

7 October 2025

Submission of  
comments on

Chapter 4

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	<p><b>General Comment 1;</b> Chapter 4 is part of Part I Eudralex Volume 4 and should be read in conjunction with the other Chapters in Part 1, and other Parts of Eudralex Volume 4.</p> <p>ISPE recommends that Quality Risk Management (QRM) is discussed in the Principles section and reference given to Volume 4, Parts I and III. QRM applies to many pharmaceutical operations. ISPE recommends it is not discussed in detail in other sections of Chapter 4 unless there are very specific QRM issues relevant to that section.</p>	<p>Attempting to repeat requirements of other parts of Volume 4 of the GMPs has the strong potential over time to lead to inconsistencies between the documents.</p> <p>QRM is mandatory for all pharmaceutical activities, for more clarity we suggest discussing use of QRM only in the Principles of the document and reduce as much as possible references to QRM in the clauses.</p>	<p>We suggest not discussing PQS, QRM and computerised systems in individual clauses in Chapter 4. Reference to PQS, QRM and computerised systems in other documents could be given in the Principles section. Additionally any discussion of computerised systems should focus the content only on WHAT for computerised systems.</p>
USA	ISPE	0	0	<p><b>General Comment 1; (continued):</b> ISPE suggests that types of documents and their definitions in the "Master Documents" section are examples of documents for which references should be given to other Chapters and Annexes of Volume 4.</p>	As above	<p>We suggest for a better clarity discussing QRM only in the Principles section with a requirement explaining all documentation has to be prepared and managed based on quality risk management. No other discussion of QRM should be required in the document as QRM applies to all Chapters and Annexes of Volume 4. QRM is clarified in part III of Eudralex vol 4 in ICH Q9.</p> <p>ISPE suggests the following additions relevant to QRM are included in the Principles section</p> <p><b>Add to 4.6 : "The degree of formality applied to documentation practices shall be commensurate with the level of risk, uncertainty and complexity. Higher-risk activities require more structured controls; lower-risk activities may be managed with less formality, provided data integrity and compliance are maintained."</b></p> <p><b>Add to 4.8: "Regulated users should apply structured risk assessment tools and involve cross-functional teams to support consistent, science-based decisions for documentation controls."</b></p>

USA	ISPE	7	7	The Principle section is an introduction to Chapter 4. We suggest having in this part of the document high-level considerations, avoiding too detailed a description which is currently proposed in the different sections of the document or in other Parts of Eudralex Volume 4.	Attempting to repeat requirements of other parts of Chapter 4 or Volume 4 has the strong potential over time to lead to inconsistencies between the documents or texts. The Principles section should concentrate on the high level WHATs of requirements and not contain detail which could be in other sections of Chapter 4 or in other PARTS of Eudralex Volume 4.	We suggest keeping in this document few clauses not describing HOW to do actions just covering WHAT is intended as applying for the Chapter 4 in Eudralex Volume 4. Examples are: 4.2, 4.3, 4.4, 4.5. 4.6 and 4.7 are considered too detailed for a Principles section. and should be edited or deleted as recommended in comments below.
USA	ISPE	12	13	We suggest removing reference to <i>technology</i> from 4.2. Alternative text is suggested.	Legal provision for documentation does not rely on the <b>technology</b> .	We suggest removing the reference to the word <i>technology</i> from the sentence: 4.2. "It should be determined by the regulated user which legal provisions apply to documentation <del>considering new technologies, hybrid solutions and services used.</del> "
USA	ISPE	19	31	We suggest for a better clarity referring to QRM only in the Principles section with a requirement explaining all documentation has to be prepared and managed based on QRM. No other discussion of QRM should be included in the document as QRM applies to all sections of Chapter 4.. Reference could be made to QRM as being in part III of Eudralex vol 4 as ICH Q9 R1. The text in sections 4.5 to 4.9 is considered to be included in Chapter 1, Pharmaceutical Quality System, PQS. We suggest not explaining requirements of a PQS in Chapter 4. These requirements are fully discussed in Chapter 1 of PART 1, Volume 4 of the GMP's and ICH Q10 in part III. We suggest leaving the different subjects in their respective chapters.	QRM applies to pharmaceutical industry as described in ICH Q9 and requirements are included in Chapter 1. We suggest not having the requirements in different wording described in different GMP guidances where there is great potential for divergence or inconsistencies over time.	We suggest removing clauses 4.4; 4.5; 4.6; 4.7; We consider all these clauses too detailed for the Principles section of the Document. The Principles section should require a robust QRM system and refer to ICHQ9 R(1). 4.5 as well is too detailed and is covered in Chapter 1 of Eudralex Volume 4, Part. I We do not see the need to repeat Chapter 1 in Chapter 4.
USA	ISPE	36	39	We also suggest removing the clause 4.9 from the Principles section. Limiting to two primary types of documentation is too prescriptive for all situations.	This point is too detailed for Principle section .	We suggest removing all of clause 4.9 from the Principles section. This point is too detailed.
USA	ISPE	41	78	ISPE suggests that data governance systems discussion summarises the high-level principle that it is important; however, it should not include details of HOW to operate data governance, nor include details of QRM activities relevant to this topic.	We suggest this clause does not describe in too much detail HOW to manage the data governance as the technologies are evolving quickly.	<b>We suggest summarising the Data Governance Systems section in one clause.</b> <b>"Data governance is required for all data and documents during the whole life cycle."</b> <b>We suggest deleting all other text in Sections 4.10 through 4.18.</b>
USA	ISPE	79	91	We recommend removing this section from Chapter 4. Risk Management is a requirement.	HOW to implement QRM in a proactive way is defined in ICH Q9 R (1) and supporting training material plus in several Industry guidances.  Further rationale is given in General Comment 1 above	We suggest removing clauses 4.19; 4.20; 4.21; 4.22 We suggest for this section just a reference to Chapter 1 and Part III (ICH Q9R(1)) of Eudralex Volume 4 is required.
USA	ISPE	93	110	We suggest removing this section from Chapter 4. All the requirements are developed in the Chapter 1 or covered by Annex 11 and Annex 22.	Rationale is given in General Comment 1, and other comments above.	We suggest having just one clause to require that all automatic review systems should remain under control and should be validated. All the generated data have to comply with the GMP's.
USA	ISPE	111	111	The title of this section is inappropriate as all these documents are not "MASTERS"	"Master" is not an appropriate word for all the documents listed.	Replace "Master Documents" with " <b>Details for Document Types</b> "
USA	ISPE	112	146	Specifically required master documents (not exhaustive list):	As this list is not exhaustive we suggest including definitions in the glossary for any document not included elsewhere in Volume 4. For those documents described in other Chapters or Annexes, we recommend that reference should be given. Please refer to ICH documents and glossaries where this referencing system is applied.	Documents not described in other Chapters and Annexes of Volume 4 should be defined in the glossary.

