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# ICH Q9(R1): Quality Risk Management

## *Step 4* document – to be implemented

**14 March 2023**

International Council for Harmonisation of Technical Requirements
for Pharmaceuticals for Human Use

# Legal Notice




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# Background

- **This document has been signed off as *Step 4* document (18 January 2023) to be implemented by the ICH Regulatory Members**
- **This document was developed based on a Concept Paper (approved 13 November 2020) and a Business Plan (approved 26 October 2020)**

# Key Principles

- **The ICH Q9 Guideline has been revised to address the following:**
  - The Quality Risk Management (QRM) principles and framework of ICH Q9 have been instrumental in introducing QRM approaches to both industry and regulators. However, the benefits of QRM, as envisaged by ICH Q9, had not been fully realized.
  - 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**
  - Guidance has been developed for each of these four areas; this new guidance is now included in various chapters and annexes of the ICH Q9(R1) guideline.
  - The revised guideline is supported by the development of official ICH Q9(R1) training materials* – these materials include examples and case studies to help illustrate the key points in the new guidance.

** Training materials in development at the time of this presentation*

# Key Principles cont'd

## Risk Review

- Risk Review was identified in the ICH Q9(R1) Concept Paper as needing additional clarity.
- This topic was addressed, via the development of ICH Q9(R1) training materials* only, by providing additional clarity on the expectations on keeping risk assessments current and on the implementation of risk review activities based on lifecycle manufacturing performance and quality feedback.
- No changes were made to the Guideline text on Risk Review.

## Hazard Identification

- The revision provided the opportunity to change the 'Risk Identification' terminology that was in ICH Q9 to the term 'Hazard Identification'.
- This change brings the guideline more in line with the current definition of Risk Assessment, which makes reference to the identification of hazards, not the identification of risks.
- Hazard Identification is the first step in Risk Assessment. Risks can then be analyzed and evaluated based on the harms associated with the identified hazards.



** Training materials in development at the time of this presentation*

# Guideline Objectives – Subjectivity in QRM

- **The Concept Paper for this revision work outlined why Subjectivity in QRM was to be addressed:**
  - It made reference to high levels of subjectivity in risk assessments and in QRM outputs, stating that 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.
  - It stated that subjectivity in QRM can lead to varying levels of effectiveness in the management of risks.
  - It indicated that, 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.
- **The above points were the basis of the new text that was developed for the revised guideline in this area.**

# Guideline Objectives – Product Availability Risks

- **The Concept Paper for this revision work outlined why Product Availability Risks were to be addressed:**
  - It indicated that, while ICH Q9 is not a supply chain guideline, quality / manufacturing issues that impact the supply chain and product availability can present risks to patients, and managing these risks is important.
  - It stated that 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.
  - It stated that 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.
- **The above points were the basis of the new text that was developed for the revised guideline in this area.**

# Guideline Objectives – Formality in QRM

- **The Concept Paper for this revision work outlined why Formality in QRM was to be addressed:**
  - It referred to a lack of understanding as to what constitutes formality in QRM, and how this area has the potential to be further developed to lead to a more effective application of QRM principles.
  - It indicated that there has been significant confusion and uncertainty as to what constitutes formality in QRM work, and how it would be useful to clarify what is expected in terms of formality.
  - It suggested 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.
- **The above points were the basis of the new text that was developed for the revised guideline in this area.**

# Guideline Objectives – Risk-Based Decision-Making

- **The Concept Paper for this revision work outlined why Risk-Based Decision-Making was to be addressed:**
  - It referred to a lack of clarity on risk-based decision-making and on what good risk-based decision-making actually means, how QRM may improve decision-making, and how risk-based decisions might be achieved.
  - It referred to peer-reviewed research in this area from other fields, but how the level of visibility (and uptake) of that research within the pharmaceutical industry may be improved.
  - It proposed addressing the expected benefits of investing in risk-based decision-making activities.
- **The above points were the basis of the new text that was developed for the revised guideline in this area.**

