patient harm. This is not reflected in the 2006-2010 training materials.
- The 2006-2010 training materials make reference to ‘passive decisions’ in relation to the acceptance of residual risks after risk control. In the ICH Q9(R1) Guideline, the concept of ‘passive decisions’ when accepting residual risks was removed. (A reference to ‘formal decisions’ in the same context was also removed.) This was because those concepts were not considered to be in line with the new guidance that had been inserted into the revised Guideline in relation to Formality in QRM and Risk-based Decision-making.

Appendix 2: Additional Issues to be resolved

In addition to the main issues that will be resolved, as listed on page 2, the following other issues will also be resolved:

- The aforementioned four concepts (Subjectivity in QRM, Product Availability Risks, Formality in QRM and Risk-based Decision-making) that were the subject of the revision of the ICH Q9 Guideline, will be incorporated into the 2006-2010 materials in cases where not referring to them there would be in conflict with the revised Guideline and its associated 2023 training materials. (It is noted that the 2006-2010 training materials already make some references to three of these topics.)
- The role of human and other causal factors in contributing to the root causes of hazards and risks will be incorporated into the 2006-2010 training materials, where those materials refer to the root causes of issues.
- The importance of detection controls in situations where such controls help reduce the probability of occurrence of harm will be addressed when updating the 2006-2010 training materials, where those materials refer to the detection of hazards, risk and harm.
- The IWG will make a proposal in relation to potential training activities that could take place after the updates are made to the 2006-2010 training materials.