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An agency of the European Union

1 March 2022

Submission of comments on ICH Q9 – R1 Draft – Quality Risk Management (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
All the cells with an asterisk (*) should be filled in prior to completing the columns "Comment and rationale" and/or "Proposed changes / recommendation".
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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)
ECA Foundation / European QP Association	0	0	General	The promotion of a science-based approach to risk management relying on knowledge management according to Q10 is really appreciated. - Such an approach requires objective risk assessment.	
ECA Foundation / European QP Association	0	0	General	The terminology change "hazard identification" replacing "risk identification" is appreciated and it is even considered being an improvement.	
ECA Foundation / European QP Association	0	0	General	The scope extension to the supply chain and widely considering the "operational capability" of the organisation/company is seen as an important topic that should allow for better consideration of this criteria in other regulatory documents, e.g. EU / PIC/S GMP Annex 11. This scope extension shall be the trigger by regulated user organisation to apply a holistic approach to Quality Risk Management, covering all relevant aspects impacting *appropriate and continued supplies of that medicinal product* , see European Directive 2001/83/EC, Article 81 (excerpt): *… The holder of a marketing authorisation for a medicinal product and the distributors of the said medicinal product actually placed on the market in a Member State shall, within the limits of their responsibilities, ensure appropriate and continued supplies of that medicinal product to pharmacies and persons authorised to supply medicinal products so that the needs of patients in the Member State in question are covered . …*	
ECA Foundation / European QP Association	0	0	General	Since it is mentioned at several places that decisions should be "objective" rather than "subjective", objectivity and subjectivity shall be introduced and explained at the beginning of the document. Such an addition would have the merit of clarifying the discussion on this point in the rest of the document.	
ECA Foundation / European QP Association	0	0	General	Recommendation for the supporting training material on Q9 >>>	Content proposal for the ICH training material on Q9: - Presentation of examples for "subjective" vs. "objective" decisions - Explanation of what science-based risk management effectively means: > Methodical, structured and rigorous approach > Available knowledge base to justify assessments and evaluation - Reminder that the enrichment of such a knowledge base benefits greatly from the results of the periodic evaluation activities (when these are properly and regularly carried out).

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ECA Foundation / European QP Association	0	0	General	Wording: this draft uses "formality" when "formalism" would be more appropriate regarding the necessary documentation effort of the risk management activities; see occurences at lines: #53, #56, #57, #79, #248, #251, #252, #253, #254, #256, #260, #266, #270, #274, #276, #277, #281, #289, #290, #299, #304, #320, #321, #322, #395, #522	Please replace "formality" with "formalism".
ECA Foundation / European QP Association	0	0	General	With the technological developments of the last 15 years leading to an increasing digitalisation of processes on the one hand, and the increasing regulatory focus on data integrity on the other, it is necessary that these topics are included in the overall scope of Quality Risk Management. Mentioning explicitly these topics would help to secure that the cross-functional teams performing QRM will be adequately populated with the corresponding SME.	
ECA Foundation / European QP Association	0	0	General	In the following remarks, IT and OT are mentioned; for clarity here are the corresponding definitions: - IT: Information Technology - OT: Operational Technology; i.e. IT for process automation, covering industrial control systems (manufacturing and facility) and laboratory equipment. See https://en.wikipedia.org/wiki/Operational_technology	
ECA Foundation / European QP Association	43	43	1	*… and computerized systems is important.* See comment at line #370	
ECA Foundation / European QP Association	98	98	4,1	It is crucial for securing the "objectivity" of the decisions that the risk management activities are carried out by an "interdisciplinary team". See comment at line #295	Quality risk management activities are usually~~, but not always,~~ undertaken by interdisciplinary teams.
ECA Foundation / European QP Association	251	251	5,1	See the above general remark about "formality" vs "formalism".	Please replace "formality" with "formalism" in the whole section 5.1 (incl. headings).
ECA Foundation / European QP Association	288	289	5,1	See the above general remark about "formality" vs "formalism".	Use of a trained quality risk management facilitator may be integral to a higher formal~~ity~~ process.
ECA Foundation / European QP Association	295	295	5,1	See comment at line #98	~~A cross functional team might not be necessary.~~
ECA Foundation / European QP Association	303	305	5,2	*Effective risk-based decision making begins with determining the level of effort, formality and documentation that should be applied during the quality risk management process.* The statement is not correct. "*Effective risk-based decision making* " is the result (the consequence) of the risk management effort.	Effective risk-based decision making ~~begins with determining the level of effort, formality and documentation that should be applied during the quality risk management process~~ is the result of the level of effort, formalism and documentation that are applied during the quality risk management process.
ECA Foundation / European QP Association	305	308	5,2	Wording: in the particular context "outcome" would be more appropriate than "output".	The outcomes of quality risk management activities include decisions in relation to what hazards exist, the risks associated with those hazards, the risk controls required, the acceptability of the residual risk after risk controls, the communication and review of quality risk management activities and outcomes.
ECA Foundation / European QP Association	376	376	6	Since "distribution" is explicitly mentioned in the document scope (section 2, line #69), the item at line #376 shall be improved accordingly.	Supply Chain Control, including distribution

