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# ICH Q9(R1) and some personal thoughts about implementing the new guidance

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# The ICH Q9 Revision – Key Milestones

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- **In 2018, HPRA initiated discussions with EMA about a revision. EMA was strongly supportive, and a proposal paper was prepared by HPRA**
- **In 2018/2019, a US FDA colleague and an industry representative were invited to give input, and the proposal was refined**
- **By early 2019, the formal proposal was made to ICH by the European Commission / EMA for a revision**
- By November 2019, ICH had considered the proposal and decided to proceed
  - *June 2020: Informal ICH Working Group put in place to prepare for the revision*
  - *November 2020: ICH Concept Paper and Business Plan agreed and published*
  - *December 2020: The Expert Working Group for ICH Q9(R1) was convened and the revision work got underway… Step 1 was reached in Oct 2021*
  - *Step 3- Public Consultation on the Draft Revised Guideline began in Dec 2021*
  - *Finalisation of the revised guideline (Step 4) January 18th 2023*
  - *Development of supportive training materials Mid 2021 - June 2023.*

# The revision concerned 6 specific topics

- ***Subjectivity in QRM***
- ***Product Availability Risks***
- ***Formality in QRM***
- ***Risk-based Decision Making***
- ***Risk Review***
- ***Hazard Identification***

Five of the above topics were addressed by adding new guidance into Q9 and by developing training materials that support the new guidance

One topic, Risk Review, did not have any new guidance written for it, but new training materials were developed for it

**Note**: This was a very targeted revision of ICH Q9 – it was not a full rewrite.

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Let's take a brief look at each of the six revision topics

# Topic 1: Subjectivity in QRM

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# Topic 1: Subjectivity in QRM

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High levels of subjectivity in risk assessments and in QRM are problematic:

- High levels of Subjectivity are not in line with 1st QRM principle of Q9: *"The evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient".*
- Subjectivity can relate to many different things:
  - *Differences in how hazards, risks and harms are perceived by different stakeholders and how risks are assessed*
  - *Teamworking influences and human heuristics*
  - *The risk scoring methods that some risk assessment tools use*
- While subjectivity cannot be eliminated from QRM activities, it may be controlled using well recognised strategies, including addressing bias and behavioral factors.

- The revision of ICH Q9 and its associated training materials are addressing the above (and other) points.

# Subjectivity in QRM cont'd

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Addressing subjectivity should be beneficial…

- Less subjective risk assessments should lead to more science-based control strategies and validation protocols
- This should lead to fewer quality defects as well as less costly validation activities
- Such improvements in QRM may support the implementation of ICH Q8, Q10, Q11 and Q12, which all expect science and risk-based approaches
  - This demonstrates the **foundational relevance of QRM**

# Topic 2: Product Availability Risks

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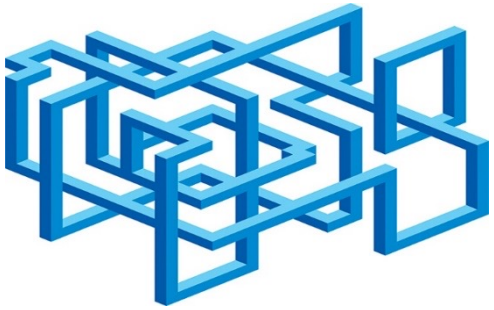
ICH Q9 is not a supply chain guideline, but quality/manufacturing issues that impact product availability can present risks to patients, and managing these risks is important.

- ICH Q9 already addresses product availability risks, as its definition of harm includes damage *'from a loss of product availability'*.
- Addressing such risks across the lifecycle is important, given the extent of globalization of medicines supply chains, their complexity and fragmentation (high number of actors)



- An increased emphasis in ICH Q9 on managing product availability risks related to manufacturing problems/issues, and on risk-based drug shortage prevention and mitigations, will serve the interests of patients.

# Topic 3: Formality in QRM

ICH Q9 states: *"The level of effort, formality and documentation of the quality risk management process should be commensurate with the level of risk."*

- But what does formality in QRM actually mean?
- A lack of understanding of this has led to confusion and uncertainty in the industry and among regulators
- The revised version of Q9 seeks to clarify what formality in QRM means
- It discusses degrees of 'formality' and the factors that might be considered when determining how much formality to apply to a given QRM activity
- It also emphasises how there is flexibility in how much formality may be applied in relation to QRM activities

# Formality in QRM cont'd

- Additional clarity on formality may help ensure that **the extent of scientific and methodological rigour** applied during QRM is commensurate with the level of risk
- It may also lead to resources for QRM being used more efficiently
  - *where lower risk issues are dealt with more efficiently via less formal means*
  - *freeing up resources for managing higher risk issues and more complex problems, which usually require increased levels of rigour and effort. (Sometimes on inspection we see that high-risk or highly complex change controls & deviations are not risk assessed well.)*

- A greater understanding of formality in QRM has the potential to lead to improved outcomes in terms of pharmaceutical quality, medicines availability, and patient protection.