# Guideline Objectives

- **Scope: The scope of the revised Guideline is unchanged from the previous version. This reads as follows:**
- *"This guideline provides principles and examples of tools for quality risk management that can be applied to different aspects of pharmaceutical quality. These aspects include development, manufacturing, distribution, and the inspection and submission/review processes throughout the lifecycle of drug substances, drug (medicinal) products, biological and biotechnological products (including the use of raw materials, solvents, excipients, packaging and labeling materials in drug (medicinal) products, biological and biotechnological products)."*

# Guideline Objectives

- **The implications and benefits of the revised guidance are expected to be the following:**
  - A revised ICH Q9 that addresses the four areas of improvement referred to in the earlier slides may help conserve regulatory and industry resources.
  - For example, addressing the above areas more explicitly could lead to 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.
  - 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.
  - Other potential benefits are addressed in Annex 1 of the ICH Q9(R1) Concept Paper of 13 November 2020.

# Table of Contents

- **The table of contents of the revised Guideline remains largely unchanged:**
  - Three new sub-sections have been added to Chapter 5 (Risk Management Methodology):
    - 5.1: Formality in Quality Risk Management
    - 5.2: Risk-based Decision Making
    - 5.3: Subjectivity in Quality Risk Management
  - A new sub-section has been added to Chapter 6 (Integration of Quality Risk Management into Industry and Regulatory Operations):
    - 6.1: The role of Quality Risk Management in addressing Product Availability Risks arising from Quality/Manufacturing Issues
  - The title of Annex 1 – 'Risk Management Methods and Tools' - has been renamed 'Quality Risk Management Methods and Tools'.
  - A new sub-section II.9 has been added into Annex II (Quality Risk Management as part of Integrated Quality Management). It is titled 'Quality Risk Management as Part of Supply Chain Control'.

# Summary of Guideline Content

- **The following slides, No. 14-20,** summarize the six topics included in the concept paper that were within scope of the revision.
- **Slides 21-22** summarize the cross references that were made to ICH Q10, and they explain why those cross-references were made.
- **Note**: The Concept Paper outlined the items that were within scope of this revision. While the sections of ICH Q9 that were not within scope of the revision were generally not changed from their original content, a number of relatively minor edits were made in some places, to provide alignment with the revised text, or to clarify certain points.

# Summary of Guideline Content

- **In relation to Subjectivity in QRM:**
  - 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 maximising the use of relevant data and sources of knowledge.
  - All participants involved with QRM activities should acknowledge, anticipate, and address the potential for subjectivity.

# Summary of Guideline Content

- **In relation to Product Availability Risks:**
  - ICH Q9 already addresses product availability issues, as its definition of harm includes damage from a 'loss of product availability'; this point is highlighted in the revised guideline, where the first QRM principle in ICH Q9 is revised to add the Note in red as shown below:
    - *"The evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient. (Note: Risk to quality includes situations where product availability may be impacted, leading to potential patient harm.)"*
  - The revised guideline addresses how quality/manufacturing issues, including non-compliance with Good Manufacturing Practice (GMP), are a frequent cause of product shortages, and that the interests of patients are served by risk-based drug shortage prevention and mitigation.
  - It indicates that an effective Pharmaceutical Quality System drives both supply chain robustness and sustainable GMP compliance.

# Summary of Guideline Content

- **In relation to Product Availability Risks:**
  - The revised Guideline addresses how an effective Pharmaceutical Quality System uses QRM and Knowledge Management to provide an early warning system that supports effective oversight and response to evolving quality/manufacturing risks from the pharmaceutical company or its external partners.
  - It indicates that the level of formality applied to risk-based drug shortage prevention and mitigation activities may vary.
  - The revised Guideline addresses several factors that can affect supply reliability, and hence product availability, and it provides guidance on each of those. The factors include the following:
    - *Manufacturing Process Variation and State of Control (internal and external)*
    - *Manufacturing Facilities*
    - *Oversight of Outsourced Activities and Suppliers*

# Summary of Guideline Content

- **In relation to Formality in QRM:**
  - The revised Guideline addresses what constitutes formality in QRM and it outlines how varying degrees of formality may be applied during QRM activities, including when making risk-based decisions. In this way, formality can be considered a continuum (or spectrum), ranging from low to high.
  - It addresses the factors that may be considered when determining how much formality to apply to a given QRM activity.
  - It provides guidance on the characteristics of higher and lower levels of formality.
  - It indicates that there is flexibility in how much formality may be applied in relation to QRM activities, emphasising that the robust management of risk should always be the overarching goal of QRM.