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ECA Foundation / European QP Association	370	376	6	Since "*digitalization and emerging technologies*" are explicitly mentioned in the document introduction (section 1, line #40), within the scope of Quality Risk Management, IT and OT infrastructure robustness as well as cybersecurity shall be considered as well. Today, a weak IT/OT infrastructure can highly jeopardize the manufacturing, QC, and supply chain processes as well as the overall business capability of the regulated organisation. The experience showed already the vital impact such IT/OT infrastructure and computerized systems can have on the operational capability of a pharmaceutical company (see NotPetya ransomware case, June 2017, at MSD, Reckitt Benckiser, Beiersdorf, ...). Likewise, IT/OT robustness as well as cybersecurity shall be added in Annex II section 4 (see comment at lines #769-777) since these topics represent the Achilles' heel of every regulated user organisation.	Examples for industry operations and activities (see Annex II): • Development; • Facility, equipment and utilities, including automation; • Materials management; • Production; • Laboratory control and stability testing; • Packaging and labeling; • Supply Chain Control, including distribution; • Supporting IT & OT infrastructures and applications.
ECA Foundation / European QP Association	405	410	6	Based on the comment related to lines 370-376, the possible weaknesses and vulnerability of supporting process control systems and applications shall be explicitly mentioned. Alternatively, this topic could be addressed in a dedicated section, since similar recommendations are necessary for the other processes, such as laboratory processes, supply chain, quality management.	A robust facility infrastructure (including the supporting process control and monitoring systems) can facilitate reliable supply; it includes suitable equipment and well-designed facilities for manufacturing and packaging. Robustness can be affected by multiple factors, such as an aging facility (including software aging such as out-of-support or poorly supported software), insufficient maintenance or an operational design that is vulnerable to human error. Risks to supply can be reduced by addressing these factors, as well as through use of modern technology, such as digitalization, automation, isolation technology, amongst others. Nevertheless consideration must be given to the IT and OT infrastructures, systems, and applications enabling digitalization and automation, but being themselves subject to vulnerability and possibly representing weaknesses for the processes and jeopardizing the related electronic data.
ECA Foundation / European QP Association	412	420	6	Following the above comments regarding the necessity to take IT & OT robustness into account within the scope of Quality Risk Management, it is necessary to explicitly mention the data supporting or related to the outsourced activities. Such an improvement is perfectly aligned with the requirements stated in EU / PIC/S GMP Part I, Chapter 7 and in WHO TRS 996, Annex 5, Chapter 7. The regulated organisation must be aware that the integrity of the data related to the outsourced activities is a vital necessity. As such, these data - and implicitly the supporting IT and OT infrastructures at contractor side - must become part of the overall Quality Risk Management acitivities.	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 (Note: such collaboration and communication include the ability to secure and to review the data supporting or related to the outsourced activities). 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). 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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ECA Foundation / European QP Association	475	475	7	Some definitions provided in the previous version have been forgotten: - Risk Management - Risk Reduction - Risk Review - Severity - Stakeholder - Trend The suppresion of "Risk Identification" is correct, since it is replaced by "Hazard Identification".	**Risk Management:** The systematic application of quality management policies, procedures, and practices to the tasks of assessing, controlling, communicating and reviewing risk. **Risk Reduction:** Actions taken to lessen the probability of occurrence of harm and the severity of that harm. **Risk Review:** Review or monitoring of output/results of the risk management process considering (if appropriate) new knowledge and experience about the risk. **Severity:** A measure of the possible consequences of a hazard. **Stakeholder:** Any individual, group or organization that can affect, be affected by, or perceive itself to be affected by a risk. Decision makers might also be stakeholders. For the purposes of this guideline, the primary stakeholders are the patient, healthcare professional, regulatory authority, and industry. **Trend:** A statistical term referring to the direction or rate of change of a variable(s).
ECA Foundation / European QP Association	684	684	Annex II.1	Following the above comments regarding the necessity to take IT & OT robustness into account within the scope of Quality Risk Management, it is necessary to explicitly mention this topic as one of the criteria to be considered by defining extent and frequency of audits resp. inspections.	... • Robustness of a company's quality risk management activities; • Digital maturity and robustness of the supporting IT & OT infrastructure and systems; ...
ECA Foundation / European QP Association	769	777	Annex II.4	The current text needs some refreshing for better reflecting the current field reality.	Computerised systems and computer controlled equipment To select the design of ~~computer hardware and software~~ computational resources and supporting IT/OT infrastructures (e.g., modular, structured, fault tolerance, (cyber)security measures); To determine the extent of validation, e.g., • identification of critical performance parameters; • selection of the requirements and design; • ~~code review;~~ • ~~the~~ extent of testing and test methods, such as: ◦ black box tests, white box tests, source code review; ◦ regression tests, integration tests; ◦ functional and performance tests; • ~~reliability~~ integrity (according to ALCOA+) of electronic records and signatures; • procedural controls.
ECA Foundation / European QP Association	786	787	Annex II.5	*To determine whether it is appropriate to use material under quarantine (e.g., for further internal processing);* Even if this statement was already provided in the current version, the formulation contradicts EU / PIC/S GMP Part I, Chapter 5.34: *Only starting materials which have been released by the Quality Control department and which are within their retest period should be used* .	To determine ~~whether it is appropriate to use material under quarantine~~ under which conditions material can be released for use (e.g., for further internal processing);
ECA Foundation / European QP Association	844	844	Annex II.9	Typo since "program" is spelled out differently in other sections.	To establish equipment and facility maintenance program~~me~~s that assure reliable facility and equipment performance;

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ECA Foundation / European QP Association	850	855	Annex II.9	It might be meaningful to move this section at line #834 (before the section "Manufacturing Process Variation and State of Control")	