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Committee for Medicinal Products for Human Use

Overview of comments received on ICH guideline Q9 (R1) on quality risk management (EMA/CHMP/ICH/24235/2006)

Please note that comments will be sent to the ICH Q9(R1) EWG for consideration in the context of Step 3 of the ICH process.

1. General comments – overview

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
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).

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
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	
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.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
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
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.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
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.
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.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
AstraZeneca Pharmaceuticals	0	0	0	General: Comment 1: Please introduce the concept that risk management is most effective when framed in terms of the Quality / Compliance / Supply Reliability goals we are trying to achieve for a process and how we may potentially fail to meet these goals. This frames all the risk discussions in terms of ensuring and defending the "positive" Quality Goals and avoids the endless path of trying to defend a negative (what can fail and what would be the impact). It may seem the same but is a fundamental change in thinking and I believe will significantly improve QRM performance and help meet the expectations. Comment 2) We think as this revision is primarily based on subjectivity and objectivity this should be stated at the introduction and explained at length .Subjectivity is a difficult concept so there should be a strong emphasis the terminology and using subjectivity to evaluate the effectiveness of a risk assessment Comment 3) The proposed revisions to ICHQ9 come at a time when the medical device industry has made recent and substantial updates to the practice of risk management. Of particular note are the release of ISO 14971:2019 Application of risk management to medical devices and the 2017 EU Medical Device Regulation (MDR) which contains a number of sections directing the practice of risk management. As compared to the time of original ICHQ9 publication, medical devices have become increasingly important to the manufacture and marketing of medicinal products. Relevant examples include drug delivery systems and digital medical devices used together medicines. As such, many manufacturers are now incorporating medical device risk management practices into their Pharmaceutical Quality Systems. The original publication of ICHQ9 was made in general alignment with ISO14971:2000. Unfortunately, the newly proposed revisions to ICHQ9 within R1 do not account for the changes that have taken place to medical device risk management over the intervening years. As part of the current editing cycle the following efforts should be undertaken: •Align terminology and definitions between ICHQ9, ISO 14971:2019, and the EU MDR •Align risk evaluation and risk acceptance standards between ICHQ9 and the EU MDR	
EFPIA	0	0	0	There is currently very limited references to scoring within ICHQ9. Custom scoring models can be a pain point in industry if they are not used correctly to make decisions	Input for EWG discussion: Suggest to add reference to high level scoring description examples like PDA TR or WHO scoring descriptions (not to be binding but to guide industry) or to clarify in training material.

2. Specific comments on text

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	7	9	1	The previous explanation and wording should be more aligned with the other ICH guidance (e.g. Q10) to focus on an effective PQMS. The “importance of quality systems” suggests some kind of felxibilities that do not support the intention and principles of this guideline.	The importance of establishing a robust Pharmaceutical Quality System of quality systems has been recognized in the pharmaceutical industry and it is evident that a proactive approach to quality risk management is a key element and valuable component of an effective quality system.
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.**"

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Sharon Shutler Genedata	8	8	1	Abbreviate quality risk management to "QRM' and use this abbreviation throughout document	quality risk management to QRM
Sharon Shutler Genedata	8	8	1	Add "efficient" as QRM not only makes quality systems more effective but also more efficient	quality risk management is a valuable component of an effective and efficient quality system.
AstraZeneca Pharmaceuticals	8	8	8	Add Medical devices — Application of risk management to medical devices ISO/TR 24971:2020	Add Medical devices — Application of risk management to medical devices ISO/TR 24971:2020
LFB BIOMEDICAMENTS	14	15	1	In the sentence "In addition, subjectivity can directly impact the effectiveness…" examples may be needed.	"In addition, subjectivity **(e.g., no rationale, no relevant data, no scientific knowledge...)** can directly impact the effectiveness…"
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..."
Sharon Shutler Genedata	18	18	1	The word "availability" is confusing and should be removed. Also, could the wording be clearer and the word "quality" removed? The scope of this guideline includes development, manufacturing, distribution & submission / review. Hence, reference to the product lifecycle and not just "quality / manufacturing" would be appropriate.	when risks arise throughout the product lifecycle
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.
Medicines for Europe	18	18	1	It is not to easy to understand the meaning of the availability since the target is not mentioned in or before the following sentence: "when availability risks arise from quality/manufacturing issues"	when **supply and product** availability risks arise from quality/manufacturing issues
Sharon Shutler Genedata	20	20	1	Include reference to development, manufacturing, regulation, distribution and use of a drug to represent the product lifecycle.	The development, manufacturing, regulation, distribution and use…

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
AstraZeneca Pharmaceuticals	20	25	1	The manufacturing and use of a drug (medicinal) product, including its components: recommend that a definition is added in the definition section. Where a device constituent is used and depending on the local market, a drug (medicinal) product definition may vary	Add New: after 25: It is often useful to frame risk management in terms of what Quality, Compliance and Supply Reliability goals your lifecycle processes must achieve and then consider potential failure modes that would result in the processes not meeting these goals. This allows you to consider what controls are needed to ensure the goals are met, or at least detect if the required goal was missed. This frames risk management clearly in terms of product / patients and allows you to defend a "Positive" ("Ensure and Defend" the required Quality/Compliance/Supply Goals is built in across the lifecycle) as opposed to defending a "negative" (endless ways a process could potentially fail and the impact this could have). It is also allows a very structured way to show how decisions and knowledge are used throughout the lifecycle to support, ensure and defend that processes are successful.
EFPIA	22	25	1	The previous wording suggests that a product "remains safe and effective". Since quality, safety and efficacy must be built into the product from beginning on we propose to have the following wording:	It is important to understand that product quality is assured based on appropriate risk-based decision-making throughout the product lifecycle, such that the attributes that are important to assure the quality, safety and efficacy of the drug (medicinal) product are built in from the beginning and over the whole product life-cycle, based on risk maintained and the product remains safe and effective.
AstraZeneca Pharmaceuticals	26	31	1	Comment 1) An effective quality risk management approach: I recommend that the term effective is added to the definition section. This to ensure that any reader has the same understanding of the meaning its conveys. Comment 2) A proactive approach to quality risk management facilitates continual improvement: in my experience, the understanding of proactive is very subjective; it would benefit from a definition for the purpose of this document. Comment 3) Increasing benefits and safety margins should also be mentioned. A not utilized opportunity is also a risk.	
Sharon Shutler Genedata	28	28	1	Include distribution and storage as they also pose risks to product quality	during development, manufacturing, distribution and storage
EFPIA	30	30	1	Suggest adding reference to ICH Q10	...pharmaceutical quality system **(ICH Q10)**
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**..."
AstraZeneca Pharmaceuticals	33	39	1	Effective and proactive quality risk management can facilitate better: this terminology is very subjective. Recommend that it is removed from the text. More informed and timely decisions is sufficient as text and not as subjective.	More informed and timely decisions is sufficient as text and not as subjective.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
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,..."
EFPIA	35	35	1	Suggest adding reference at least ICH Q8 & 11	...stimulate continual improvements (ICH Q8, ICH Q11, ICH Q10)'. The EWG should consider relevance of referencing here.
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."
Sharon Shutler Genedata	38	38	1	A real benefit is the reduction in regulatory oversight. Hence, "affect" could be changed to "reduce".	beneficially reduce
AstraZeneca Pharmaceuticals	40	43	1	Line 40 The application of digitalization and emerging technologies in the manufacture and control of medicinal products can present certain challenges. This appears to give a negative slant on the use of emerging technologies . Needs to be rewritten to demonstrate why in the case of emerging technologies it is important to have an effective risk management system with the QMS to capture learnings and ongoing improvement Comment 2) Suggest to add areas like Clinical Trials (to cover GCP area) and not only manufacture and control of medicinal products (GMP). Could be more explored and discussed to add an even broader approach. Recomment to add "clinical trials" to the statement as follows “The application of digitalization and emerging technologies in clinical trials, manufacture and control of medicinal products can present certain challenges. The application of quality risk management to the design, development, validation and technology transfer of advanced production processes and analytical methods, advanced data analysis methods and computerized systems is important”.	
EFPIA	40	43	1	The text in the paragraph is currently unclear. It is not clear what "certain" challenges mean, and the specific mention of digitalisation and energing technologies in the first (but not the second) sentence gives grounds for misinterpretation.	Proposal: include digitalization/emerging tech into second sentence and remove first sentence
Medicines for Europe	41	41	1	inconsistent use of terms	drug (medicinal) product, line 41 "medicinal products"
Sharon Shutler Genedata	42	42	1	Start sentence with "Hence," or "Therefore" as this sentence is dependent on the previous statement. Change advanced production processes to "mature" production processes to avoid repetition of the word "advanced".	Hence, the application of…..mature production processes and analytical methods
ECA Foundation / European QP Association	43	43	1	*… and computerized systems is important.* See comment at line #370	
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."

