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15 March 2022

Quality Working Party
Committee for Medicinal Products for Human Use
European Medicines Agency
PO Box 71010
1008 BA Amsterdam
The Netherlands

Reference: ICH draft guideline Quality Risk Management Q9 (R1) on quality risk management Step 2b EMA/CHMP/ICH/24235/2006

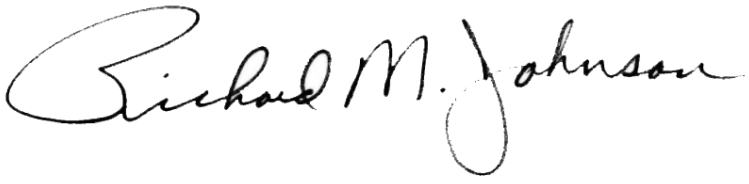
Dear Madam or Sir,

PDA appreciated the opportunity to comment on the draft guideline on Quality Risk Management Q9 (R1), EMA/CHMP/ICH/24235/2006. We present our comments in the attached table. We would like to note that there are numerous definitions, that were in the original ICH Q9, that appear to be omitted from ICH Q9 draft Section 7.0 Definitions. We were unsure if this omission was made intentionally or in error.

PDA is a non-profit international professional association of more than 10,000 individual members scientists having an interest in fields of pharmaceutical, biological, device manufacturing, and quality. Our comments have been prepared by a committee of PDA members with expertise in the areas covered in this draft guidance on behalf of PDA's Regulatory Affairs and Quality Advisory Board and Board of Directors.

If you have any questions, please do not hesitate to contact me via email at johnson@pda.org.

Sincerely,



Richard Johnson
President and CEO

cc. Glenn Wright, PDA; Carrie Horton, PDA; Falk Klar, PDA

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An agency of the European Union

15 March 2022

Submission of comments on ICH draft guideline Quality Risk Management Q9 (R1) on quality risk management Step 2b EMA/CHMP/ICH/24235/2006

Please note that these comments and the identity of the sender will be published unless a specific justified objection is received.
When completed, this form should be sent to the European Medicines Agency electronically, in Excel format (not PDF), to the following address:
ICH@ema.europa.eu
For more details on how to use this template please refer to the tab "Manual for commenter".

Name of organisation or individual*	Line from * (line Nr or 0 for general comment)	Line to* (line Nr or 0 for general comment)	Section number	Comment and rationale (to go to next line within the same cell use Alt + Enter)	Proposed changes / recommendation (if applicable - to be used if you want to propose specific text changes)
Parenteral Drug Association	7	8	1	PDA proposes that the concept of the ICH Q10 enabler be expanded upon. While it is true that QRM is a "valuable component" of a PQS, consider using the language from ICH Q10 – "enabler". **Current text**: "The importance of quality systems has been recognized in the pharmaceutical industry and it is evident that quality risk management is a valuable component of an effective quality system."	**Proposed change**: "... and it is evident that quality risk management is a valuable component of an effective quality system **by enabling better, more informed decisions.**"
Parenteral Drug Association	14	14	1	PDA proposes including "bias" in conjunction with subjectivity as a factor that can impact the risk assessment. **Current text**: "In addition, subjectivity can directly impact the effectiveness of risk management activities and the decisions made."	**Proposed change**: "In addition, subjectivity, **as well as unintentional bias,** can directly**..."**
Parenteral Drug Association	17	18	1	PDA proposes that in line 18 where "risk to quality" is referenced that ICH consider adding safety and effectiveness to broaden the concept and also align with line 25, "safe and effective" **Current text**: "...practitioners as well as government and industry, the protection of the patient by managing the risk to quality and availability, when availability risks arise from quality/manufacturing issues, should be considered of prime importance."	**Proposed change**: "... managing the risk **to safety, effectiveness,** quality, and availability..."