# Summary of Guideline Content

- **In relation to Risk-Based Decision-Making:**
  - The revised Guideline provides clarity on what effective risk-based decision-making is, and it indicates that approaches to risk-based decision-making are beneficial, because they address uncertainty through the use of knowledge. This facilitates informed decisions in a multitude of areas, including when allocating resources.
  - The revised Guideline provides guidance on how there are different processes that may be used to make risk-based decisions, and how these are directly related to the level of formality that is applied during the QRM process.
  - It addresses how there can be varying degrees of structure with regard to approaches for risk-based decision-making, and guidance on such approaches is provided.

# Summary of Guideline Content

- **In relation to Risk Review:**
  - As noted earlier, there is no change made to the current guidance in ICH Q9 on Risk Review.
  - The ICH Q9(R1) training materials* that have been developed to support the revised Guideline have content in relation to Risk Review, in line with the Concept Paper, which stated the following:
    - *"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."*

* *Training materials in development at the time of this presentation*

# Summary of Guideline Content

- **In relation to Hazard Identification:**
  - The only change made in the Guideline on this topic is to replace the term 'Risk Identification' with the term 'Hazard Identification'.
  - ICH Q9(R1) training materials* support the revised Guideline in this area – they have content in relation to Hazard Identification, in line with the Concept Paper, which stated the following:
    - *"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."*

** Training materials in development at the time of this presentation*

# Summary of Guideline Content – There are four cross-references in ICH Q9(R1) to ICH Q10

- **The first is in the new text that relates to Subjectivity in QRM. It states:**
  - 'While subjectivity cannot be completely eliminated from quality risk management activities, it may be controlled by addressing bias, the proper use of quality risk management tools and maximising the use of relevant data and sources of knowledge (see ICH Q10, Section 1.6.1).'
- **The second cross-reference is in the new sub-section 5.2 on Risk-based Decision Making. The new text states the following:**
  - 'As all decision making relies on the use of knowledge, see ICH Q10 for guidance in relation to Knowledge Management.'
- **These cross-references to ICH Q10 serve to highlight the importance of using available sources of knowledge (e.g., pharmaceutical development studies, process validation studies, change management activities, etc.) and Knowledge Management in general during QRM activities.**

# Summary of Guideline Content – Cross-references to ICH Q10 cont'd

- **The third, in Chapter 6 of the revised Guideline, is in a new section titled *"The role of Quality Risk Management in addressing Product Availability Risks"*. In relation to oversight of outsourced activities and suppliers, it states:**
  - 'When substantial variability is identified in the quality and safety of supplied materials or in the services provided, enhanced review and monitoring activities are justified (See Section 2.7 of ICH Q10).'
- **The fourth cross-reference is in the new Annex II.9, titled 'Quality Risk Management as Part of Supply Chain Control'. In relation to supplier oversight and relationships, it states:**
  - 'To enhance review and monitoring activities (see Section 2.7 of ICH Q10) when substantial variability is identified in the quality and safety of supplied materials or in the services provided.'
- **These cross-references to ICH Q10 serve to highlight the importance of QRM in ensuring that processes are in place to assure the control of outsourced activities and the quality of purchased materials.**

# Results of Public Consultation

- **Approx. 775 comments were received and reviewed during the *Step 3* public consultation**
- **All revisions made as a result of the comments received were made based on a consensus process within the Expert Working Group (EWG)**
- **Summary of major revisions:**
  - Moved the text relating to 'Subjectivity in QRM' to its own dedicated section (5.3) within Chapter 5, to stress its importance.
  - Revised the guidance relating to the application of digitalization and emerging technologies, by highlighting their role in risk reduction when such new technologies are fit for their intended use, and how such technologies can introduce other risks that may need to be controlled.
  - Stressed the importance of an appropriate application of root cause analysis to address root causes and other contributing factors along the causal chain.
  - Provided a clearer distinction between hazards, harms, and associated risks and their use throughout the guideline.
  - Modified the definition for 'risk-based decision-making' to make it clearer.