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Sharon Shutler Genedata	45	45	1	Change "decisions" to "decision making" as it reads better	better, more informed, and timely decision making
Chartered Institute of Ergonomics & Human Factors. Pharmaceutical Special Interest Group.	48	48	Introduction	Regulatory environment is too vague and not specific enough. QRM applies to regulators as much as it applies to industry.	….and regulatory authorities. It specifically…..'
Sharon Shutler Genedata	50	50	1	Change "decisions" to "decision making" as it reads better	decision-making
PPTA	53	56	1	This line implies that lower risk issues could be dealt with less formality and higher risk issues with higher formality, but it is not clear if the path to understanding whether something is a low risk vs. a high risk issue needs to consider formality as well. A decision on the level of formality would need to be made to understand if an issue is low risk or high risk. Also, in section 5 the implication is that the formality of QRM process is based on complexity, uncertainty and criticality. It is not clear if the formality is part of the risk "assessment" or only part of decision making.	Suggestion to remove the details on formality in section 1 and move it to section 5. Proposal to keep only the following line - "An understanding of formality in quality risk management (see Chapter 5 below) may lead to resources being used more efficiently".
Lonza	53	69	1	This section is an important new addition to the Quality thought process for defining formal and informal process use. If there is a glossary it would be good it they could include examples or in the associated ICH training materials. Even later on it is not clear - Is formal use of FMEA, HAZOP etc, informal - SOP, process control flow diagram, decision tree?	Keep - add examples
Takeda	53	56	1	This line implies that lower risk issues could be dealt with less formality and higher risk issues with higher formality, but it is not clear if the path to understanding whether something is a low risk vs high risk issue needs to consider formality as well. As in, you would need to make a decision on level of formality before you would even understand if an issue is low risk vs high risks. Also, in section 5 the implication is that the formality of QRM process is based on complexity, uncertainty and criticality. It is not clear if the formality is part of the risk "assessment" or only part of decision making.	Suggestion to remove the details on formality in section 1 and move to section 5. Propose to keep only the following line - "An understanding of formality in quality risk management (see Chapter 5 below) may lead to resources being used more efficiently"
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)."
LFB BIOMEDICAMENTS	56	59	1	The sentence “an understanding of formality can also support risk-based decision-making, where the level of formality that is applied may reflect the degree of importance of the decision, as well as the level of uncertainty, complexity and criticality which may be present.” is not clear.	“an understanding of formality can also support risk-based decision-making, where . The level of formality that is applied may reflect the degree of importance of the decision, as well as the level of knowledge uncertainty, complexity and criticality which may be present. “

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Gilead Sciences	59	249	5	Criticality not defined (while importance, uncertainty and complexity are discussed in section 5). Contradictory statements for consideration of risk formality in lines 248-250 and section 5.1.	
AstraZeneca Pharmaceuticals	60	63	1	Line 60 : This needs to be clearer in terms of the use of risk management where there is emphasis on product and knowledge management allowing the use of risk management to facilitate the patient. Industry and Regulator. Guidance should be removed as this is not a legal obligation.	
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."
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.
EFPIA	64	64	1	Suggest using appropriate legal and ICH terminology - Not clear what 'official' guidance is	~~official~~ **regulatory** guidance
EFPIA	66	72	2	Medical Devices and ISO are out of scope? But it is unclear how to handle drug device combination products in this context.	Please clarify whether Medical Devices and ISO are out of scope or not, and how drug device combination products should be handled.
EFPIA	66	72	2	Comment: The SCOPE is currently written for GMP only but with the endorsement of ICH E6(R2) on 05Jun2014 ICH Q9 principles have been extended to Good Clinical Practices (see ICH E6(R2) concept paper). We suggest that the Rapporteur clarifies the scope and remit of ICH Q9(R1) in relation to ICH E6(R2).	Proposed change (if any): This guideline provides principles and examples of tools for quality risk management that can be applied to different aspects of pharmaceutical quality in the context of GxP (see also e.g., ICH E6, ICH E2E). Which would also include e.g. designing, conducting, recording and reporting trials that involve the participation of human subjects.
Chartered Institute of Ergonomics & Human Factors. Pharmaceutical Special Interest Group.	67	68	2	All risks have a technical element AND an organizational element including technical contributors, organizational contributors, and the work using human factor approaches helps understand the interactions between these contributors to events occurrence and consequence. Rationale: Expanding the scope to focus on the risks connected with human activity during investigations or risk assessments can help widen the scope.	"This guideline provides principles and examples of tools for quality risk management that can be applied to different aspects of pharmaceutical quality and human performance". We attach a document which reflects are current thinking about organisational learning and just culture and how that relates to human performance and quality risk management.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
AstraZeneca Pharmaceuticals	67	72	2	Add a note within the scope section that reads, "The development and manufacture of medical devices is subject to unique regulations and consensus standards. Whilst the general principles of risk management are equally applicable to pharmaceutical and medical device quality systems and efforts have been made to align terminology contained within this document with medical device risk management practices, pharmaceutical manufacturers producing medical devices or combination products must be aware of the particular risk management requirements that apply to medical devices (see References). Comment 2) Suggest to add areas like Clinical Trials (to cover GCP area) and not only manufacture and control of medicinal products (GMP). Could be more explored and discussed to add an even broader approach. Recomment to add "clinical trials" to the statement as follows "The application of digitalization and emerging technologies in clinical trials, manufacture and control of medicinal products can present certain challenges. The application of quality risk management to the design, development, validation and technology transfer of advanced production processes and analytical methods, advanced data analysis methods and computerized systems is important".	"The development and manufacture of medical devices is subject to unique regulations and consensus standards. "Whilst the general principles of risk management are equally applicable to pharmaceutical and medical device quality systems and efforts have been made to align terminology contained within this document with medical device risk management practices, pharmaceutical manufacturers producing medical devices or combination products must be aware of the particular risk management requirements that apply to medical devices (see References)."
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.**"
EFPIA	68	72	2	Are ATMPs inlcuded in the scope of this guideline? We suggest that the Rapporteur clarifies the scope to be included in ICH Q9(R1) and potentially revise current wording accordingly.	- Propose to add wording to ensure new modalities, ie ATMPs are in scope. Or add ATMPs as an example of biotechnological product.
Sharon Shutler Genedata	71	71	2	Full stop after products as the sentence is too long.	products. They also include the use of raw materials….
Sharon Shutler Genedata	73	73	2	What is out of scope of this guideline?	Include a statement as to what is out of scope?
Chartered Institute of Ergonomics & Human Factors. Pharmaceutical Special Interest Group.	76	77	3	Include the terms scientific knowledge and organisational science as they fundamentally underpin risk management and reflect the reality for many working in the pharmaceutical sector across the lifecycle.	The evaluations of the risk to quality should be based on scientific knowledge and organisational sciences including human factors and systems thinking which are intrinsically linked to the interests and protection of the patient.
Sharon Shutler Genedata	77	77	3	Change "link" to past tense to complement the first part of the sentence.	ultimately linked….
PPTA	77	78	3	It is not clear if the intent is to create an expectation to specifically evaluate product availability harm from each quality risk or just to specify that product availability risks, when identified from quality risks, should also be based on scientific knowledge and linked to the protection of the patient.	Suggestion to rephrase: Risk to quality includes situations where the quality hazard may lead to product availability harm.
Takeda	77	78	3	It is not clear if the intent is to create an expectation to specifically evaluate product availability harm from each quality risk or just to specify that product availability risks, when identified from quality risks should also be based on scientific knowledge and linked to protection of the patient	Suggest to rephrase: Risk to quality includes situations where the quality hazard may lead to product availability harm

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
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."
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.
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.
Chartered Institute of Ergonomics & Human Factors. Pharmaceutical Special Interest Group.	100	100	4.1	Pharmacovigilance and a company's medical function are critical members of the team and so should be mentioned	Add the following to the list of experts from the appropriate areas: pharmacovigilance, medical
PPTA	103	114	4.1	The description of subjectivity seems out of place. Eventually, the onus seems to be on the decision maker per lines 120-121.	Suggestion to remove lines 103-114 from this section and move it to section 5 as part of a subsection.
Chartered Institute of Ergonomics & Human Factors. Pharmaceutical Special Interest Group.	103	105	4.1	Subjectivity and effective identification of hazards relies on a speaking up culture.	Add the following sentence: 'For effective processes, a healthy speaking up culture helps'
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'
Takeda	103	114	4.1	The description of subjectivity seems out of place. Eventually, the onus seems to be on the decision maker per lines 120-121.	Suggest to remove lines 103-114 from this section and move it to section 5 as its own subsection
EFPIA	103	105	4.1	include "severity of harm" as element of subjectivity as it often cannot be clearly quantified (at least initially), can be multi-factorial and depending on the range investigated.	Subjectivity can impact every stage of a quality risk management process, especially the identification of hazards and estimates of their probabilities of occurrence as well as their severity of harm, the estimation of risk reduction and the effectiveness of decisions made from quality risk management activities

