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15 March 2022

Submission of comments on

ICH guideline Q9 (R1) on quality risk management Step 2b
EMA/CHMP/ICH/24235/2006

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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)	ICH Disposition
International Society for Pharmaceutical Engineering (ISPE)	0	0	General Comment	One of the stated objectives of ICH Q9 R1 is to expand on the concept of "formality" in Quality Risk Management. The Principles of Quality Risk Management (section 3) correctly states that "the level of effort, formality and documentation of the QRM process should be commensurate with the level of risk". Formality in Quality Risk Management (section 5.1) also correctly states that QRM is not binary (formal vs informal) but rather a continuum ranging from low to high. However, when the characteristics of risk assessments are described in lines 281 to 300, the impression of a binary system is given. High levels of formality are described as having a cross-functional team, use various QRM tools with all steps of the QRM process explicitly performed. By contrast the characteristics of lower formality are implied to always be imbedded and documented in other elements of the Quality System. ISPE considers that all Quality Risk Management exercises begin with the most informal of activities; that of asking a question. Questions are described in section 4.3 Risk Assessment as "What might go wrong?" Additional, "What is the likelihood that it will go wrong?" These questions may be asked by any colleague at any time whenever something is seen that is unusual or unexpected. It may be determined quickly (by trained personnel) that, in fact, nothing can go wrong, or it is extremely unlikely to go wrong, and the process or activities is allowed to continue. This most basic and informal type of Risk Assessment may not even be documented. However, it may alternatively be determined that something might go wrong and that a level of increased formality is appropriate. This may trigger the steps of a defined process within the Quality System or it may trigger the initiation of a significantly more formal QRM exercise.	ISPE believes that asking the initial fundamental 'risk question' is the foundation of all QRM activities, regardless of what level of formality is ultimately used. It is also believed that, depending on the initial answers, the process may end there with minimal or no documentation. It is recommended that language be added to section 5.1 "Formality in Quality Risk Management" to acknowledge the existence of this most informal type of QRM exercise and to set this scenario as the lower extreme of the QRM formality continuum. It is also recommended that the language is written describing what should occur in less formal risk management exercises and not what may not occur. Consideration should be given to adding to the steps that might be included in the Initiating Step (section 4.2): - identifying the level of formality to be applied - identifying decision makers and/or decision making process.	
International Society for Pharmaceutical Engineering (ISPE)	0	0	General Comment	The section on formality gives the impression that informal risk assessment are always covered by a QMS/PQS procedure. This is not always the case e.g. equipment selection against CPP's/CAs, preliminary risk management exercise applied in the early phases of risk assessment when comparing proposed process steps using, for example preliminary hazard analysis tool.	What ISPE would like developed is the essence of a risk culture that is proactive and the perceived risk could be positive or negative. We suggest adding guidance around a continuum of informal to formal risk assessment but not always tying this to a PQS element is key.	
International Society for Pharmaceutical Engineering (ISPE)	0	0	General Comment	The evaluation and use of new technologies including for example new equipment, facilities (pod, modular), modalities, processes, digitization and more use of advanced computerized systems are typically evaluated and implemented to improve efficiency, enhance analytical accuracy, reduce process variability, etc. As such, they are intended to reduce risk to the product i.e. patient, process and overall supply chain. ISPE agrees that the application of the QRM process is entirely appropriate when evaluating the use of various new technologies. However, the use of new technologies is given a somewhat negative connotation in the Introduction (section 1.) of the document. Specifically in lines 40-43, the use of new technologies is described as "presenting certain challenges". This is inconsistent with language in lines 404-410 and also Annex II lines 847-849 where new technologies are more appropriately described as valuable tools that can reduce risk.	It is recommended that the language throughout the document, but especially in lines 40-43, be aligned to describe the positive risk reducing attributes of new technologies.	
International Society for Pharmaceutical Engineering (ISPE)	0	0	General Comment	A Formal Quality Risk Management exercise forms the upper extreme of the formality continuum described in section 5.1 Formality in Quality Risk Management. ISPE believes that the fundamental elements of a successful Formal Quality Risk Management exercise include 1) A cross-functional team of experienced subject matter experts to reduce the level of subjectivity among the team, 2) The use of a well crafted problem statement (or risk question) which guides to team without bias and 3) A defined decision-making process or individual. While these elements are included in the current Q9 text, they are spread out in different sections and therefore lose a level of impact. For example, the problem statement is described in section 4.2. Elements of higher levels of formality are described in section 5.1. Decision Making has its own section in section 5.2.	It is recommended that section 5.1 "higher levels of formality" be retitled to "attributes of formal quality risk management". The subsequent text should be expanded to include references to the importance of the three elements described to the left. A summary of these suggestions should also be considered as part of the QRM Initiation steps in section 4.2.	
International Society for Pharmaceutical Engineering (ISPE)	0	0	General Comment	There are many terms that should now be included in the glossary or definitions.	**Add the following terms:** Complexity Risk based decision making Subjectivity	