# Results of Public Consultation cont'd

- **Summary of major revisions (continued):**
  - Addressed 'detection controls' and their link to reducing the probability of occurrence of harm in Chapter 5
  - Revised the guidance in relation to the use of a facilitator for situations which call for higher levels of QRM formality
  - Modified the pre-existing text in relation to 'risk acceptance' (section 4.4) in order to remove reference to 'formal' decisions
  - Added 'Equipment' to the Manufacturing & Facilities section title within section 6.1
  - Linked drug shortage prevention and mitigation activities with formality in Chapter 6.1
  - Addressed the importance of QRM with regards to 'distribution' practices in the Introduction
  - References – added reference to ICH Q11 and Q12, and revised several of the ISO Standard references to bring them up to date

# Considerations

- The guideline revisions in ICH Q9(R1) are intended to support the effective implementation of QRM and result in improvements in the application of QRM. These should result in more value-adding approaches to quality risk management.
- Given the impact of drug shortages over ten or so years in many markets, the revisions made to the Guideline which highlight the need to manage product availability risks are important for stakeholders to consider.
- The revised guideline recognises the importance of digitalization and emerging technologies, as they can lead to improved control strategies and risk reduction. The guidance also indicates that such technologies can present certain challenges, and it highlights how 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 important.

# Guideline for Implementation

- ICH Q9(R1) is a foundational guideline, as it supports the implementation of ICH Q7, Q8, Q10, Q11, ICH Q12, ICH Q13 and other Quality Guidelines. Those other Guidelines are dependent, to some extent, on the effective application of Quality Risk Management, and this renders the revisions made to the ICH Q9 Guideline important to consider.
- Industry and regulatory authorities who have already implemented QRM should refer to the revisions made in the Guideline, so as to make their QRM activities more effective and value-adding. In particular, the guidance relating to the four key topics areas listed below should be considered:
    - Subjectivity in QRM
    - Product Availability Risks
    - Formality in QRM
    - Risk-based decision-making

# Guideline for Implementation cont'd

- The revisions made to the Guideline are intended to serve as useful guidance for both industry and regulators. ICH Q9(R1) should be applied by both industry and regulators in a manner that is appropriate to each of the product lifecycle stages and the related regulatory activities, recognising the differences among, and the different goals, of each stage.
- In relation to the terminology change from 'Risk Identification' to 'Hazard Identification', while it is not foreseen that all past risk assessments would be updated now to reflect that change, future QRM activities should be reflective of this revised terminology.
- ICH Q9(R1) should be read in conjunction with the official ICH Q9(R1) training materials*. These materials expand upon the concepts introduced into the guideline and they contain a number of examples and case studies to aid with learning.

** Training materials in development at the time of this presentation*

# Conclusions

- This revision of ICH Q9 provides guidance in four main areas, as follows:
  - 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
- A change in terminology from 'Risk Identification' to 'Hazard Identification' has been made, to better reflect the text concerning Risk Assessment.
- The revisions are supported by official ICH Q9(R1) training materials*, with examples and case studies included.
- Risk Review activities are also addressed in the training materials.
- Approx. 775 comments were received and reviewed during the *Step 3* public consultation. A number of revisions were made to the Guideline as a result of the comments received. These were made based on a consensus process within the Expert Working Group (EWG).

** Training materials in development at the time of this presentation*

# Contact

- **For any questions please contact the ICH Secretariat:**

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