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Sharon Shutler Genedata	104	104	4.1	Remove typo "-"	…and risks are perceived by…
Medicines for Europe	108	109	4.1	the actual tools used may be inappropriate for a specific situation or tools may used improperly	Subjectivity can also be introduced through the use of inappropriate tools, for example tools with poorly designed scoring scales, or through improper use of tools
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."
Medicines for Europe	109	112	4.1	Which content of ICH Q10 is relevant to 'ICH Q10, Section II.E.1' described in the below line 111-112 of draft ICH Q9? We were not able to find the specified section in the ICH Q10 guideline (https://database.ich.org/sites/default/files/Q10%20Guideline.pdf). While subjectivity cannot be completely eliminated from quality risk management activities, it may be controlled by addressing bias, the proper use of quality risk management tools and maximising the use of relevant data and sources of knowledge (see ICH Q10, Section II.E.1).	Update the section with the relevant section.
Parenteral Drug Association	110	110	4.1	Bias is one area where this can be controlled; the other is heuristics. **Current tex**t: "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**..."
PPTA	111	112	4.1	The reference of ICH Q10 Section II.E.1 in the ICH Q10 guideline is missing/ is incorrect.	Please clarify referencing 'see ICH Q10, Section 112 II.E.1'.
EIPG	111	112	4.1	Reference is given to ICHQ10 Section II.E.1. However, such a section cannot be found in ICH Q10	Clarify section of ICH Q10 as referred.
Lonza	111	112	1	Recommend excluding the refeence to ICH 10, and include a statement that bias can be removed by utilising scientific evidence around the product from sources such as the Knowledge management system related to products, manufacturing processes, and components. Sources of knowledge include, but are not limited to, prior knowledge (public domain or internally documented); pharmaceutical development studies; technology transfer activities; process validation studies over the product lifecycle; manufacturing experience; innovation; continual improvement; and change management activities." Rationale this support the flow of the document for the reader. Should the ICH 10 get updated this reference may be become out of date and then caus confusion for the reader of this document.	add - bias can be removed by utilising scientific evidence around the product from sources such as the Knowledge management system related to products, manufacturing processes, and components. Sources of knowledge include, but are not limited to, prior knowledge (public domain or internally documented); pharmaceutical development studies; technology transfer activities; process validation studies over the product lifecycle; manufacturing experience; innovation; continual improvement; and change management activities."
EFPIA	111	112	4.1	Current text: "…see UC Q10, Section II.E.1)." ICH Q10 does not include a section II.E1. It is unclear to what this reference is intended to point. Correct cross-reference to ICH Q10.	Revise reference to the correct section in the ICH published document.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
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**."
European Association of Hospital Pharmacists (EAHP)	115	117	4.1	The point on responsibility for coordinating quality risk management should be expanded to also include giving feedback.	Proposed changes are highlighted in green: "Decision makers should take responsibility for coordinating quality risk management across various functions and departments of their organization **which also includes giving feedback to everyone involved in this process**; and"
AstraZeneca Pharmaceuticals	115	116	4.1	Comment 1) Wouldn't also a responsibility be that the quality risk management process covers all life cycle area. This is emphasized a lot earlier on in the text so would have thought that this is also a key responsibility in addition to the 3 listed this terminology is not so telling. In our industry, it is more about ownership than decision making. If there is a possibility to relabel to Decision owner, it would be, in our opinion, more telling. Comment 2) Addition of identification and assuring resources from the correct disciplines is a responsibility for decision makers as a non identified risk in assessment may have more of an impact on the overall value of the risk assessment than subjectivity or bias of the scoring of identified risks.	
PPTA	120	121	4.1	Not clear if the decision maker is a senior leader who can make final decisions for the organization or if it is the person making decisions within the QRM process, i.e., a risk owner.	Suggestion to clarify the type of decision maker (senior leader vs. risk owner).
Takeda	120	121	4.1	Not clear if decision maker is a senior leader who can eventually make decisions for the organization or the person making decisions within the QRM process, i.e., a risk owner	Suggest to clarify the type of decision maker (senior leader vs risk owner)
EFPIA	120	121	4.1	How can the control of subjectivity be ensured? wording on control of subejctivity is not aligned with line 110. propose to reword to align	assure that subjectivity in quality risk management activities is controlled **by above described means** ~~and minimised,~~ 121 to facilitate scientifically robust risk-based decision making.
AstraZeneca Pharmaceuticals	122	125	4.2	After Line 122. Quality Risk Management is a holistic approach to pro-actively mitigate potential Hazards that may impact the Quality, Compliance and/or Supply Reliability of the products we provide to patients. Risk assessment, Risk Based decisions and/or Risk Based Quality strategies are just elements of the risk program.	
Medicines for Europe	122	132	4.2	Inappropriate tools may render a QRM process ineffective	add bullet "identify appropriate tool"
Lonza	128	129	4.2	Add if possible Walk the process as a team. Where this can be done all team members understand the process under evaluation reducing the introduction of bias or guess work	Add process walk down as an example preparation activity
Chartered Institute of Ergonomics & Human Factors. Pharmaceutical Special Interest Group.	130	130	4.2	When ICH says' identify a leader': a leader of what or whom?	ICH need to explain what the leader mentioned here is a leader of.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
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.
Sharon Shutler Genedata	131	132	4.2	Add "implementation" of the risk management process to enhance the meaning.	…for the implementation of the risk management process"...
AstraZeneca Pharmaceuticals	136	138	4.3	Line 136 Text revision suggestion; I would suggest to use justify rather than defend… we want of be proactive and on the offensive rather than reactive/defensive	begin with a well-defined problem description, risk question or specific goal we are trying to achieve. When the risk in question is well defined, or the goals we must achieve well defined an appropriate risk management tool (see examples in Section 5) and the types of information needed to address the risk question or ensure and [defend] justify we have appropriate controls to meet the Quality goals, will be more readily identifiable. As an aid...
AstraZeneca Pharmaceuticals	141	143	4.3	What is the likelihood (probability) it will go wrong? Detectability is in the definition table. For consistency, so should probability. What are the consequences (severity)? Detectability is in the definition table. For consistency, so should severity	141, 142, 143, Update to / or include the option to base the risk assessment in terms of the Quality goals we are trying to achieve. What Quality, Compliance, Supply Reliability Goals must we achieve? What are the consequences (severity to the Patient) of not meeting a given goal? What might go wrong to make us fail to be successful meeting that goal ? What is the likelihood (probability) it will go wrong AND result in the Consequence (To the Patient of the missed goal) defined ? What controls / protections do we have in place to reduce the likelihood and/or detect the potential Impact to the Quality goal?
Medicines for Europe	143	143	4.3	Hazard Identification: "What are the consequences (severity)?": no relation to Harm; when the Harm is not identified, the severity is incorrectly related to Hazard	"What Harm may be caused and what is the severity of that Harm?"
Takeda	144	148	4.3	Recommend introducing "hazardous situation" as a concept. It has helped clear up significant gaps in medical device risk management processes. More details on this may assist with improved definitions of hazard, transforming into a hazardous situation, leading to harm and eventually improved risk assessments. Recommend including hazardous situation a flow diagram of how a hazard may lead to a harm to a patient or user.	
EFPIA	144	144	4.3	Comment: The move to use the term Hazard instead of Risk should be more clear. Previously the Lifecyle used the term risk at each step now the lifecycle and definitions use the term Hazard only in the identification step and then continue to use the term risk. The way the term Hazard has been deployed in the document implies there is a fundamental difference in the identification step from previous versions. Without directly addressing the terminology change. This can potentially add confusion when looking at the Lifecyle.	Proposed Change: Clarify the difference between a hazard and a risk either with a sentence in the guidance, or at as part of the training. An example could be: Hazard identification addresses the what could go wrong (what might cause harm) and a risk is when an understanding of the risk related to the hazardous situation is understood including the probability of that situation occuring and the severity of harm”
Sharon Shutler Genedata	145	146	4.3	Add "real-time data" to the list. The hazard might be there in the present, actual time waiting to cause harm.	Information can include real-time data, historical data, theoretical analysis….

