<Date of submission>

Submission of comments on

Revision of Good Manufacturing Practice (GMP) Guidelines Chapter 1 (Pharmaceutical Quality System)

Please note that these comments and the identity of the sender will be published unless a specific justified objection is received.
*When completed, this form should be sent to the European Medicines Agency via the EU survey, in Excel format **(not PDF)**.*
Columns A to E should mandatorily be filled in prior to completing the columns "Comment" and "Rationale" and/or "Proposed wording".
For more details on how to use this template please refer to the tab "Manual for commenter" below.

Country	Organisation raising comment (if no organisation, name of individual)	Line from	Line to	Comment (only one topic per comment) (max 600 characters)	Rationale (must be included when proposing a change) (max 600 characters)	Proposed wording (must be included when proposing a change) (max 600 characters)
USA	ISPE	0	0	**Genera 1:** ISPE recommends moving the section on Quality Risk Management (QRM) into the Pharmaceutical Quality System section as point 1.2 of the Pharmaceutical Quality system section. Reference should be made to ICH Q0 (R1) in Part III of EudraLex - Volume 4 - Good Manufacturing Practice (GMP) guidelines.	QRM is a key enabler of a PQS as described in ICH Q10 and has been introduced early in the Principles section (lines 1 to 3). By including QRM early, referencing ICH Q9 (R1) and including appropriate wording there is no need to repeat refereence to QRM in later parts of Chapter 1.	Please move the section on QRM to be point 1.2 in the PQS section and include reference to ICH Q9 (R1) in Part III of EudraLex - Volume 4 - Good Manufacturing Practice (GMP) guidelines. Please include appropriate wording that QRM applies to many activities described later in Chapter 1 as being part of a PQS.
USA	ISPE	0	0	**General 2.** ISPE recommends that detailed descriptions of QRM processes are NOT included in Chapter 1. A high level reference to key elements of QRM such as Formality, Subjectivity, Risk-Based Decision Making and application of QRM to Product Availability is considered appropriate, however, detailed discussion is given in Q9(R1).	Repetition of details of QRM processes in Chapter 1, and other Chapters and Annexes of EudraLex - Volume 4 - Good Manufacturing Practice (GMP) guidelines has the strong potential over time to differences in wording between Chapter 1 and ICH Q9(R1) and consequently difficulties of interpretation by stakeholders. A good example is given in lines 4 to 6 where the wording is unclear and different from that in ICH Q9(R1) - see comment below.	ISPE recommends removing sections 1.15, 1.16 and 1.17 of the QRM section and ~~replacing a~~ introooducing a sentence summarising and referring to topics on "Formality, Subjectivity, Risk-based Decision Making since they are are important considerations when conducting a QRM exercise.
USA	ISPE	0	0	**General 3.** In line with the comments in the rows above, ISPE recommmends that specific references to QRM, particularly any detail concerning QRM are removed from sections after its suggested introduction as section 1.2 of the PQS.	ISPE requests that all clauses referring to QRM are included in a dedicated section in Chapter 1 to PQS with appropriate references to ICH Q9 (R1). ISPE received many comments requesting clarification and changes to lines 9 to10, and 11 to 14, which have not been included in this response. A potentially major consequence of different language in Chapter 1 to that in ICH Q9(R1) is ISPE's specific comment on lines 15 to 17.	ISPE recommends that references to QRM should be deleted in: lines 9 and 10 lines 11 to 14 and lines 15 to 17 lines 65 to 74
USA	ISPE	4	5	Introduction of "quality/manufacturing risk" may cause confusion.	Wording should align with that in ICH Q9(R1), which is "...addressing product availability risks arising from quality/manufacturing issues." It may lead to scope creep and uncertainty around the terms quality risk vs. manufacturing risk as these are not defined and may be interpreted very differently.	~~"risk to product quality and availability, when availability risks arise from quality/manufacturing issues"~~ ISPE recommends revised text. "The use of risk-based drug shortage prevention and mitigation activities with respect to ~~product quality/manufacturing risks~~ risks arising from quality/manufacturing issues should be considered. (See also Chapter 5 for 5 guidance in relation to product shortages due to manufacturing constraints.)"
USA	ISPE	15	17	"(v) External product availability risks relating to quality/manufacturing, (e.g., from raw material suppliers, contracted organisations, service providers, etc.) are adequately managed" refers to outsourced activities	This clause refers to outsourced activities and the issue of application of QRM to outsourced activities should be discussed in Chapter 7, Outsourced activities rather than Chapter 1.	~~External availability products should be considered in relation with chapter 7 outsourcing activities.~~ Please delete lines 15 to 17.
USA	ISPE	24	31	Deviations during non-production periods are more likely to be facility/equipment related, not product-specific. Reviewing previous PQR without new manufacturing data may not provide additional quality insights.	It ~~makes sense~~ is appropriate to perform PQR and review topics which can generate new data despite no manufacturing, such as customer complaints, recalls and stability results. However, the limited scope of new data for the period without manufactured products does not provide sufficient context to warrant formal review of last PQR, and review of relevant deviations, since deviations in the period may not be product-specific.	In cases where no batches of a product were manufactured during the 12-month review period, the product quality review should still be performed; this should address at least the following: stability results, returns, complaints, recalls, and regulatory background (e.g. marketing authorisation variations submitted, granted or refused, including those for third country (export only) dossiers, and any relevant post-marketing commitments). A review of follow ups and proposed actions from the last product quality review should also be conducted.

