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ICH Q9(R1) Quality Risk Management Revision – Public Consultation

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Revision of the ICH Q9 Quality Risk Management (QRM) guideline was released for public comment in December 2021. In the EU, the public consultation period begins on mid December and will continue for 3 months. ICH Q9 is a key guideline associated with risk-based change management and validation. The original version of ICH Q9 was issued more than 15 years ago; this is its first revision. Reference documents associated with this issue are linked below (1-4).

The ICH Q9 revision project was endorsed by the ICH Assembly in November 2020 (5). Two primary activities were to be addressed in this project:

- Limited and specific adjustments to chapters and annexes in the current ICH Q9
- Specific training materials with examples to supplement current ICH Q9 and proposed revisions.

Expected benefits of the revision include the following:

- Revised sections could help conserve regulatory and industry resources. More effective, efficient, and science-based control strategies in manufacturing should improve consistency, lower costs, and reduce likelihood of defects, recalls, and shortages. Manufacturing and supply chain problems should decrease.
- Less subjective risk assessments should lead to fewer quality defects that could present risks to patients. The foundational relevance of QRM will enable and accelerate implementation of Q8, Q10, Q11, and Q12.
- Additional clarity on concepts of formality in QRM may help ensure that the level of scientific and technical rigor in QRM is commensurate with the level of risk and should help with resource allocation.
- Additional guidance in the area of risk-based decision making should help improve decision quality generally.
- Other potential issues benefiting from the Q9 revision include digitization and emerging technologies in manufacturing processes.

Anticipated finalization of the revised guideline is expected in September 2022.

Rapporteur for this project is Dr. Kevin O'Donnell (EC, Europe). Regulatory Chair is Alex Viehmann, FDA.

KEY PRINCIPLES

Document Revision

Four key areas for improvement are the main subject of the revision:

- 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. (Note: Understanding the concept of formality in Quality Risk Management by O'Donnell*et al* was previously reported (6).)
- Lack of clarity in risk-based decision-making.

A discussion on each of the above is provided below. A brief summary of the ICH Q9(R1) Concept Paper considerations on each topic is included, followed by a summary of what is in the draft revised version of the guideline. Relevant line numbers in the revision document are identified for each topic. It is anticipated that official ICH training materials supportive to the above will also become available during late 2022.

Risk Review

Risk review was also identified as a Q9 topic needing additional clarity. Revision work through training materials will address this need. This work will address recommendations stated in the Concept Paper as follows:

> *"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. Rick 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 addition training materials on this topic".*

No changes to text in the current guideline have been made in this area.

Hazard Identification

The current "Risk Identification" terminology has been changed in the revision to "Hazard Identification." Figure 1 in the current Q9 has also been updated to reflect this change. The Concept Paper indicated 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."*

New training materials will be developed in relation to hazard identification.

SUBJECTIVITY IN QRM

The Concept Paper identified high levels of subjectivity in risk assessments and in QRM outputs, potentially caused by highly subjective risk scoring methods and risk perception by stakeholders. This may lead to varying levels of effectiveness of quality risk management activities. It indicated that subjectivity may be controlled using well-recognized strategies.

Revision Summary

The revision indicates how subjectivity can impact every stage of a QRM process including identification of hazards, estimates of probabilities of occurrence, estimation of risk reduction, and effectiveness of decisions. Subjectivity can be introduced through differences in how risks are assesses and how hazards, harms, and risks are perceived. Subjectivity can also be introduced through tools with poorly designed scoring scales. Subjectivity may be controlled by addressing bias, proper use of tools, and maximizing use of relevant data and sources of knowledge. All participants in QRM should acknowledge, anticipate, and address the potential for subjectivity.

New Text Lines

- 14-15
- 103-114. This is the main section on Subjectivity.
- 120-121

PRODUCT AVAILABILITY RISKS

The Concept Paper indicated that quality and manufacturing issues that impact the supply chain and product availability can present risks to patients. ICH Q9 already addresses product availability issues; its definition of harm includes damage from "loss of product availability." Addressing lifecycle risks to manufacturing reliability and quality assurance is the foundation for supply predictability. Increased emphasis on this would be beneficial, while recognizing the need for flexibility in formality relative to drug shortage prevention and mitigation.