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Sharon Shutler Genedata	158	158	4.3	Change "Uncertainty is due to combination" to "Uncertainty is due to a combination" to correct English grammar	Uncertainty is due to a combination….
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."
Sharon Shutler Genedata	159	159	4.3	Remove second reference to "gaps" from "include gaps in knowledge gaps". Include gaps in knowledge is sufficient for the syntax and avoids repetition.	…include gaps in knowledge….
Chartered Institute of Ergonomics & Human Factors. Pharmaceutical Special Interest Group.	159	161	4.3	Common causes of uncertainty are fluctuating or poor situational awareness and reliance on assumptions especially when unconscious.	Add 'situation awareness and invalid assumptions' as two typical sources of uncertainty
Medicines for Europe	159	160	4.3	missing comma	"Typical sources of uncertainty include gaps in knowledge, gaps in pharmaceutical science..."
Medicines for Europe	160	160	4.3	Relation to hazard missing in 'sources of harm'	"sources of harm (hazards, e.g. failure modes…)"
Medicines for Europe	161	161	4.3	"probability of detection of problems" is inconsitent with line 151 "the ability to detect the harm (detectability)" - both, the detection of Hazards and of Harm can be factors in Risk Evaluation	[..], and probability of detection of problems (hazards and harm).
European Association of Hospital Pharmacists (EAHP)	171	171	4.3	The calculation of risk assessment with the risk priority number (NPR) should be added to evaluate the severity, probability and detectability of risk.	The following sentence should be added at the end of line 171: "The Risk Priority Number, or RPN, is a numeric assessment of risk assigned to a process, or steps in a process, as part of Failure Modes and Effects Analysis (FMEA), in which a team of experts assigns each failure mode numeric values that quantify likelihood of occurrence, likelihood of detection, and severity of impact."
AstraZeneca Pharmaceuticals	172	176	4.4	Comment 1: It is surprising that this section does not convey that the risk control should aim first at removing the risk, by design, every time possible. It doesn't encourage this first line of thoughts but instead discusses a benefit vs cost approach. Isn't this approach a little too "soft"? Comment 2: The proposed changes made to the document to account for “risks to product availability” seem to be made in isolation rather than in consideration of the larger concept of “patient benefit”. Generally, the document should focus more on the enumeration and evaluation of product benefit in consideration and acceptance of product risks. The risk acceptance section would be the best place to locate this content, which could provide an overview of available techniques to evaluating product benefit and weighing against product risk.	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
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."	
AstraZeneca Pharmaceuticals	182	189	4.4	Processes that improve the detectability of hazards and quality risks might also be used as part of a risk control strategy. Our understanding is that risk community of practice (the industry wide) was discouraging the use of detectability as a criteria because it may be overused as a risk control measure and as a result, may be chosen over one that could actually remove the risk. Suggest this sentence better convey that detectability should not be overused/misused.	Suggest this sentence better convey that detectability should not be overused/misused.
Medicines for Europe	184	185	4.4	"process that improve the detectability of hazards and quality risks…" is inconsistent with line 151 ""the ability to detect the harm (detectability)": what is a "quality risk", considering the terms "hazard" and "harm"?	"process that improve the detectability of hazards and harm quality risks…"
EIPG	190	196	4.4	Risk Acceptance. In order to increase objectivity and avoid subjectivity during Risk Acceptance, criteria for risks acceptance and an official record of of Acceptable Quality Risks should be defined beforehand based on case by case during the Quality Risk Management and Assessment exercise.	
AstraZeneca Pharmaceuticals	190	196	4.4	Or it can be a passive decision in which residual risks are not specified. This is a strange expectation from a process which is meant to be proactive, and therefore "owning decision" (are passive decisions owned?). Suggest this should be rephrased, omitting the passive terminology	Suggest this should be rephrased, omitting the passive terminology.
Sharon Shutler Genedata	192	192	4.4	"some types of harms" should be changed to "some types of harm" to make the meaning grammatically correct.	some types of harm…
Sharon Shutler Genedata	196	196	4.4	Change "decided on" to "justified on" to reduce subjectivity and convey use of scientific evidence	should be justified on…..
Sharon Shutler Genedata	199	199	4.5	Change "others" to "other stakeholders" to be more specific	…other stakeholders….
Sharon Shutler Genedata	202	203	4.5	Remove reference to "industry or regulatory authority" from line 203 as it is a repeat from line 202	Remove repeat reference.
EFPIA	202	205	4.5	Editorial comment, for consistency use regulatory authorities. Original text: "e.g., regulators and industry, industry and the patient, within a company, industry or regulatory authority, etc. "	e.g., ~~regulators~~ **regulatory authorities** and industry, industry and the patient, within a company, industry or regulatory authority, etc.
EFPIA	206	208	4.5	Should 'effected' be replaced with 'conducted'? Consider revising, as it may be hard to interpret as written.	"Between the industry and regulatory authorities, communication concerning quality risk management decisions might ~~be effected~~ **be conducted** through existing channels as specified in regulations and guidances".
AstraZeneca Pharmaceuticals	212	219	4.6	Line 216 "...unplanned (e.g., root cause from failure investigations, recall)." Would this example include complaints? Or should you specifically list it, as complaints are common quality events. Typically, a risk management process would be able to identify what complaints will be expected; new complaints would potentially trigger review of the risk management. So complaints are an obvious example to list.	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Chartered Institute of Ergonomics & Human Factors. Pharmaceutical Special Interest Group.	216	216		Root Cause -Suggest we evolve the definition of root cause to reflect practice or understanding that there are multiple contributing factors rather than relying on identifying a single (implied) root cause. And to avoid the misinterpretation We recommend consideration of 'causal factors' to signal the change in understanding and practice. This reflects regulation wording and regulatory expectations during inspections, conferences, presentations. - Rationale: The Science has moved on and there is an opportunity for the ICH regulatory to reflect the evidence and learning from Organisational science such as human factors and in the light of contemporary thinking of complex systems. We suggest of causal factors may assist improved understanding of the original intent of root cause. This proposal we believe is consistent with the existing definitions of root cause in ISO 9001 and reflect the intent of the definition in ICH E56 and EudraLex Vol 4. However our experience is that the use of non- conformance software that has drop down menus of root cause categories leads you to only selecting one, and this single root is implied in some regulatory guidance on CAPAs.	establish a definition of Root Cause to improve clarity of meaning consider using 'causal factors' and set the expectation that this means including system elements : the organisation, job design and individual. Suggested example is the definition of Root Cause(s) used by NASA: One of multiple factors (events, conditions or organizational factors) that contributed to or created the proximate cause and subsequent undesired outcome and, if eliminated, or modified would have prevented the undesired outcome. Typically, multiple root causes contribute to an undesired outcome https://supplychain.gsfc.nasa.gov/sites/supplychain/files/docs/2014/O.%20Ceritelli%20-%20SC2014.pdf
Medicines for Europe	216	217	4.4	Inconsistency of singular/plural form of bullet points	* change control**s** * recall**s**
Gilead Sciences	217	218	4.6	The frequency of risk review should be based on the level of residual risk after controls have been implemented and control performance/effectiveness measured.	Clarify that it should be based on the residual risk, after implementation and measure of performance of implemented risk controls. Supported via scientific study, production data, or effectiveness verification.
EFPIA	218	218	4	QRM documentation is living documentation, updated with risk reviews	Please consider adding the following sentence: **"Quality risk management documentation, including Risk Assessments, should be updated accordingly."** also, in training, describe difference between periodic review (risk-based) and new knowledge (all risk)
Medicines for Europe	220	220	5	Proposal to change the headline 'risk management methodology', due to "methodology" vs "tools", inconsistent use of terminology; "tools" being the preferrable term to emphazise that competence in using the respective tool, i.e. knowledge on strenghts and weaknesses of the respective tool is required, supplemented by experience.	"risk management tools"
Medicines for Europe	223	224	5	wording is inconsistent with "hazard" and "harm"; "risk" being the result of an evaluation of the likelihood of occurrence of an identified hazard, its detectability and the severity of the consequential harm (and the detectability of that harm).	[…] "current knowledge about tools that facilitate the identification of hazards, their likelihood of occurrence, their detectability and the severity of the consequential harms (and sometimes their detectability)".
AstraZeneca Pharmaceuticals	243	243	5	add after 243: Process Quality Risk Assessment	Suggest add after 243: Process Quality Risk Assessment
Medicines for Europe	245	246	5	"methodology" vs "tools", inconsistent use of terminology; "tools" being the preferrable term to emphazise that competence in using the respective tool, i.e. knowledge on strenghts and weaknesses of the respective tool is required, supplemented by experience	"Quality risk management tools can be used in combination…"
EFPIA	248	250	5	Comment: "The degree of rigor and formality of quality risk management should reflect available knowledge and be commensurate with the complexity and /or criticality of the issue being addressed." This single sentence is cueing up lines 251 to 274 . Can it be clarified whether this section is now referring to the type of risk tool selected for a particular risk objective or the formality of a QRM program as a whole? If for selection of tool type, the factors listed are not the only ones for consideration: rather it is the risk question or objective that should determine the approach needed. For example: if the risk question is to make a decision whether a change in equipment/process could result in increased risk, you may opt to use one tool over another (such as FMEA, which is not meant as a comparison tool). Understanding the context/scope here would be helpful.	Proposed change: add to line 249- consideration of the risk question or objective as a pre-requisite or further criteria - for example, where the objective is to understand failure modes, FMEA might be the preferred tool, regardless of what formality may otherwise be expected , futher elaborate in section 5

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Gilead Sciences	251	300	5.1	Does ICH envision formality being “scored” (similar to risk scoring) as a function of listed uncertainty, importance and complexity factors ?	
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).
Lonza	251	300	3	It would be helpful to give some examples different degrees of formality. e.g. is an FMEA considered formal and a simple assessment done in a Change Control considered informal?	Provide examples of different degress of formality.
AstraZeneca Pharmaceuticals	251	255	5.1	This section to be overall quite "heavy" to read and I had to read it 2 or 3 time to really get its meaning. Working at simplifying its content / wording would be beneficial. Line 251 should include the purpose of formality here why use it and what does it actually mean in this context.	
PPTA	252	255	5.1	The different levels of formality on a spectrum need more clarification, including examples. Examples are needed for a combination of different factors and how important is one factor, compared to another. 1) Use of formal/ less inherently formal tools or unrecognized tools, 2) Formality within the use and documentation of tools, 3) Effort and input considered (is a cross-functional extended team considered or not?) and 4) Are parts of QRM lifecycle (risk assessment, control, review and communication) used in the process?. Lower formality could be attributed to less effort, therefore, examples covering the spectrum of formality using a variety of combination of factors to ensure harmonized understanding within the industry, should be provided, preferably in a matrix form.	N/A
EIPG	252	255	5.1	Formality in Quality Risk Management. Formality and informality are very subjective concepts.	Additional information on how to define the level of formality could be included, with examples of different types of QRM.
Takeda	252	255	5.1	The different levels of formality on a spectrum need more clarification, including examples. Examples needed for a combination of different factors and how important is one factor vs another. 1) use of formal/ less inherently formal tools or unrecognized tools 2) Formality within the use and documentation of tools 3) effort and input considered (cross functional extended team considered or not) 4) Parts of QRM lifecycle (risk assessment, control, review and communication) used in the process?. Lower formality could be attributed to less effort. Need examples covering the spectrum of formality using a variety of combination of factors to ensure harmonized understanding within the industry, preferably in a matrix form.	N/A
Gilead Sciences	258	265	5.1	The importance and complexity both include statements to describe the higher the level the higher the formality. Is this intentionally not included in uncertainty or is the expectation that a higher uncertainty also means higher formality?	
PPTA	258	265	5.1	It is not clear how uncertainty relates to formality. Does higher uncertainty (e.g. early in process with less data availabile) require formal tools? If yes, some highly formal tools may not be as effective with higher uncertainty. Some methods need a degree ofprocess/product knowledge to be really effective and useful.	More clarification on how uncertainty leads to more/less formality needs to be provided.
Lonza	258	264	5.1	When discussing Uncertainty it would be important to additionally discuss familiarity and experience with the system that is being assessed, particularly in relation to likelihood of occurence. For example with new systems, historical data on occurence would not be available.	Add, "It is important to take into account familiarity and experience with the system that is being assessed, particularly in relation to likelihood of occurence. For example, with introduction of new systems, historical data on failure occurence would not be available."

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
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"
Takeda	258	265	5.1	Not clear how uncertainty relates to formality. Does higher uncertainty (e.g. early in process with less data availabile) require formal tools? And if so, some highly formal tools may not be as effective with higher uncertainty. Some methods need a degree ofprocess/product knowledge to be really effective and useful	Requires more clarification on how uncertainty leads to more/less formality
EFPIA	258	265	5.1	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. For example: - 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 - there are definitions in Guide 73 that are not used in ICH Q9 (R1), but would be useful e.g. Risk Review	Recommend alignment of definitions with ISO. Propose a general comment to align with ISO definitions and give examples of definitions not currently aligned "uncertainty", "risk review", "risk acceptance".
EFPIA	258	270	5,1	Recommend adding examples of uncertainty, importance and complexity as used for QRM decision making and use of tools decisions. Broad potential use and would help if additional context/examples could be referenced (in ICH training material?).	Please consider providing a matrix example or spectrum for how uncertainty, importance, and complexity inform the level of formality of risk assessments. Probably best suited in the training material
Medicines for Europe	258	259	5.1	risk level is something that is assessed with probability of occurrence and severity of hazard (and detectability of harm), based on knowledge about potential harms	"The term “uncertainty” in quality risk management means lack of knowledge about hazards."
EFPIA	259	259	5.1	This could be an opportunity to keep the terms as defined; knowing the 'risk' is the desired state; uncertainty occurs because the understanding is lagging to manage 'hazards' (see change in chapter 4.1)	Lack of knowledge about ~~risks~~ **risk scenarios**.
International Society for Pharmaceutical Engineering (ISPE)	260	260		QRM formality is recommended and not required.	change "require" to "should use"
EFPIA	260	265	5.1	The information on how to manage knowledge to reduce uncertainty is useful but doesn’t seem best placed under this bullet point as it does not inform on the key topic, which is the relationship between uncertainty and decision-making.	Suggest providing more detail in training material.
EFPIA	261	261	5.1	Comment: The word "analyzing" is misspelled as analysing.	Please ensure consistent use of either British English or American English spelling throughout the document
Medicines for Europe	262	263	5.1	Not clear what is meant by the following sentence: "Systematic approaches for acquiring, analysing, storing and disseminating scientific information are essential for generating knowledge, which in turn informs all quality risk management activities."	Systematic approaches for acquiring, analysing, storing and disseminating scientific information are essential for generating knowledge, which in turn **impacts** all quality risk management activities"