# Topic 4: Risk Based Decision Making

- This doesn't just apply to the industry….
- The Covid-19 pandemic illustrated the importance of effective risk-based decision making by regulators in a myriad of areas – e.g. in the assessment and approval of conditional marketing authorisations, in inspection strategies, in granting GMP regulatory flexibilities, etc.

# Topic 4: Risk Based Decision Making

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While ICH Q9 refers to decision-making, there was a lack of clarity on what good risk-based decision-making is, how it might be achieved, and how QRM may improve decision-making generally

- While there was a breadth of peer-reviewed research in this area, the uptake of that research within the pharmaceutical industry may be improved.
- There have been many formal initiatives undertaken by other industries (e.g. nuclear power, aeronautics, the US Coast Guard) to clearly define and develop risk-based decision-making processes and guidance.
- The Q9 revision seeks to provide clarity in this area and addresses the expected benefits of investing in risk-based decision-making activities.
- This may facilitate access to new medicines for patients, especially for fast-tracked applications, which require robust risk-based decision making.

# Topic 5: Risk Review

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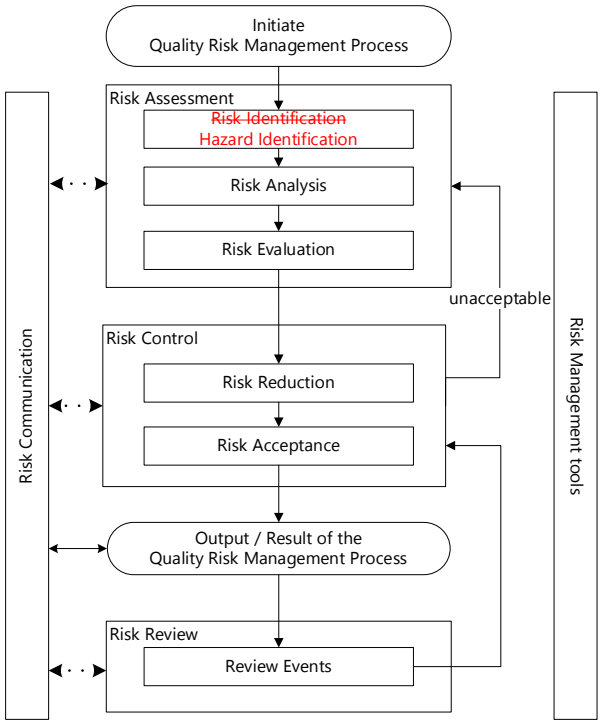
The Q9 revision will provide additional clarity on the expectations relating to keeping risk assessments current and on the implementation of risk reviews

- This area is being addressed by developing training materials on this topic
- These will take lifecycle manufacturing performance and quality feedback into account, with the aim of having supply resilience and reliability
- Risk Review ties in with the concept of continuous improvement as expressed in ICH Q10 and in the lifecycle management guidelines (ICH Q12/Q14)

# Topic 6: Hazard Identification

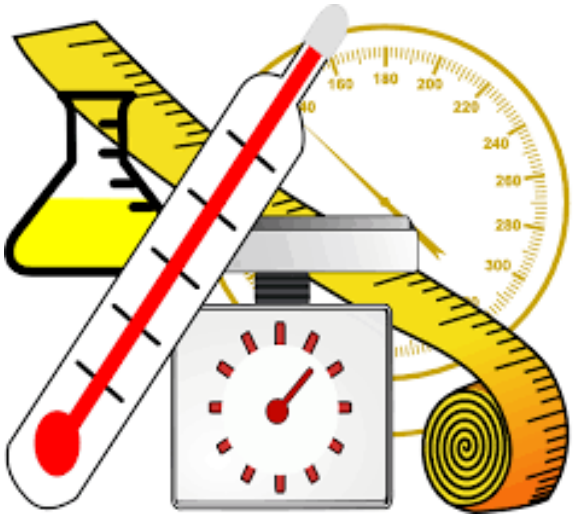



The term 'Risk Identification' has been changed in the revised guideline to 'Hazard Identification'

- This was done to better reflect the guidance in ICH Q9 on Risk Assessment…
  - *"Risk assessment consists of the **identification of hazards** and the analysis and evaluation of risks associated with exposure to those hazards…"*
- The figure in ICH Q9 depicting the QRM process was also changed, to replace Risk Identification with Hazard Identification.

This change aligns with the expectation to identify hazards relevant to patients when evaluating risks, and it may improve how hazards are perceived and assessed.