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Parenteral Drug Association	30	31	1	PDA proposes adding clarity to the "quality problems" by expanding upon the concept. **Current text**: "Additionally, the use of quality risk management can improve the decision making if a quality problem arises."	**Proposed change**: "...can improve the decision making process if quality problem arrise, **harm is incurred or product quality is impacted**..."
Parenteral Drug Association	34	35	1	There is a potential to bias this process as a thought exercise that excludes, unintentionally, existing data and other objective evidence that can better and more robustly inform all phases of the QRM process. **Current text**: "In this context, knowledge is used to make informed risk-based decisions,..."	**Proposed change**: "In this context, **scientific knowledge and objective evidence are** used to make informed risk-based decisions,..."
Parenteral Drug Association	37	39	1	It is not only regulators who want to effectively deal with potential risks and avert problems, but company leadership as well. Consider expanding the interested parties here. **Current text**: "This can provide regulators with greater assurance of a company's ability to deal with potential risks and avert problems."	**Proposed change**: "This can provide **both an organization's leadership and** regulators greater assurance of the organization's capabilities to effectively manage potential risks and averts problems."
Parenteral Drug Association	44	45	1	PDA proposes considering replacing "for" with wording that is more results-focused. **Current text**: "The purpose of this document is to offer a systematic approach to quality risk management for better, more informed, and timely decisions."	**Proposed change**: "...approach to quality risk management **that results in** better, more informed, and timely decisions."
Parenteral Drug Association	53	53		PDA suggests considering including a definition of "formality" in this document.	**Proposed definition: "Formality: The relative amount of detail, rigor, integration with other quality system elements, documentation, and level of adherence to methods, protocols, and accepted practices used when making risk-based decisions. Formality is a range or spectrum that could go from a simple risk-based rationale used to identify critical components (low level of formality) to the use of a risk check sheet in selecting a vendor (medium level of formality) to a highly detailed failure modes effect analysis for an end-to-end process risk assessment (high level of formality)."**

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Parenteral Drug Association	60	64	1	PDA proposes wording that contrasts with the undesirable "justify"; quality risk management is really meant to use a variety of tools and methods to investigate an issue to determine if it is a significant impact (positive or negative). **Current text**: "Quality risk management should not be used in a manner where decisions are made that justify a practice that would otherwise, in accordance with official guidance and/or regulations, be deemed unacceptable."	**Proposed change**: "Quality risk management should not be used in a manner where decisions are made that justify a practice that would otherwise, in accordance, with official guidance and/or regulations, be deemed unacceptable. **Instead, Quality risk management should be used to examine, study, and evaluate a potential unwanted event using available information to determine the best path forward."**
Parenteral Drug Association	67	72	2	PDA proposes adding the following to the scope section, as an addition to the overall ICH-Q9 R1 guidelines would include impacted product availability as potential harm. **Current text**: "This guideline provides principles and examples of tools for quality risk management that can be applied to different aspects of pharmaceutical quality."	**Proposed change**: "This guideline provides principles and examples of tools for quality risk management that can be applied to different aspects of pharmaceutical quality**, including ones that could potentially impact product availability.**"
Parenteral Drug Association	83	84	4	The current text is missing language regarding driving decision-making using the principles mentioned. Note: Output of the quality risk management should inform the decision-making process. **Current text**: "Quality risk management is a systematic process for the assessment, control, communication and review of risks to the quality of the drug (medicinal) product across the product lifecycle."	**Proposed change**: "Quality risk management is a systematic process for the assessment, control, communication, and review of risks to the quality **and availability** of the drug (medicinal) product across the product lifecycle. **The output of quality risk management program informs the organization's decision-making process."**
Parenteral Drug Association	108	109	4.1	PDA proposes there are additional sources of system-based subjectivity beyond risk scoring that can be captured in this sentence. **Current text**: "Subjectivity can also be introduced through the use of tools with poorly designed risk scoring scales."	**Proposed change**: "Subjectivity can also be introduced through inadequately defined risk questions and/or scope, use of unsuitable tools and/or scoring scales, and not recognizing limitations in data and scientific knowledge."
Parenteral Drug Association	110	110	4.1	Bias is one area where this can be controlled; the other is heuristics. **Current text**: "While subjectivity cannot be completely eliminated from quality risk management activities, it may be controlled by addressing bias..."	**Proposed change**: "While subjectivity cannot be completely eliminated from quality risk management activities, it may be controlled by addressing bias **and heuristics**..."