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EIPG	266	268	5.1	"Importance" is not an objective concept. How should importance be established?	Propose to substitute "Importance" with another term and provide guidance on what constitutes critical risk-based decisions.
Lonza	266	268	5.1	"Importance"is not objective. "Criticality" can be defined around impact to product quality or patient safety.	Propose to substitute "Importance" with "Criticality" with guidance statement(s) on what constitutes critical risk-based decisions.
Lonza	266	266	5.1	Importance could be subjective, "Impact" might be a better word, to signify the weight of the decision.	Recommend use Impact instead of Importance.
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.
EFPIA	266	268	5.1	Would it be possible to define the factor "Importance" in more detail espacially with regard to the aspect product quality?	Provide clarification of the term and what it includes.
Parenteral Drug Association	266	268		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."
Lonza	269	280	5.1	Proposal to tie in the level of effort into this section. If the level of effort should be commensurate with the level of risk, the level of formality should also be commensurate with the level of complexity.	Add, "the level of formality should be commensurate with the level of complexity."
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.
PPTA	274	275	5.1	This line appears to create a new expectation. It needs to be clarified what is expected. Is a prescriptive framework necessary (e.g. such as a decision tree) or are guiding principles sufficient which would clarify understanding on formality as a factor within the use of QRM?	Clarification needs to be provided on the expectations regarding the use of formality and the approach within the QMS.
Takeda	274	275	5.1	This line appears to create a new expectation. Needs to be clear on what is expected. Is a prescriptive framework necessary (e.g. decision tree) or simply guiding principles so that here is understanding on formality as a factor within the use of QRM?	Clarify the expectations regarding the use of formality and the approach within the QMS.
EFPIA	275	277	5.1	This is understood as a general GMP principle (and not necessarily related to QRM). Also the statement could be perceived as judgemental. Propose to remove it	Resource constraints 276 should not be used to justify the use of lower levels of formality in the quality risk management 277 process.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
PPTA	277	278	5.1	This line seems to suggest that robustness of assessment is completely independent of formality	Clarification is needed on what constitutes a robust management of risk.
Takeda	277	278	5.1	Seems to suggest that robustness of assessment is completely independent of formality	Clarify what robust management of risk entails
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.**"
Lonza	281	300	5.1	Characteristics of formality may also dictate whether the risk assessment is living or ad hoc, considerations to risk review, and to what frequency.	Add, "Characteristics of formality may also dictate whether the risk assessment is living or ad hoc, considerations to risk review, and to what frequency."
EFPIA	281	298	5.1	Guidance is in the text above. This sections provides examples on what characterises higher or lower levels. It can be discussed whether this level of detail belongs in the core guidance or should rather be covered in training material. Some will find it too detailed and restrictive, others helpful.	Consider moving to training material. Under all circumstances expand on this in the training material
EFPIA	286	286	5.1	Current text: "Recognized or other quality risk management tools…" It is unclear what is mean by a recognized risk management tool. Based on lines 230-233, it appears this is intended to refer to the list starting at line 234 and the quality risk management tools also discussed in Appendix I. Additional clarity would help the reader make that connection.	Proposed text: "Recognized **(see Annex I)** or other quality risk management tools…"
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 formali**~~ty~~** process.
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).
EFPIA	288	289	5.1	Current sentence states: A cross-functional team is assembled for the quality risk management activity. Use of a trained quality risk management facilitator may be integral to a higher formality process. (this leads to a lack of operational ownership-culture of not owning risks where they actually occur but pushing it to 'trained' facilitators - creating of lengthy facilitation trainings at companies etc)	Suggest to change wording: Involvement of team members who have demonstrated experience and knowledge of quality risk management principles can be highly beneficial if a higher formality approach is taken.
Medicines for Europe	288	289	5.1	Further elaboration on the "trained quality risk mangement facilitator" would be helpful. A cross-functional team is assembled for the quality risk management activity. Use of a trained quality risk management facilitator may be integral to a higher formality process.	We would like to suggest describing further explanation regarding 'trained quality risk management facilitator' such as a required and/or expected qualifications.
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.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
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"
ECA Foundation / European QP Association	295	295	5.1	See comment at line #98	A cross functional team might not be necessary.
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.	
PPTA	302	308	5.2	Risk-based decision making could be perceived as a lower formality application of QRM. It needs to be clrified that risk-based decision making does not necessarily mean a less formal application of QRM activities.	
Takeda	302	308	5.2	Risk Based decision making could be perceived as a lower formality application of QRM. Needs to be clear that risk based decision making does not necessarily mean a less formal application of QRM activities	
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.
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
AstraZeneca Pharmaceuticals	303	308	5.2	Line 303 Risk Decision making needs to start with identifying the problem which you need to do before making effective risk-based decisions -Effective risk-based Decision making begins with identifying the problem, then determining the level of effort. Within this sentence, subjectivity should be addressed. Include addressing subjectivity, formality and documentation. Important to get the uniform understanding of the problem and how the evaluation will be used to make the decision/documented accordingly	
Medicines for Europe	303	304	5.2	decision making starts with the understanding that a certain scenario requires initiating a QRM process and the determination of an appropriate QRM tool	"Effective risk-based decision making begins with **understanding the risk scenario and** determining the appproriate quality risk management tool and the level of rigour, formality and documentation…"
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.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
International Society for Pharmaceutical Engineering (ISPE)	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.
EFPIA	305	305	5.2	Consider adding reference to chapter 3	...risk management process **(see chapter 3).**
Medicines for Europe	305	307	5.2	Inconsistent wording regarding 'hazard' and 'harm'	"The output of quality risk management activities include decisons in relation to what hazards exist, **the consequential harm and the associated risks**, the risk controls required…"
PPTA	309	314	5.2	It is not clear what "approaches to risk-based decision making" mean in this section. This section describes the benefits of risk-based decision making, regardless of the approach undertaken. The approaches to risk-based decision making have not been introduced within the document up until this point. Also, improved detectability as part of risk controls does not need to be explicitly stated as it is covered in risk reduction under the risk control section.	Risk-based decision-making is beneficial, because it addresses uncertainty through the use of knowledge, facilitating informed decisions by regulators and the pharmaceutical industry in a multitude of areas, including when allocating resources. Risk-based decision-making also helps recognize where uncertainty remains, so that appropriate risk controls may be identified
Takeda	309	314	5.2	Not sure what "approaches to risk based decision making" means in this section. It seems like this section talks about benefits of risk-based decision making, regardless of the approach undertaken. The approaches to risk-based decision making haven't been introduced within the document up until this point. Also, improved detectability as part of risk controls does not need to be explicitly stated as it is covered in risk reduction under the risk control section.	Risk-based decision-making is beneficial, because it addresses uncertainty through the use of knowledge, facilitating informed decisions by regulators and the pharmaceutical industry in a multitude of areas, including when allocating resources. Risk-based decision-making also helps recognize where uncertainty remains, so that appropriate risk controls may be identified
EFPIA	309	309	5.2	Revise by using guidance terminology as this is the main part of Q9	Approaches to risk-based decision-making ~~are beneficial, because they~~ address uncertainty through the use of knowledge
EFPIA	311	311	5.2	unclear what the purpose of this statement is and why a quality guidance refers to ressources in this context. Propose to remove	including when allocating resources.
EIPG	315	317	5.2	Reference is given to ICH Q10 regarding Knowledge Management. Additional guidance on how to apply Knowledge Management in Quality Risk Management could be provided.	Additional guidance on how to apply Knowledge Management in Quality Risk Management could be provided.
Lonza	316	317	5.2	Not only the integrity of the data, but the accuracy and the availability of the data. Risk-based decision making should be based in facts, scientific knowledge, and data.	Add, "In addition to the integrity of the data, the accuracy and availability of the data is relevant. Risk-based decision making should be based in facts, scientific knowledge, and data."
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.	
LFB BIOMEDICAMENTS	316	317	5.2	The sentence "It is important also to ensure the integrity of the data that are used for risk-based decision making." Should be reinforced by suggesting that ALCOA principles apply.	"It is important also to ensure the integrity of the data (**ALCOA principles**) that are used for risk-based decision making."