# The Q9 revision focused on the application of Good Science in the management of risk



Scientific approaches to QRM were stressed in the ICH Concept Paper for the revision work

- *"Experience from the recent quality defects (e.g. nitrosamines…`)* illustrates the need for **a more scientific approach** by manufacturers to risk assessment and QRM activities…
- "A revised ICH Q9 … could lead to more effective and **science–based control strategies**…, improving manufacturing consistency, lowering costs and reducing the likelihood of quality defects, recalls, and medicine shortages."

# New Technologies & Innovation were also an area of focus in the ICH Q9 revision

The ICH Concept Paper indicated that the revision may support *Digitalisation and Emerging Technologies* (e.g., new manufacturing technologies, automation, and use of big data, PAT)

- *e.g. "As digitalisation is implemented into manufacturing facilities, the application of QRM to the design and validation of production processes, … may become increasingly important."*

With regard to **implementation** of the revised guideline…

*Here are some personal thoughts and points for consideration… they should not be taken to represent the views of the ICH Q9(R1) EWG or any ICH party*

# 1. Guidance Applicability

It is important to remember that the revisions made to the guideline are relevant for **both** the industry and its regulators

- Both parties can make use of the new guidance in their day-to-day work when seeking to apply QRM principles
- But while all six revision topics are highly relevant to regulators, the guidance on ***Product Availability Risks*** is somewhat different from the guidance in the other five areas:
  - *This guidance addresses quality/manufacturing issues that may give rise to product availability risks*
  - *It is primarily the manufacturing sites that would control such risks – and not only by addressing those quality/manufacturing issues, but also by ensuring that an effective Pharmaceutical Quality System is in place, and by undertaking drug shortage prevention and mitigation activities, when these may be important and needed*

# 2. Making use of the official ICH training materials

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Official ICH training materials are being developed on all six revision topics, to support the changes to the guideline. These materials will soon be completed and published.

**These materials are designed to help with implementation of the new guidance in ICH Q9(R1), emphasising the 'how'.**

**Any party that is working to implement the revised guideline should make full use of those training materials.**

# 3. There is a lot in the revision and in the accompanying training materials

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There is substantial new guidance in ICH Q9(R1), and the training materials are also quite extensive – so where might one start?

- When thinking about this, it is useful to recognize that three of the revision topics may be quite **new** for some companies and regulators – e.g. Subjectivity in QRM, Product Availability Risks, Formality in QRM
  - So, focusing on some **basic learning** before a deep-dive into the implementation work starts may be useful
- In some organisations, a number of the topics may have received **little direct attention** to date, e.g., Risk-based Decision-making and Risk Review, even though all organisations probably undertake those activities
- There are also certain **interdependencies between the topics** that can help inform implementation strategies:
  - e.g., can an organisation do effective Risk-based Decision-making if its risk assessments are highly subjective?

# 4. There are many ways one could go about implementing the new guidance

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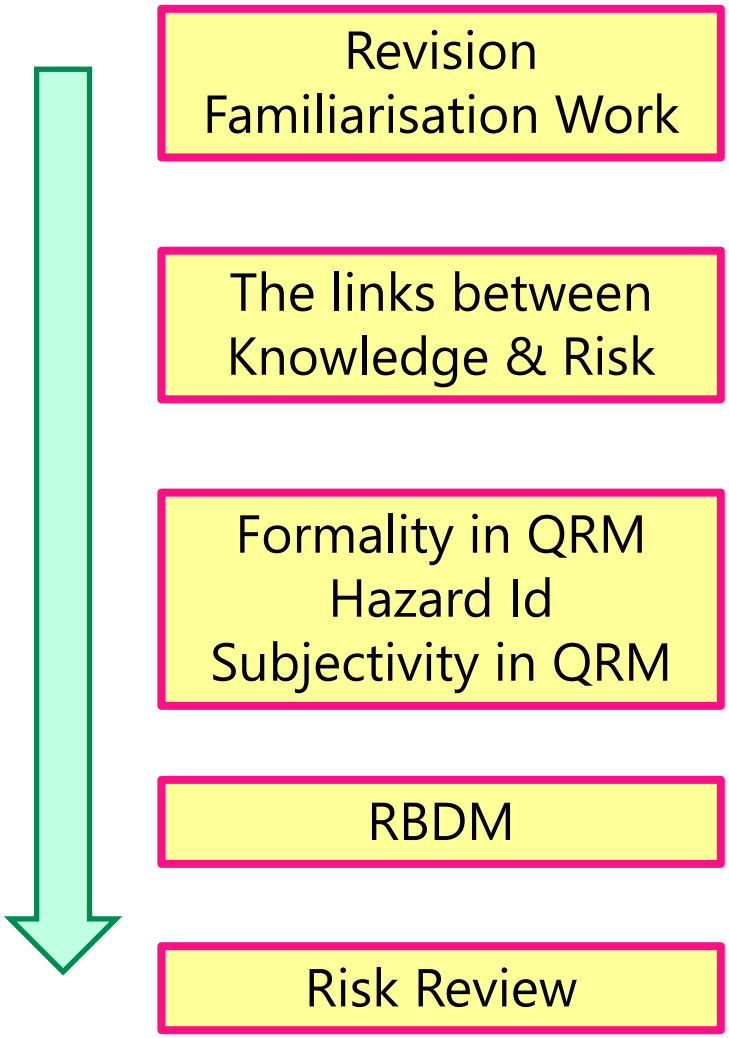
***This is one potential way to tackle the implementation of the new guidance in ICH Q9(R1)***