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Parenteral Drug Association	113	114	4.1	PDA proposes rewording to allow companies flexibility in their approach to managing subjectivity. The new text is a very open statement and could be interpreted that all risk assessment participants should be trained on subjectivity. This can lead to unnecessary practical and logistical constraints. **Current text**: "All participants involved with quality risk management activities should acknowledge, anticipate, and address the potential for subjectivity."	**Proposed change**: "**Mechanisms should be put in place to recognize and manage subjectivity during the quality risk management process**."
Parenteral Drug Association	158	161	7	The proposed change in text would align both the references to uncertainty under one unifying definition. PDA proposes the expanded explanation of uncertainty detailed in Line 158 be added to the definitions section 7.0 for clarity that all types of uncertainty be considered. This is more expansive than the statement in Line 258, "The term uncertainty in quality risk management means a lack of knowledge about risk." The additional underlined and bolded text is adapted from section 4.1 UNCERTAINTY of ISO 31010:2019 Risk Management: Risk Assessment Techniques. **Current text**: "Uncertainty is due to a combination of incomplete knowledge about a process and its expected variability. Typical sources include gaps in knowledge gaps in pharmaceutical science and process understanding, sources of harm (e.g., failure modes of a process, sources of variability), probability of detection of problems."	**Proposed change:** "Uncertainty is due to a combination of incomplete knowledge about a process and its expected variability, or **other forms of uncertainty, including decision uncertainty i.e. uncertainty associated with value systems, professional judgment, company values, and stakeholder expectations.** Typical sources include gaps in knowledge, gaps in pharmaceutical science and process understanding, sources of harm (e.g., failure modes of a process, sources of variability), probability of detection of problems, **and lack of adequate control of subjectivity in quality risk management and Risk-Based Decision Making.**"
Parenteral Drug Association	266	268		PDA proposes adding further clarity as to what factors may drive the level of importance within a quality risk management activity. Recommending adding further detail as to what would be expected to drive the level of importance across a continuum as lines 274-275 outline the expectation that "...the overall approach for determining how much formality to apply during quality risk management activities should be described within the quality system." **Current text**: "Importance: The more important a risk-based decision is, the higher level of formality that should be applied, and the greater the need to reduce the level of uncertainty associated with it."	**Proposed change:** "Importance: The more important a risk-based decision is **(e.g. risk to patient health and safety)** the higher the level of formality that should be applied, and the greater the need to reduce the level of uncertainty associated with it."
Parenteral Drug Association	301	303	5.2	PDA recommends the inclusion of the concept of **risk-informed decision making** in addition to **risk-based decision making** as risk-based decision making focuses primarily on making decisions using the outputs of the QRM process (which is not always sufficient), while risk-informed decision making allows for consideration of other factors in addition to the outputs of the QRM process.	
Parenteral Drug Association	279	279		PDA proposes removing "justification" and providing the types of evidence that will support the justification. **Current text**: "...supported by data or by an appropriate justification or rationale."	**Proposed change**: "...supported by data or by **a documented rationale.**"

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Parenteral Drug Association	337	337	0	"Rule-Based Decision Making" is a new concept being introduced and should enable the industry to align to the ideas presented, in a consistent fashion, if there is additional clarity around this concept.	**Proposed change**: PDA proposes that ICH expand upon this concept in the text and/or provide a definition.
Parenteral Drug Association	405	406	6	PDA suggests including testing in this sentence. **Current text**: "A robust facility infrastructure can facilitate reliable supply; it includes suitable equipment and well-designed facilities for manufacturing and packaging."	**Proposed change**: "A robust facility infrastructure can facilitate reliable supply; it includes suitable equipment and well-designed facility for manufacturing, **testing,** and packaging."

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Parenteral Drug Association	413	418	6	Referenced ICH Q10 Section 2.7 describes responsibilities for outsourced activities. In current ICHQ9 Revision draft lines, 416-418 the reference to this section is in the context of "when substantial variability is identified and safety of supplied materials or in the services provided...". Believe the intent is not to state responsibilities listed in ICHQ10 in section 2.7 are only needed under these conditions but can be misunderstood as such. Please see the proposed change. **Current text: "**Oversight of outsourced Activities and Suppliers: Quality system governance includes assuring the acceptability of supply chain partners over the product lifecycle. Approval and oversight of outsourced activities and material suppliers is informed by risk assessments, effective knowledge management, and an effective monitoring strategy for supply chain partner performance. A successful manufacturing partnership is strengthened by appropriate communication and collaboration mechanisms. When substantial variability is identified and safety of supplied materials or in the services provided, enhanced review and monitoring activities are justified (See Section 2.7 of ICH Q10). In some cases, it may be necessary to identify a new supply chain entity (e.g. a pre-qualified backup option) to perform a function." ICH Q10 2.7 Management of Outsourced Activities and Purchased Materials The pharmaceutical quality system, including the management responsibilities described in this section, extends to the control and review of any outsourced activities and quality of purchased materials. The pharmaceutical company is ultimately responsible to ensure processes are in place to assure the control of outsourced activities and quality of purchased materials. These processes should incorporate quality risk management and include: (a) Assessing prior to outsourcing operations or selecting material suppliers, the suitability and competence of the other party to carry out the activity or provide the material using a defined supply chain (e.g., audits, material evaluations, qualification); (b) Defining the responsibilities and communication processes for quality-related activities of the involved parties. For outsourced activities, this should be included in a written agreement between the contract giver and contract acceptor; (c) Monitoring and review of the performance of the contract acceptor or the quality of the material from the provider, and the identification and implementation of any needed improvements; (d) Monitoring incoming ingredients and materials to ensure they are from approved sources using the agreed supply chain	**Proposed change**: "Oversight of Outsourced Activities and Suppliers: Quality system governance includes assuring the acceptability of supply chain partners over the product lifecycle. Approval and oversight of outsourced activities and material suppliers is informed by risk assessments, effective knowledge management, and an effective monitoring strategy for supply chain partner performance. A successful manufacturing partnership is strengthened by appropriate communication and collaboration mechanisms **(See Section 2.7 of ICH Q10)**. When substantial variability is identified **in safety of** supplied materials or in the services provided, enhanced review and monitoring activities **are warranted given increases in uncertainty, complexity, and importance.** In some cases, it may be necessary to identify a new supply chain entity (e.g. a pre-qualified backup option) to perform a function."