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
AstraZeneca Pharmaceuticals	319	326	5.2	Line 319 "Formality" needs to be explained in terms of level of risk. In level of effort we have lots of risk logs across the business which can be discreet to a project / supply chain /development/regulatory. Depending on the risk depends on the level of effort deployed and potential escalation required. What shouldn't happen is every risk carries a formal assessment.	
EFPIA	325	342	5.2	These lines provide exemplification of how risk based decision making shall be implemented. It can be discussed whether this would be more appropriate in the Annex II as section II.10, meeting the original expectation of the concept paper. Some may find the current text too binding and restrictive in its current place. The suggested (potential) correction keeps the what to do in the main part and moves the how to in the annex.	Consider moving the text as Annex II.10 and (if chosen) slightly adopt the language without changing the meaning e.g., Annex II.10. Approaches to risk-based decision-making Below are potential approaches how QRM can be used for highly structured vs. less structured processes, and for rule-based processes when making risk-based decisions • Highly structured approaches can involve a formal analysis of the available options that exist before making a decision. They involve an in-depth consideration of relevant factors associated with the available options. Such processes might be used when there is a high degree of importance associated with the decision, and when the level of uncertainty and/or complexity is high. • Other risk-based decision making processes are less structured approaches: here, simpler approaches are used to arrive at decisions, and they primarily make use of existing knowledge to support an assessment of hazards, risks and any required risk controls. Such processes might still be used when there is a high degree of importance associated with the decision, but the degree of uncertainty and/or complexity is lower. • Decisions might also be made using rule-based (or standardised) approaches: They, which do not require a new risk assessment to make such decisions. This is where there are SOPs, policies or well understood requirements in place which determine what decisions must be made. Here, rules (or limits) may be in place which govern such decisions; these may be based on 340 a previously obtained understanding of the relevant risks and they usually lead to predetermined actions or expected outcomes. Potentially keep the three types as a short bullet list within the main guideline.
Medicines for Europe	334	334	5.2	Inconsistent wording regarding 'hazard' and 'harm'	"[…] an assessment of hazards, **the associated harm and risk** as well as any required risk controls."
PPTA	337	342	5.2	Rule-based decision making seems to be an approach where specific requirements are in place to make decisions consistently and repeatedly based on previously obtained understanding of risks (knowledge). The relationship between consistent, formal risk management and rule-based decision making needs to be simplified and clarified.	
Takeda	337	342	5.2	Rule-based decision making seems to be an approach where specific requirements are in place to make decisions consistently and repeatedly based on previously obtained understanding of risks (knowledge). Relationship between consistent, formal risk management and rule based decision making needs to be simplified and clarified.	
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.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Sharon Shutler Genedata	342	342	5.2	Change "predetermined actions or expected outcomes." to "predetermined actions and / or expected outcomes." Both actions and outcomes may be predetermined and not either predetermined actions or expected outcomes.	"predetermined actions and / or expected outcomes".
AstraZeneca Pharmaceuticals	346	352	6	Line 349 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- and more informed science risk-based decisions Line 351-might affect the level and extent of regulatory oversight (burden) commensurate with the level of identified risk.	Line 350- and more informed **science** risk-based decisions Line 351-might affect the level and extent of regulatory oversight (burden) **commensurate with the level of identified risk.**
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"
Sharon Shutler Genedata	352	352	6	Reference to "all parties" is unclear as only two parties (i.e. industry and regulatory personnel) are previously referred to. Change to "both" parties.	"by both parties".
Chartered Institute of Ergonomics & Human Factors. Pharmaceutical Special Interest Group.	353	355	6	Training together of those who have to cooperate together would help quality risk management. It is not clear what is meant by the term 'regulatory personnel'? Is that within a company or an authority or both.	Suggest ' Training of both industry and regulatory authority personnel, ideally together where possible, provides for greater understanding and a shared mental state required for decision-making…'
AstraZeneca Pharmaceuticals	353	355	6	Line 353 Training examples need to also include examples from Regulators so Industry can understand risk management and decision understanding from a regulators perspective.	
European Association of Hospital Pharmacists (EAHP)	356	357	6	In relation to the integration and documentation of quality risk management it should be noted that documents and data management should be dealt with technology and computerized systems, qualified and validated by Annex II.	In the paragraph on the quality risk management it should be underlined that "Both industry and hospital pharmacies should be supported by computerized systems, qualified and validated , to validate the procedures and the instruments related. Moreover, computerized systems assure data integrity, accuracy and coherence."
EFPIA	357	361	6	Not sure, why the aspect on availability is added at the beginning of this chapter. Although, we agree the application of QRM to availability is important and perhaps not appropriately implemented, currently it is highlighted in the principles (Chapter 3), as well as in the Annex.	Suggest deleting this stand alone addition to the guideline, as the entire section on adressing product availability risk is just below. Or clarify text and focus to make causal relations clear.
Sharon Shutler Genedata	359	359	6	Change "systemic quality/manufacturing risks" to just "systematic risks" to cover other risks such as product availability due to distribution & customs etc.	Change to "systematic risks".
Sharon Shutler Genedata	359	361	6	Change "Application of quality risk management can proactively mitigate these risks. Preventive measures supporting product availability may be identified through quality risk management activities" to "Application of quality risk management can proactively mitigate these risks and preventive measures supporting product availability may be identified". This prevents repetition and reinforces the relationship between quality risk management, the mitigation of risks and the identification of preventive actions.	Change to "Application of quality risk management can proactively mitigate these risks and preventive measures supporting product availability may be identified".

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Lonza	360	361	6	Preventative measures identified through quality risk management activities will also serve to support quality by design; potential systems that embed quality as an element in the workflow/process.	Add, "Additionally, preventative measures identified through quality risk management activities will also serve to support quality by design; potential systems that embed quality as an element in the workflow/process."
International Society for Pharmaceutical Engineering (ISPE)	360	361	5	Delete the last sentence - it is repetitive.	
Sharon Shutler Genedata	369	369	6	Examples for industry operations and activities (see Annex II): Change to "Examples for industry operations" What other activities are there apart from industry operations?	"Examples for industry operations"
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.
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.
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**
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.
EFPIA	376	376	6	Alignment needed with section386ff (re which supply chain risks fall under the scope of this guidance). Propose to reword to clarify scope of this document with regards to product availability risk. Several comments recieved form companies on difficulty to understand teh term supply chain control.	Suggest to use more descriptioon along the lines of Control of factors that can affect supply reliability
European Association of Hospital Pharmacists (EAHP)	377	378	6	The list of examples for regulatory operations should be expanded to also include internal and external communication.	Insertion of additional bullet point referring to "Communication (internal/external)."

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
European Association of Hospital Pharmacists (EAHP)	384	384	6	In section 6 (integration of quality risk management into industry and regulatory operations) it would be beneficial to add examples for hospital pharmacies and not only for industry.	Proposal to include examples for hospital pharmacies in Section 6.
Sharon Shutler Genedata	386	386	6	The role of Quality Risk Management in addressing Product Availability Risks. Why is this line a heading and not section 6.1? It does not fit with the format with the rest of the document.	Make this line section 6.1
EIPG	386	420	6	The role of Quality Risk Management in addressing Product Availability Risks. The same information is included as a part of Section II.9.	The duplicated information could be removed
Lonza	386	419	6	The role of Quality Risk Management in addressing Product Availability Risks. This section describes Manufacturing Process, Facilities Design and Oversight of Activities and Suppliers. It would be clearer if the 3rd point (Oversight of Activities and Suppliers) is expanded to address more aspects of Supply Chain Risks including distribution challenges & interruption of supply due to natural/man-made disasters or pandemic.	expand to address more aspects of Supply Chain Risks including distribution challenges & interruption of supply due to natural/man-made disasters or pandemic.
EFPIA	386	386	6	This is an additional headline.	Consider renaming as sub chapter 6.1 (similar to the added chapters 5.1 and 5.2).
Sharon Shutler Genedata	388	388	6	Change "GMP" to "cGMP" or better still "cGxP" to convey the application of good practice to other disciplines and not just manufacturing.	Change to "cGMP" or "cGxP".
EFPIA	388	388	6	The text can benefit from being neutral. There is no comparison on how frequent 'frequent' is.	Suggest deleting the word 'frequent'.
Sharon Shutler Genedata	392	393	6	Change "It also uses quality risk management and knowledge management" to "It also uses knowledge management and quality risk management" as we have to know facts before we can apply them in a quality risk management process.	Change to "It also uses knowledge management and quality risk management"
European Association of Hospital Pharmacists (EAHP)	392	395	6	The section on the role of Quality Risk Management in addressing Product Availability Risks should include a reference to other stakeholders for the early warning system.	Proposed changes are highlighted in green: "It also uses quality risk management and knowledge management to provide an early warning system, **linked with other stakeholders (regulators; wholesalers; national authorities),** that supports effective oversight and response to evolving quality/manufacturing risks from the pharmaceutical company or its external partners."
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.	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	396	420	6	This section provides examples and is somewhat redundnat to lines 828 to 855 (Annex II.9).	Suggest reducing lines 396 to: Factors that can affect supply reliability, and hence product availability, may include the following e.g., manufacturing process variation and state of control (internal and external, manufacturing facilities, and oversight of outsourced activities and suppliers. Delete the remaining text (lines 398 - 420) and refer to Annex II.9 in line 397.
EFPIA	396	396	6	The term Chapter or Section is not used consistently	**Proposed Change:** change Chapter 5 to Section 5 throughout
EFPIA	401	401	6	Yield has a different importance during the different stages of the life cycle; it is specifically important for the commercial phase but less for development activities.	...may adversely impact quality, timeliness, yield (as applicable to the specific life cycle stage), and consequently product availability
Chartered Institute of Ergonomics & Human Factors. Pharmaceutical Special Interest Group.	403	403		Consider evolving the language from "investigate root causes" to understand and define the causal factors or system performance that contributed to the issue. We are concerned that the term 'Root cause analysis' has been interpreted to be the search for one cause when in fact it refers to multiple causal and organisational factors. Causal factors include how the work is organised, how the job is designed and how the person is developed to competency. such factors are defined commonly by CIEHF as PIFs Performance Influencing Factors. These are the root causes'.	Consider evolving the language from "investigate root causes" to understand and define the causal factors that influence human performance and develop a definition for the glossary.
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.
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."
EFPIA	408	409	6	Current text: "Risks to supply can be reduced by addressing these factors, as well as through use of modern technology, such as digitalization, automation,…" We recommend adding 'in some cases' as digitization and automation do not necessarily reduce risk and in some cases (as noted in lines 40-43) can introduce their own risk management challenges.	Proposed text: "Risks to supply can **in some cases** be reduced by addressing these factors, as well as through use of modern technology, such as digitalization, automation,…"
Sharon Shutler Genedata	409	409	6	Add reference to "digitization" as well as "digitalization" as the digitization of manual processes e.g. approval of documents may also reduce risks as well as the digitalization for the processes and analysis of large data sets.	Add "digitization" to the list.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
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.
EFPIA	413	418	6	Examples of how differing levels of criticality is determined in terms of "outsourced activities and suppliers" would be helpful. Difference between outsourced WIP vs. Raw Materials vs. QC Test lab contracts. Clarify whether this applies to CMOs explicitly. Could be done in ICH training material vs. language addition in document.	Please consioder to provide examples of how Work-In-Progress Materials vs. Raw Materials vs. Contracted services or service labs vs. CMOs would have quality risk management applied to "outsourced activities and suppliers scope" in document. Potentially in the training material
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."