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International Society for Pharmaceutical Engineering (ISPE)	0	0	General Comment	ICH Training package. ISPE strongly supports the use of new training material to exemplify the strengthened revision to ICH Q9.	We appreciate that this revision is a limited and focussed review and the training packages will be a supplement to the revision. **We feel the following examples of training are key:** Subjectivity Product Availability Formality Decision-making New Technology (Digital) New Drug Modality. More specific examples should include: -Equipment Selection -Process Development -Clinical launch facility -Process Risk assessment (PRA) -Contamination Control Strategy (CCS) -Informal RA associated with a PQS element -Informal RA associated with a non PQS element e.g. equipment comparability -Outline of a training package for RA facilitation. ISPE would propose a detailed review is completed of the existing ICH Q9 training package to ensure alignment with the focus and intent of the revision.	
International Society for Pharmaceutical Engineering (ISPE)	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 supports objective risk assessment.		
International Society for Pharmaceutical Engineering (ISPE)	0	0	General	The terminology change "hazard identification" replacing "risk identification" is appreciated and it is even considered being an improvement.		
International Society for Pharmaceutical Engineering (ISPE)	0	0	General	The scope extension to the supply chain, considering the "operational capability" of the organisation/company is seen as an important topic that should allow for better consideration of these in other regulatory documents, e.g. EU / PIC/S GMP Annex 11.	The scope extension to the supply chain, considering the "operational capability" of the organisation/company is seen as an important topic that should allow for better consideration of these in other regulatory documents, e.g. EU / PIC/S GMP Annex 11.	
International Society for Pharmaceutical Engineering (ISPE)	0	0	General	ISPE agrees that the topic of "subjectivity" is extremely important and, therefore, suggests that it is given even more importance by including a preliminary reference to its importance in the Introduction (e.g. moving some of the text in lines 103 to 107 to the Introduction) and creating a new, stand-alone section e.g. 5.2 "Reduction of subjectivity". This section could discuss steps to reduce subjectivity during risk assessment and, potentially separately, in decision-making.	The introduction should discuss briefly introduce the concept of each of the main topics of the revision - Subjectivity, formality, decision making, product availability. A separate section is recommended on "Reduction of Subjectivity", following "Formality" and before "Risk-based Decision Making". This section should describe steps to reduce subjectivity and increase objectivity during risk assessment and, separately, when taking decisions. **Examples could be:** - inclusion of appropriate range of expertise - level of experience of SMEs - availability and access to relevant knowledge - ability to place risk management outcomes into perspective with similar situations - use of trained, risk facilitators in the risk management process Use of training examples would be appropriate.	

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International Society for Pharmaceutical Engineering (ISPE)	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.	Appropriate wording relating to digitization should be added to the Scope in line 72.	
International Society for Pharmaceutical Engineering (ISPE)	0	0	General	ISPE recommends that the Introduction is restructured The first sentence does not add value- Risk management principles are effectively utilized in many areas of business and government including finance, insurance, occupational safety, public health, pharmacovigilance, and by agencies regulating these industries.	ISPE recommends that the Introduction is restructured to emphasise that QRM and hence ICH Q9 is a fundamental enabler to assure a quality product is available to the patient by: - using a science- and risk-based approach to product and process development as in ICH Q8 and Q11 - using Good Engineering Practices for pharmaceutical installations. - applying in the management of the product lifecycle as in ICH Q12 - applied to the PQS as in ICH Q10 - applied to product availability as in this revision We recommend that these concepts are stated clearly at the start of the Introduction perhaps instead of reference to application of risk management to other industries	
International Society for Pharmaceutical Engineering (ISPE)	0	0	General	Risk is used where maybe it should be harm to patient.	An example may be line 77 where "risk to quality" should be "harm to the patient" A related example could be to change "event" to "risk" or "hazards" in lines 210 and 211.	
International Society for Pharmaceutical Engineering (ISPE)	18	19		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. Risks also arise from different regulatory requirements between agencies as discussed in the article in Pharmaceutical Engineering - https://ispe.org/pharmaceutical-engineering/january-february-2022/toward-single-global-control-strategy-industry	A suggestions for improving this sentence is given below. The protection of the patient by managing the harm to patients and product availability is of prime importance. Availability risks arise from quality/manufacturing or supply chain issues or different of regulatory requirements between agencies.	
International Society for Pharmaceutical Engineering (ISPE)	62	64		QRM is an appropriate approach to justify a science or risk based alternative to a non-binding guideline, although it cannot be used to bypass regulations or laws. Consideration should be given to moving this sentence further up the document.	Many Guidelines and Regulations allow for alternative approaches where justified. In these cases, QRM may be used as a justification for these alternate approaches.	
International Society for Pharmaceutical Engineering (ISPE)	97	114		A well designed problem statement can mitigate subjectivity. Conversely, a poorly designed problem statement can inject subjectivity into the QRM process.	Add in text pertaining to the definition of the risk statement and details of the scope of the RA.	