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Parenteral Drug Association	415	420	6	PDA proposes adding wording on also contemplating "pharmaceutical distribution practices" in the section addressing the product availability risks, as issues and risks related to Good Distribution Practices and third-party logistics oversight might pose an equally significant risk on product quality and availability.	**Proposed changes**: Line 415: "A successful manufacturing **and distribution** partnerships are strengthened by appropriate communication and collaboration mechanisms." After Line 420 add: " **An effective pharmaceutical quality system enables supply chain robustness and considers sustainable GDP compliance to ensure product quality and availability. Risks to product distribution can be reduced by applying risk-based decision making and QRM practices across the entire supply chain, inclusive of quality oversight and monitoring of logistics suppliers, warehousing, cold chain management, and theft and counterfeiting deterrents, ensuring a controlled state of materials and product."**
Parenteral Drug Association	422	475	7	PDA suggests adding these definitions to add clarity to the quality risk management process. It was noted that there are a number of definitions, that were in the original ICH Q9, omitted from section 7.0 DEFINITIONS.	**Proposed change**: Include the following definitions from the original text - **Risk Management, Risk Reduction, Risk Review, Severity, Stakeholder**, and **Trend Justification.**
Parenteral Drug Association	422	423	7	PDA suggests considering including a definition of "bias" in this document.	**Proposed definition: "Bias: an intentional or unintentional preference for or against a particular concept, item, or person."**
Parenteral Drug Association	422	435	7	PDA suggests considering including a definition of "heuristics" in this document.	**Proposed definition:** "**Heuristic: a mental shortcut that allows an individual to make a decision, pass judgment, or solve a problem quickly and with minimal mental effort.**"

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Parenteral Drug Association	456	475	7	The revision should encourage alignment with the language of the ISO Risk Management Standards, where possible, thereby enabling companies to align with the risk management systems of platform technology providers and other business partners. Examples: - The proposed definition of Uncertainty is not consistent with ISO Guide 73.:2009 Risk Management Vocabulary - The glossary of ICH Q9 (R1) refers to definitions in ISO Guide 73 that have since been updated (e.g., Risk Acceptance in the ICH Q9 (R1) "the decision to accept risk", definiton in ISO "informed decision to take a particular risk") - there are definitions in Guide 73 that are not used in ICH Q9 (R1), but would be useful e.g. Risk Review	
Parenteral Drug Association	456	475	7	The opportunity of a revision should encourage alignment with the language of the ISO Risk Management Standards, thereby enabling companies to align with the risk management systems of platform technology providers and other business partners. PDA recommends the ISO definition of risk communication.	**Proposed definition:** "Risk Communication: Continual and Iterative process that an organization conducts to provide, share or obtain information and to engage in dialogue with stakeholders regarding the management of risk (ISO Guide 73)." (Definition from ISO Guide 73:2009)
Parenteral Drug Association	456	475	7	The opportunity of a revision should encourage alignment with the language of the ISO Risk Management Standards, thereby enabling companies to align with the risk management systems of platform technology providers and other business partners. PDA proposes a definition for knowledge alinged with ISO.	**Proposed definition:** "Knowledge: Knowledge is a collection of information and a justified belief that this information is true with a high level of certainty (ISO 9001:2015); knowledge is usually actionable, action can be taken based on the knowledge."
Parenteral Drug Association	844	845	II.9	PDA suggests adding testing to this sentence. **Current text**: "To ensure that facility infrastructure and equipment are suitable and well-designed for manufacturing and packaging;"	**Proposed change**: "To ensure that facility infrastructure and equipment are suitable and well-designed for manufacturing, **testing,** and packaging;"