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Gilead Sciences	414	415	6	Q9(R1) references Q10 and necessitates knowledge management practices being incorporated into formality, risk-based decision making, and the oversight of outsourced activities and suppliers. What is ICH's expectations of knowledge management practices for acquiring, analyzing, storing, and disseminating information related to products, manufacturing processes, and components regarding QRM? (Also referenced in lines 310, 315-317)	
Sharon Shutler Genedata	414	414	6	"informed" isn't really the right word. How about "effected" or "facilitated" by…	Change "informed" to "effected" or "facilitated" by.
Sharon Shutler Genedata	415	415	6	The partnership many not just be manufacturing e.g. wholesale dealing etc…	Change to "effective partnership".
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."
EFPIA	419	420	6	This is multifactorial topic and not easily explained in a simple sentence, and as a solution it is but one out of many.	Propose to delete the sentence: In some cases, it may be necessary to identify a new supply chain entity (e.g. a pre420 qualified backup option) to perform a function. Alternatively a rewording is proposed: In some cases, it may be necessary to identify a new supply chain entity (e.g. an alternative pre-qualified backup option) to perform a function.
EIPG	422	466	7	Some definitions are missing in the draft version of the ICH Q9: - Risk identification - Risk management - Risk reduction - Risk review - Severity - Stakeholder - Trend	Consider the inclusion of the missing definitions.
Lonza	422	473	7	It would be helpful to add a definition for formality/informality as it pertains to risk management	Provide definition for formality/informality

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Lonza	422	466	7	"Definitions" Following definitions missing in the draft version of the ICH Q9: Risk evaluation; Risk identification; Risk management; Risk reduction; Risk review; Severity; Stakeholder; Trend. Hazards	Clarify if the definitions are or will be replaced by new terms or are missing from the draft.
Medicines for Europe	422	475	7	Request for clarification why the following definitions were removed?: Risk management Risk reduction Risk review Severity Stakeholder Trend	
LFB BIOMEDICAMENTS	422	422	7	It is proposed to add definition for the term “subjectivity” and “ALCOA principles”	Subjectivity: Discussions and/or decisions taken with neither rationale, nor relevant data, nor scientific knowledge. ALCOA: Principles that ensure data are “Attributable, Legible, Contemporaneous, Original and Accurate”.
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.**"
Medicines for Europe	427	427	7	Incorporate 'harm' in the definition of detectability	"The ability to discover or determine the existence, presence or fact of a hazard **(or harm)**."
Sharon Shutler Genedata	428	429	6	Definition of harm. What about harm to an operation that could impact efficiency and is not related to damage to heath?	Consider a broader definition of harm to accommodate other significant impacts of hazards that are not directly related to health but to the efficiency of a business process.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Gilead Sciences	435	437	7	Consider adding in additional definitions, such as initial risk, residual risk, hazardous situation, hazards analysis, individual risk, and overall risk.	initial risk - evaluation of an identified risk during a risk assessment prior to any implemented controls or in the case of remediation, the current risk level with implemented controls. residual risk - remaining risk level after implementation of demostratively effective risk controls. Hazardous Situation - The scenario where a hazard leads to a forseeable sequence of events resulting in a potential or real life harm. Hazards Analysis - An analysis that includes a list of hazards and their associated level of harm ~~based on clinical data and post-market data of adverse events for any clinical or commercial indication. Preceded by the Preliminary Hazards Analysis (PHA).~~ ~~Individual Risk - Identified risk line item within a Risk Assessment~~ ~~Overall Risk - Summarized qualification of Risk based on the overall evaluation of the Risk Assessment. This Risk is qualitative in nature and provides a recommendation for decision makers if a process or design is at an acceptable risk level for implementation~~ or use.
EIPG	436	438	7	Product Lifecycle in ICH Q10 is defined "including" discontinuation.	Replace "until" with "including" to allign with ICH Q10
EFPIA	439	442	7	The proposed definition of quality is not mentioned in ICHQ6A as suggested by the reference. The definition of quality in ICHQ6A: The suitability of either a drug substance or drug product for its intended use. This term includes such attributes as the identity, strength, and purity.	The degree to which a set of inherent properties of a product, system or process fulfills requirements The suitability of either a product, system or process for its intended use (see ICH Q6A definition specifically for "quality" of drug substance and drug (medicinal) products.)
Medicines for Europe	446	446	7	Alignment with ICH Q10 and the definition	**Pharmaceutical** Quality System
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	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
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."
European Association of Hospital Pharmacists (EAHP)	460	463	7	In the paragraph on the risk assessment the NPR calculation (Severity x Probability x Detectability) should be added.	The proposed change contains the inclusion of the NPR calculation (Severity x Probability x Detectability).
PPTA	464	466	7	Definition of risk-based decision making does not seem to include risk-based decision to determine level of effort, formality and documentation within the QRM process (see lines 303-305). It only focuses on the decision made using output of QRM process.	An approach or process that considers existing knowledge and data to determine the application of QRM process, as well consideration of whether risks are acceptable or not, is needed to make better, more informed and timely decisions.
Takeda	464	466	7	Definition of risk based decision making does not seem to include risk-based decision to determine level of effort, formality and documentation within the QRM process (as described in lines 303-305). It only focuses on the decision made using output of QRM process	An approach or process that considers existing knowledge and data to determine the application of QRM process as well consideration of whether risks are acceptable or not to make better, more informed and timely decisions.
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).

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
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).
EFPIA	475	475		Cosnider reinstating the removed definitons for Risk identification, risk management, risk reduction, risk review, severity, stakeholder, trend.	Add the existing definitions, that were removed
EFPIA	476	476	8	ICH Q12 has as an objective to improve supply by more operational and regulatory flexibility, based on product and process understanding (Q8 (R2) and Q11), Quality Risk Management (ICH Q9) and an effective pharmaceuticeutical quality system (ICH Q10). Since the update of ICH Q9 has now the availability of medicines in scope, it is recommended to mention ICH Q12, see below.	Add ICH Q12 under References
LFB BIOMEDICAMENTS	476	476	8	Reference to ICH Q12 should be added.	ICH Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management.
EFPIA	492	493	9	This is a good article. However, the ICH guideline is not a scientific publication. Thus, references to individual articles, which are state of the art when the revision was established, but not maintained can be misleading after some years.	Consider deleting in the guideline and using for training
EFPIA	507	508	9	This is a good article. However, an ICH guideline is not a scientific publication. Thus, references to individual articles, which are state of the art when the revision was established, but which are not maintained can be misleading after some years.	Consider deleting in the guideline and using for training
EFPIA	509	511	9	This is a good article. However, an ICH guideline is not a scientific publication. Thus, references to individual articles, which are state of the art when the revision was established, but which are not maintained can be misleading after some years.	Consider deleting in the guideline and using for training
Sharon Shutler Genedata	513	513	Annex 1	Consider adding diagrams of methods and tools to give more guidance to inexperienced readers.	Add diagrams to help the reader understand the tools better.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Chartered Institute of Ergonomics & Human Factors. Pharmaceutical Special Interest Group.	513	513		The list of QRM of tools omits critical task analysis tools for human performance and therefore the proposed change is to add in critical task analysis in Annex 1.	Add critical task analysis to Annex 1
EIPG	513	653	I	Risk ananlysis methods and tools	In order to reduce subjectivity, more information or guidance could be provided for each assessment tool on how to define risk scales and on defining acceptance limits.
EFPIA	513	513	Annex I	In support of applying QRM in "design", the proposal is to add New I.9 Layer of Protection (Swiss Cheese Model). Although this is not mentioned in teh concept paper, it may be a valuable concept to elaborate on potentially in the training material.	Layer of Protection (Swiss Cheese Model). This requires evaluation of multiple qualitative factors for each risk. The overall effect based on the layered risk factors that must be in place to realize the risk. The tool involves breaking down each added factors to understand the cumulative effect and qualitative risk. Potential area of uses: Layer of protection can be used to analyzing the existing design, systems, or hazards where layer of protection provides a more extensive understanding of risk to product, process, and facility design. Typically, hazards have to align directly for the risk to be realized (swiss cheese).
Medicines for Europe	513	654	Annex I	"methodology" vs "tools", inconsistent use of terminology; "tools" being the preferrable term to emphazise that competence in using the respective tool, i.e. knowledge on strenghts and weaknesses of the respective tool is required, supplemented by experience. Additionally, it should be explained that the term "failure" should be understood synonymously with the term "hazard", to evaluate risk, also the harm needs to be determined	
Medicines for Europe	518	518	Annex I	Inconsistent use of terminology	"[…] in which a quality risk management **process is initiated**."
Sharon Shutler Genedata	523	523	I.1	Could include a reference to "force field analysis" as this simple tool can be quick to use and extremely effective for decision-making.	Add "force field analysis" to the list.
Sharon Shutler Genedata	529	530	I.1	Maybe add a title for "Quality Risk Management Tools" to differentiate between methods and tools.	Add title "Quality Risk Management Tools"
Chartered Institute of Ergonomics & Human Factors. Pharmaceutical Special Interest Group.	529	529		Consider the addition of an Ishikawa example of human factors to promote causal factor and systems thinking This example will help the Regulation users to understand how to apply human factors and system thinking to risk management.	Consider the addition of an Ishikawa example of human factors to promote causal factor and systems thinking.
Sharon Shutler Genedata	531	531	I.2	Remove "for" after "provides". Basic English grammar.	"FMEA provides an evaluation….."
European Association of Hospital Pharmacists (EAHP)	531	531	Annex I	In relation to Failure Mode Effects Analysis (FMEA) it should be noted that the multidisciplinary team should be involved.	Proposed changes are highlighted in green: "FMEA (see IEC 60812) **is conducted by multidisciplinary teams and** provides for an evaluation of potential failure modes for processes and their likely effect on outcomes and/or product performance."