# 4. Potential implementation approach, cont'd

In my own group at the HPRA (*Market Compliance*), the approach we are taking to implement the new guidance is the following:

- Following familiarisation work on the guideline revisions as a whole, we will focus on how the guideline links **knowledge** and **risk**, and on what this means a) in our day-to-day work and b) in our planning and strategic work.
- Then, focusing on the following **three revision topics**, we will work to develop increased competencies in each of those areas:
  - ***Formality in QRM***
  - ***Hazard Identification***
  - ***Subjectivity in QRM***

For these three areas, we will seek to make improvements in our risk assessment and QRM processes

**Note: Our work on these three areas will be done *in parallel*, not sequentially.**

# 4. Potential implementation approach, cont'd

Then, when implementation of the guidance in the above three areas is well advanced, we will start to focus on **RBDM** and, after that, **Risk Review**

- Much work has already been done in relation to **RBDM** over many years within the Market Compliance section and at the HPRA in general, but advancements will be sought by leveraging off the preceding work on **Formality** in QRM, **Subjectivity** in QRM & **Hazard** Identification.
  - e.g., being able to consider the levels of **uncertainty, importance and complexity** that exist when deciding how much formality to apply to a given QRM activity will help apply the guidance in ICH Q9(R1) on **RBDM**, e.g. in relation to **recall decision making** for Quality Defect issues
  - e.g., reduced **subjectivity** in the **product and company risk assessments** that we perform should support **decision making** in our Sampling & Analysis and inspection programmes – in relation to what to spend our available surveillance and inspection resources on

# 4. Potential implementation approach, cont'd

What about the guidance in ICH Q9(R1) on **Product Availability Risks**?

- The nature of this guidance is such that it can be usefully applied across **several different areas of work** at HPRA
- e.g. **GMP Inspection** – the three factors outlined in the guideline are all areas of focus for GMP inspections:
  - *Manufacturing Process Variability and State of Control*
  - *Manufacturing Facilities and Equipment*
  - *Oversight of Outsourced Activities and Suppliers*
- e.g. **Recall decision making** arising from quality defect investigations and serious GMP non-compliances
- The HPRA has a dedicated **Medicines Shortages group**, and its input into applying the guidance, e.g., in relation to risk-based drug shortage prevention and mitigation activities, will be very important

# Why this suggested order?

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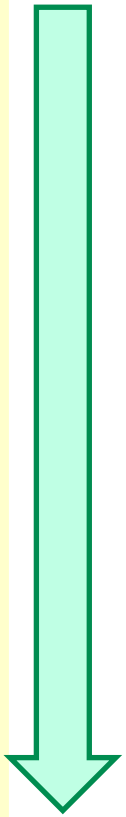
Working on Formality, Hazard Id and Subjectivity before starting to implement the guidance on **RBDM** appears to be a useful approach:

- Effective RBDM relies to a large extent on having applied the right degree of formality to Risk assessments and the QRM process
  - Important decisions about highly complex issues require a commensurate level of formality in risk assessments and in the QRM process
- Effective RBDM cannot be achieved if important hazards have been overlooked or if the wrong hazards were focussed on
- The quality of our decisions during RBDM can be impacted by high levels of subjectivity

Then, focussing on **Risk Review** after RBDM ties in with the fact that Risk Review involves a review of earlier risk-based decisions (among other things)



Revision Familiarisation Work

The links between Knowledge & Risk

Formality in QRM
Hazard Id
Subjectivity in QRM

RBDM

Risk Review

The preceding slides present a few **personal thoughts** about a potential implementation approach for the new guidance in ICH Q9(R1)

- The topics of concern in the revision are challenging – none is easy!
- Further consultation with colleagues is needed, but our work has started
- ICH Q9(R1) is a guideline of **foundational relevance**, and its implementation will benefit from teamwork and multi-disciplinary thinking

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***Thank you for your attention.***