Quality Risk Management, ICH Q9(R1)

Step 3

Step 3 document – to be released for comments

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Legal Notice

Learning Objectives

- **Discuss the impetus for revising the ICH Q9 guideline.**
- **Highlight some major focus areas in the guideline (Step 3).**

Background

- **This document was developed based on a Concept Paper (approved 13 November 2020) and a Business Plan (approved 26 October 2020)**
- **This document was signed off as a *Step 2* document (18 November 2021) to be issued by the ICH Regulatory Members for public consultation. It was then approved for *Step 3*, which will include review of public comments to be submitted.**
- **Anticipating finalization as a *Step 4* document to be implemented in the local regional regulatory system: September 2022**

Key Principles

- **The ICH Q9 Guideline has been revised to address the following:**
  - The 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, have not yet been fully realized.
  - There are four areas for improvement with the current 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 has been inserted into various chapters and annexes of the current guideline.
  - The new guidance will be supported by the development of official ICH training materials – these materials will include case studies to help illustrate the key points in the guidance.

Guideline Objectives

- **Scope: The scope of the revised Guideline is unchanged from the current version of ICH Q9. 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 (listed in slide 4) could 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:**
  - Two 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
  - 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). The new sub-section is titled 'Quality Risk Management as Part of Supply Chain Control'.

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.

Challenge Question #1

Excessive subjectivity will not affect the accuracy of a risk assessment.

(True or False)

A. True

B. False

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*

Challenge Question #2

Many drug shortages can be prevented by vigilant ongoing oversight of risks relating to facilities, processes, and suppliers.

(True or False)

A. True

B. False

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:**
  - There is no change made to the current guidance in ICH Q9 on Risk Review.
  - The new training materials that will be developed to support the revised Guideline will 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."*

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.’
  - The new training materials that will be developed to support the revised Guideline will 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.”*

Summary of Guideline Content: Cross-references 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 two 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 further 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.

Considerations

- It is considered that the new guidance in ICH Q9(R1) supports the existing guidance in ICH Q8 and Q10, as well as ICH Q12 and other Quality Guidelines. Those other Guidelines all rely, to some extent, on the application of quality risk management principles.
- This revision of ICH Q9 is intended to result in more value-adding and effective approaches to quality risk management.
- The new guidance recognises that digitalization and emerging 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.
- When finalised, this revision of ICH Q9 should be read in conjunction with the official ICH Q9(R1) training materials that will be developed prior to the completion of Step 4 of the ICH process.

Conclusions

- While ICH Q9 was instrumental in introducing QRM approaches to both industry and regulators, the benefits of QRM have not yet been fully realized.
- Four areas for improvement with the current application of QRM have been identified. These are 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
- This revision provides guidance on each of these four areas, and it will be supported by official ICH training materials, including case studies. Risk Review activities will also be addressed in the training materials.
- A change in terminology from Risk Identification to Hazard Identification has been made in the revised guideline, to better reflect the existing text concerning Risk Assessment.