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Chartered Institute of Ergonomics & Human Factors. Pharmaceutical Special Interest Group.	535	535		The inclusion of Human Reliability Assessments which actively include risk aspects of human interaction within the system. FMEAs can be very process focused and the understanding of 'how work is done' and tacit knowledge can be missed limiting the risk mitigation power of FMEAs and permit repeat non conformances.	The inclusion of Human Reliability Assessments which actively include risk aspects of human interaction within the system
Chartered Institute of Ergonomics & Human Factors. Pharmaceutical Special Interest Group.	535	535		The inclusion of causal and event factors tools would support the use of FMEAs	Supplement FMEA with causal and event factor tools
Sharon Shutler Genedata	539	539	I.2	Can't other tools be used "to prioritize risks and monitor the effectiveness of risk control activities"? This seems a very general statement that is not specific to FMEA.	Consider having a statement that is more specific to FMEA.
Sharon Shutler Genedata	540	540	I.2	Isn't FMEA also applicable for the use of computerised systems and software in regulated environments?	Add a reference to computerised systems / software.
Sharon Shutler Genedata	552	553	I.3	"FMECA application in the pharmaceutical industry should mostly be utilized for failures and risks associated with manufacturing processes" could be changed to "FMECA application should mostly be utilized for failures and risks associated with pharmaceutical manufacturing processes" for better sentence structure.	Change to "FMECA application should mostly be utilized for failures and risks associated with pharmaceutical manufacturing processes"
Sharon Shutler Genedata	609	612	I.7	Change "PHA is a tool of analysis based on applying prior experience or knowledge of a hazard or failure to identify future hazards, hazardous situations and events that might cause harm, as well as to estimate their probability of occurrence for a given activity, facility, product or system." to "PHA is an analysis tool used to apply prior experience or knowledge of a hazard or failure to identify future hazards, hazardous situations and events that might cause harm. PHA is also used to estimate their probability of occurrence for a given activity, facility, product or system." Better sentence structure.	"PHA is an analysis tool used to apply prior experience or knowledge of a hazard or failure to identify future hazards, hazardous situations and events that might cause harm. PHA is also used to estimate their probability of occurrence for a given activity, facility, product or system."
AstraZeneca Pharmaceuticals	654	654	I.9	After 654: Process Quality Risk Assessment: Similar to FMEA - but the focus of the risk assessment is on the Quality, Compliance and Reliability goals the process and/or system is required to achieve (as part of the overall product lifecycle) and then define all the ways we could potentially fail to meet these goals. Advantage: Severity is now very clear as it is framed in terms of not achieving a given Quality / Compliance / Reliability Goal Likelihood is also very clear - what is the probability of a given mode of failure / error that will result in the goal being missed (To the level of Severity Described). We only need to be concerned with failures that may lead to the goal(s) being missed. Detectability - Becomes very valuable we are now looking to detect Either the failure/error OR more importantly the impact to the goal. Plus it is detectability prior to the patient so now allows downstream processes / testing to be considered. It can be used to define requirements for a process / system - what Quality are we trying to achieve in the proposed system, how might we fail to achieve this? and therefore what controls / functionality must we design in to ensure success. This is a very Powerful tool in Quality Risk Management.	
EFPIA	669	669	Annexes	Computer systems and computer controlled equipment: Propose to add an example on digitalization, since digitaliztion has been introduced to the guidance and specifically mentioned (line 40)	Add example on digitalization

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
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;** …
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;
EFPIA	698	698	Annex II.1	Comment: Please consider to cross reference ICHQ12	Proposed change : add "in accordance to ICHQ12
Sharon Shutler Genedata	708	709	II.2	Current title "Quality Risk Management as Part of Regulatory Operations Inspection and assessment activities" could be changed to "Quality Risk Management as Part of Regulatory Inspection and Assessment Activities" as there is no need for the word "operations".	Change title to "Quality Risk Management as Part of Regulatory Inspection and Assessment Activities"
Sharon Shutler Genedata	715	715	II.2	Change "To evaluate information submitted…" to "To evaluate applications and queries submitted…." This avoids the use of the word "information" twice and has a clearer meaning.	Change to "To evaluate applications and queries submitted…"
EFPIA	717	717	Annex II.2	ICH Q12 promotes risk-based approaches for regulatory operations such as risk-based definition of Established Conditions and change categories. It is proposed to mention this here.	To evaluate impact of proposed variations or changes and reflect this in the dossier accordingly to facilitate later life cycle management (see ICH Q12)
EFPIA	741	748	II.4	Clarify how 'zones' should be interpreted in the sentence: 'To determine appropriate zones when designing buildings and facilities' (line 741). It is not clear in relation to the examples in line 742-748.	Provide clarification/correction
Sharon Shutler Genedata	769	769	II.4	Could include a reference to use of artificial intelligence / machine learning to make the list more technologically current.	Include reference to machine learning, artificial intelligence…..
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.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
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.
LFB BIOMEDICAMENTS	775	775	II.4	"Code review" is not clear. Please further for what "code review" stand for.	n/a
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);
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).
Medicines for Europe	819	819	Annex II	Current order of subchapters not properly set up, the preferred arrangement should be to start with CCS , then labelling and finally with secondary packaging	Proposal to re-arrange the order of the subchapters: * Selection of container closure system * Label controls * Design of packages
EIPG	828	855	II.9	"Quality Risk Management as Part of Supply Chain Control"	More level of information in this paragraph (risks related to the GDP, warehousing, transport) could be useful. Importance of risk analysis of backup options in case of equipment fault at manufacturing facilities should be mentioned to assure reliable facility performance.
Lonza	828	855	II.9	"Quality Risk Management as Part of Supply Chain Control" The paragraph seems to focus on the manufacturing only. There is no specific mention to the warehousing/distribution/transportation activities carried out through the supply. GDP requirements, custom clearance, cold chain assurance and transport validation must be probably listed to highlight the risks related to the supply chain.	Suggest to increase the level of information in this paragraph to list the risks related to the Good Distribution Practice, warehousing/distribution/transportation/custom clearance.
EFPIA	828	828	Annex II.9	The term Supply Chain Control is difficult to uunderstand (see also earlier comment)	Proposed change: Update title to "QRM as contributing to shortage prevention or product availability"

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	829	833	Annex II.9	Propose to add Supplier to the sentence	With regard to product availability risks related to quality/manufacturing/**supplier** issues, lifecycle oversight of the supply chain includes maintaining current knowledge of quality/manufacturing hazards and prioritizing efforts to manage such risks.
EFPIA	831	832	Annexes	Propose to remove the sentence as it is mostly redundant and supply predictability and a multifactorial topic	~~Understanding hazards 832 to quality/manufacturing is critical to maintaining supply predictability.~~ When risks to **quality/manufacturing** are well 833 understood and minimized, a higher confidence in product availability can be attained.
EFPIA	833	833	II.9	We should maintain ICH terminology by referencing risk control in the flow chart, and not risk minimisation.	Suggest replacing 'minimized' with '**controlled**'.
EIPG	834	840	II.9	Manufacturing Process Variation and State of Control can better go in Section II.6, Quality Risk Management as part of Production Validation	
Lonza	834	840	II.9	Rows 834 to 840 Manufacturing Process Variation and State of Control may fit in better in Section II.6, Quality Risk Management as part of Production Validation	Consider moving wording to section II.6
EFPIA	834	834	II.9	This should be a sub heading "a)" for better reference and according to ICH terminology	Suggest revising as "a)"
EIPG	841	849	II.9	Manufacturing Facilities can better go in Section II.4 Quality Risk Management of Facility, Equipment & Utilities.	
Lonza	841	849	II.9	Rows 841 to 849, Manufacturing Facilities may fit better in Section II.4 Quality Risk Management of Facility, Equipment & Utilities.	Consider moving wording to section II.4
EFPIA	841	841	II.9	This should be a sub heading "b)" for better reference and according to ICH terminology	Suggest revising as "b)"
EFPIA	842	843	II.9	The point is misleading here, as the design is controlled with the facility (see Annex II.4). The availability of the hazard control is the capacity.	Proposed language: To ensure that facility infrastructure and equipment are suitable **to cover the required amounts** ~~and well-designed~~ for manufacturing and packaging
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;
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.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
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;"
LFB BIOMEDICAMENTS	846	846	II.9	“To ensure that the operational design of equipment is not vulnerable to human error” It is important to highlight this applies to new equipment in place after the revision of ICH Q9 enters into application.	To ensure that the design of **new** equipment is not vulnerable to human error.
PPTA	847	849	II.9	Efficiency gains are made through utilization of digitalization, automation, isolation technology and other innovations. The value of QRM application in this example is not clear. It needs to be clarified that QRM should applied during the design, validation and tech transfer of these innovations. This section should be aligned with lines 40-43.	
Takeda	847	849	II.9	The efficeincy gains are from utilization of digitalization, automation, isolation technology and other innovations. Not clear about value of QRM application in this example. Needs to be clarified that QRM should applied during the design, validation and tech transfer of these innovations. Align with lines 40-43	
EFPIA	847	849	Annexes	The term investing can be misleading in this context. Propose rewording.	The utilization of innovations in manufacturing such as digitalization, automation, isolation technology contributes to efficient and robust manufacturing processes
Sharon Shutler Genedata	850	855	II.9	Could lines 779 to 781 be combined with this section to avoid repetition or vice versa?	Combine information in lines 779 to 781 with this section or vice versa.
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")	
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.
EALTH	855	855		ICH Q9 is a reference for GDP also and there is no decription concerning risk management and supply chain considering distribution	We recommend that an example should be introduced for this part of the chain