USA	ISPE	36	45	~~Quality reviews ……..is not considere acceptable~~ This paragraphe could be simplified. do not need to be extended, with information on products containing same API…. To group products by types. We suggest just adding the possibility for API	this section could be simplified using less wording and less description on HOW to od the work.	Quality reviews may be grouped by product type, e.g. solid dosage forms, liquid dosage forms, sterile products, products containing the same (or similar) active substances, processes. Any such groupings should be appropriately justified. *Delete the rest of the paragraph.*
USA	ISPE	46	49	ISPE recommends that the new text "and agreed strategies (e.g. product groupings)" should be deleted	~~No need to extenc the requirement which are described in the chapter 7 outsourced activities.~~ The original wording is sufficient. If additional information is required it should be included in Chapter 7, Outsourced activities. ~~This section should be considered with the chapter 7 oursourced activities which requires a contract between the companies.~~ ~~The process description should follow QRM ICH Q9 flow .~~	Where the marketing authorisation holder is not the manufacturer, there should be a technical agreement in place between the various parties that defines their respective responsibilities and agreed strategies (Chapter 7) ~~(e.g. product groupings)~~ in producing the product quality review.
USA	ISPE	53	57	~~We suggest~~ ISPE recommends removing this clause.	This clause introduces too many concepts and is too specific for Chapter 1 . If required it should be considered for inclusion ~~All this clause 1.13 shoudl takes place in the chapter 5 for production and~~ in Chapter 6 Quality control. ~~These points are too speciifc to be part of the PQS~~.	ISPE recommends deleting the clause ~~1.13 Product quality should be assured based on appropriate risk-based decision-making throughout the product lifecycle, such that the attributes that are important to the quality of the medicinal product are maintained and the product remains safe and effective. In this regard, knowledge should be used to make informed decisions, trigger re-evaluations and stimulate continual improvement.~~
USA	ISPE	61	64	(Note: Risk to quality includes situations where product availability may be impacted, leading to potential patient harm. Each site in the manufacturing supply chain and distribution for a medicinal product should manage, within its area of responsibility, any manufacturing / quality risks that could impact upon product availability.) The last sentence should be deleted.	~~For better clarity we suggest removing the last sentence of the clause in brackets it's remove clarity to the ICH document.~~ The last sentence is not in ICHQ9(R1) and is hard to interpret. The term "manage within its area of responsibility" is not defined and hard to interpret. This comment should be considered alongside our comment above relating to lines 15 to 15, section (v),.	(Note: Risk to quality includes situations where product availability may be impacted, leading to potential patient harm. ~~Each site in the manufacturing supply chain and distribution for a medicinal product should manage, within its area of responsibility, any manufacturing / quality risks that could impact upon product availability.~~)