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International Society for Pharmaceutical Engineering (ISPE)	103	107		As an addition to the General Comment on "subjectivity" above, there is not mention of sources of subjectivity [the main source: competing interests] and no ideas given regarding how to address bias and which preventive measures to consider. The sentences should be made more specific. Subjectivity does impact… Subjectivity is introduced… Subjectivity needs to be recognized, identified and called out when present - also keep in mind that in the real world risk decisions often assemble experts from appropriate areas - but the "D" for decision maker is best served with a single point of accountability - meaning that risk management by a consensus of large group of experts may be a poor process.	The potential sources of subjectivity should be defined here or in the Glossary. Clarification is required please around addressing bias. We propose stating: 'Bias may be minimised by ensuring representation from appropriate team members, a risk assessment facilitation process that promotes individual unbiased inputs and an ultimate decision maker that evaluates all key inputs and makes a final resolution'	
International Society for Pharmaceutical Engineering (ISPE)	130	130		Recommend that Initiation of the process involves identifying decision makers and stakeholders who should be informed.	Risk Communication is key to dissemination of the RA outputs, we recommend the risk initiation process should identify decision makers and stakeholders that should be informed.	
International Society for Pharmaceutical Engineering (ISPE)	179	179		Recommend deletion of "or eliminate". Elimination of risks is not compatible with statements in the Introduction (e.g. lines 20 and 21) that "The manufacturing and use of a drug (medicinal) product, including its components, necessarily entail some degree of risk."		
International Society for Pharmaceutical Engineering (ISPE)	258	265		Uncertainty = lack of knowledge of risk Uncertainty can be reduced by incorporating into the QRM team experts with right knowledge on the topic.	It is recommended that the section on Uncertainty should be shortened, with maybe bullets of what kind of uncertainty could occur in the different areas of QRM. Presence or level of uncertainty should be evaluated during the risk assessment process. Uncertainty is minimised by using expert team members. A suggested sentence is: "Uncertainty may be reduced by using an effective knowledge management system applied by expert team members"	
International Society for Pharmaceutical Engineering (ISPE)	260	260		QRM formality is recommended and not required.	change "require" to "should use"	
International Society for Pharmaceutical Engineering (ISPE)	266	268		"Importance" is very subjective and is hard to understand. Does level of importance relate to level of harm to the patient? Importance and uncertainty should not be linked. An important risk based decision does not necessary require more formality. It can be a very important decision, but very easy to determine.	It is recommended that the section on Importance is deleted.	
International Society for Pharmaceutical Engineering (ISPE)	271	271		QRM formality is recommended and not required.	Change "require" to "should use"	
International Society for Pharmaceutical Engineering (ISPE)	271	273	5	This language in this section is confusing and needs to be clarified. If uncertainty and complexity are issues, then uncertainty needs to reduced and issues relating to complexity need to be understood - this does not reduce the level of risk, it only makes the need for risk statement clearer, more concise and actionable.	*Suggested wording is:* In general, situations which have more complexity and uncertainty need more consideration of the risk statement, decision maker(s), team membership and risk management tools to be applied.	
International Society for Pharmaceutical Engineering (ISPE)	288	289	5.1	Use of a trained risk management facilitator - it is recommended that attributes of the facilitator role should be given in the text or better in the Glossary?	Suggested expansion in text is: It is recommended that the use of a trained quality risk management facilitator requires expertise in risk management/assessment training covering the RA preparation (risk statement drafting, key knowledge inputs, stakeholders required), RA process, RA review and RA Communication including managing project team interactions and probing for uncertainties).	
International Society for Pharmaceutical Engineering (ISPE)	290	300		Recommend if possible that the text in this section is phrased more positively.	For example, Lower levels of formality could be associated with decisions being taken and documented by a small group of decision makers who have a high degree of expertise.	
International Society for Pharmaceutical Engineering (ISPE)	290	298		Documentation of QRM activities in the quality system should be optional, and not required for some activities, such as those meriting lower levels of formality.	Line 292 - delete "of the quality system" Line 297-298 - delete "in the relevant parts of the quality system"	
International Society for Pharmaceutical Engineering (ISPE)	303	305		Risk Decision making needs to start with identifying the problem which you need to do before making effective risk-based decisions.	Line 303- Effective risk-based decision making begins with identifying the problem, then determining the level of effort ----	
International Society for Pharmaceutical Engineering (ISPE)	303	305		Within this sentence , subjectivity should be addressed	Line 304-include addressing subjectivity, formality and documentation. Please see General Comment regarding "subjectivity	