Revision Summary

An additional note has been added to the first principle of QRM, as follows:

> *"The evaluation of the risk to quality should be based on scientific knowledge and ultimately link to protection of the patient. (Note: Risk to quality includes situations where product availability may be impacted, leading to potential patient harm.)"*

The revision addresses how quality/manufacturing issues, including GMP non-compliance, are a frequent cause of product shortages, and that patients are served by risk-based shortage prevention and mitigation. An effective Pharmaceutical Quality System drives both supply chain robustness and sustainable GMP compliance; it also uses QRM and Knowledge Management to support effective oversight and response to evolving quality/manufacturing risks. The level of formality applied to risk-based drug shortage prevention and mitigation may vary. Factors that may affect supply reliability include manufacturing process variation and control, manufacturing facilities, and oversight of outsourced activities and suppliers; guidance of these factors is provided.

New Text Lines

- 18
- 77-78
- 357-361
- 376
- 386-420. This is the main part of the new guidance.
- 828-855

FORMALITY IN QRM

The Concept Paper identified a lack of understanding as to what constitutes formality in QRM, and how this area may be further developed to result in a more effective application of the QRM principles. There has been significant confusion as to what constitutes formality in QRM. There is flexibility in how much formality may be applied.

Revision Summary

The revision addresses what constitutes formality in QRM, and how varying degrees of formality may be applied during QRM activities, including in decision-making. Formality may be considered a continuum or spectrum, ranging from low to high. It addresses factors to be considered when determining how much formality to apply and provides guidance on the characteristics of higher and lower levels of formality. There is flexibility in how much formality may be applied, emphasizing that robust management of risk should be the overarching goal of QRM.

New Text Lines

- 53-59
- 251-300. This is the main section on Formality.
- 510-511
- 519-522
- There is also reference to formality in the new section 5.2 on*Risk-Based Decision Making*, lines 301-342.

RISK-BASED DECISION MAKING

The Concept Paper 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. Peer-reviewed research in this area from other fields is available; visibility and uptake of this research within the pharma industry may be improved. It proposed addressing the expected benefits of investing in risk-based decision-making activities.

Revision Summary

The revision provides clarity on effective risk-based decision making. It indicates that approaches to risk-based decision making are beneficial by addressing uncertainty through knowledge. This facilitates decisions in many areas, including resource allocation. Different processes may be used to make decisions; these are related to formality in the QRM process. There may be varying degrees of structure in decision making, and guidance on such approaches is provided.

New Text Lines

- 22-25
- 30-35
- 44-45
- 120-121
- 301-342. This is the main text on this topic.

ADDITIONAL CHANGES

- Some changes have been made to the text in the Introduction section. See lines 1-9.
- A new paragraph has been added on digitalization and emerging technologies. See lines 40-43.
- There is a new sentence in lines 62-64 on the improper use of QRM.

Cross References to ICH Q10

ICH Q9(R1) contains several cross references to ICH Q10. These cross references are in the new guidance relating to subjectivity, risk-based decision making, and product availability risks (including supply chain control). These cross references serve to highlight the importance of knowledge and knowledge management in QRM activities.

SUMMARY AND FINAL THOUGHTS

While ICH Q9 was instrumental in introducing QRM approaches to industry and regulators, its full benefits have not yet been realized. Four areas of improvement have been identified and are addressed in this revision. Training materials on these areas will be developed along with training on risk review activities. A change in terminology from risk identification to hazard identification has also been implemented in the revised guideline, to better reflect existing text concerning risk assessment. The scope of the revised guideline is unchanged from that of the current version. The table of contents is largely unchanged, excepting two new sub-sections in Chapter 5 on Risk Management Methodology, and a new Annex II.9, titled ‘Quality Risk Management as part of Supply Chain Control’.

The revised ICH Q9 (R1) guidance supports the existing ICH Q8, Q10, Q12 and other guidelines – as these other guidelines all rely on the application of QRM principles. The revision of ICH Q9 is intended to result in more value-adding and effective approaches to QRM. It recognizes that digitization and emerging technologies can present challenges, and it highlights the value of QRM to the design, validation and technology transfer of advanced production processes and analytical methods, advanced data analysis methods and computerized systems.

ICH Q9((R1) should be read in conjunction with the future training materials that will be developed prior to Step 4 of the ICH process.

ICH Q9(R1) EWG QUALITY RISK MANAGEMENT EXPERT LIST

Members of the Expert Working Group assembled for the ICH Q9 revision are listed below (3).

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