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International Society for Pharmaceutical Engineering (ISPE)	305	308	5	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.	
International Society for Pharmaceutical Engineering (ISPE)	316	317		Recommend deletion of sentence in lines 316 and 317. Data integrity is a GMP principle and need not be restated in this guidance.		
International Society for Pharmaceutical Engineering (ISPE)	349	351		Increase the weighting on science and evidence to support the extent and level of regulatory oversight , this very much supports ICH Q12 thinking using risk assessments on EC's to determine the reporting category i.e. risk assessment gives the evidence to a regulator reducing the extent of the regulatory burden.	Line 350- add ".. and more informed science- and risk-based decisions …" Line 351 add "...might affect the level and extent of regulatory oversight (burden) commensurate with the level of identified risk"	
International Society for Pharmaceutical Engineering (ISPE)	360	361	5	Delete the last sentence - it is repetitive.		
International Society for Pharmaceutical Engineering (ISPE)	370	376	6	Since "*digitalization and emerging technologies*" are explicitly mentioned in the document introduction (section 1, line #40), and are within the scope of Quality Risk Management, information technology (IT) and operational technology (OT) infrastructure robustness as well as cybersecurity should be considered. 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. Experience has shown 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, ...). Consequently, IT/OT robustness as well as cybersecurity should be added in Annex II section 4 (see comment at lines #769-777) since these topics represent a potential Achilles' heel of every regulated user organisation.	ISPE recommends adding the text highlighted below: 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 labelling; • Supply Chain Control, including distribution; • Supporting IT & OT infrastructures and applications.	
International Society for Pharmaceutical Engineering (ISPE)	376	376	6	Since "distribution" is explicitly mentioned in the document scope (section 2, line #69), the item at line #376 should be improved accordingly.	Supply Chain Control, including distribution.	
International Society for Pharmaceutical Engineering (ISPE)	396	420		It is recommended that the examples of factors that impact supply reliability are deleted for the following reasons: - the choice of examples may not reflect the main quality causes of supply unreliability - there are other identified approaches to improvement in supply reliability identified in the 2019 FDA Drug Shortages, Root Causes and Potential Solutions report such as implementation of ICH Q12 (in a globally harmonized manner) - including these factors may lead to increased regulatory expectations, which is contrary to text in lines 51 and 52 - there are comments on the text which show absence of consideration of use of robust IT systems - the level of detail is incompatible with an ICH guidance.		
International Society for Pharmaceutical Engineering (ISPE)	475	475	7	Some definitions provided in the previous version have been forgotten: - Risk Management - Risk Reduction - Risk Review - Severity - Stakeholder - Trend The omission 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).	
International Society for Pharmaceutical Engineering (ISPE)	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.	Suggest adding • Robustness of a company's quality risk management activities; • Digital maturity and robustness of the supporting IT & OT infrastructure and systems;	

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International Society for Pharmaceutical Engineering (ISPE)	769	777	Annex II.4	The current text needs some refreshing to better reflect the current reality.	**Computerised systems and computer controlled equipment:** To select the design of computational resources and supporting Information Technology /Operation Technology (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; •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; • integrity (according to ALCOA+) of electronic records and signatures; • procedural controls.	
International Society for Pharmaceutical Engineering (ISPE)	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 which material can be released for use (e.g., for further internal processing).	
International Society for Pharmaceutical Engineering (ISPE)	844	844	Annex II.9	Typo since "program" is spelled out differently in other sections.	To establish equipment and facility maintenance programs that assure reliable facility and equipment performance.	
International Society for Pharmaceutical Engineering (ISPE)	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")		
International Society for Pharmaceutical Engineering (ISPE)	855	855		Examples should be created where quality risk management is applied by Regulators.	**For example:** - Inspections, - Harmonisation of the Classification of Deficiencies, and in assessment, - Harmonized approach to risk between regulators during implementation of ICH Q12 and application of risk management to provide a common, - Global control strategy - see reference, PE article https://ispe.org/pharmaceutical-engineering/january-february-2022/toward-single-global-control-strategy-industry. -Consider using examples of risk-based decision making during dossier review.	