USA	ISPE	147	336	Most of these documentation types are described in many other documents related to Pharmaceutical industry, and Pharmacopoeia, for example in the Chapters 1, 5; 6; 7. 9.	We suggest not describing in detail the content of the different documents which could change following evolution of ICH in other Chapters and Annexes of Volume 4. Many of these documents are included in Chapter 1, Chapter 5, Chapter 6 GDP and do not need to be duplicated in this chapter 4. We strongly recommend not duplicating the same information in different parts of the Eudralex vol 4 part 1 and Annexes. If needed the list and content of all documents as per Site Master file could be a separate guidance included in Part III of Eudralex Volume 4.	We suggest removing the documents list and definitions from this section and including them in a guidance/document which could take place in the Part III of Volume 4.  Clauses 4.46 and 4.47 are already described by other GMP Chapters. These requirements are already covered in the Part 1 Eudralex Volume 4, Chapters 1, 5, 6, and 7
USA	ISPE	338	338	At the WHAT level, <b>Generation and Control of Documentation</b> is not connected to the technology. The requirement for documentation generation and control is described in Chapter 1. We suggest not creating a description of this section in Chapter 4. We suggest removing this section which is redundant with Chapter 1.	For Good Documentation practices, we suggest having a summary description, which is an initial chapter, such as the Principles chapter. We suggest not making Chapter 4 a standalone document disconnected from the documents in other chapters of Part 1. The requirement for management and control of documentation is already included in Chapter 1.	ISPE suggests this section is deleted and summary text placed in the Principles section.
USA	ISPE	339	347	All text in section 4.49 is not clear and understandable.	Clause 4.49 seems unclear and should be improved for better understanding.	If the section on " <i>Generation and Control of Documentation</i> " is not completely deleted, we suggest that 4.49 is amended using the following proposal: <b>"All types of document regardless of technology used, should remain stable. Management of approval, and distribution of documents should include QRM principles (Chapter 1 Eudralex Volume 4). Master Documents should be controlled and copies of a master for use should be reviewed to the copying process validated to avoid missing information following the copying process."</b>
USA	ISPE	348	353	Documents should be designed, prepared, reviewed, and distributed in a controlled manner. They should comply with the relevant parts of Product Specification Files, Manufacturing and Marketing Authorisation dossiers, or dossiers of Investigational Medicinal Products, as appropriate. ....	This clause is already addressed in Chapter 1 of Eudralex Volume 4. We recommend not duplicating in different Chapters the same requirement with different wording.	If the section on "Generation and Control of Documentation" is not completely deleted, we suggest for this clause to refer to Chapter 1 clause 1.8 only.
USA	ISPE	354	371	Document reviews and change control are addressed in Chapter 1.	We suggest not duplicating the same information in different ways across different chapters of the Part 1 Eudralex Volume 4 and Annexes.	We suggest removing these clauses from the document.
USA	ISPE	380	381	As written, this clause suggests each copy needs to be verified.	Verifying individual copies is time and resource intensive and potentially prone to failure. Using a validated process instead would ensure every copy is accurate.	Propose: " <b>A validated process should be used to create a true copy of data</b> ". For hybrid or manual systems verification is needed.
USA	ISPE	385	387	We suggest changing "alteration" to "change" and removing "where appropriate". In GMP every change has to be recorded.	In GMP documentation, traceability and accountability are important. Recording the reason for any change should be mandatory to ensure data integrity and compliance. The phrase "where appropriate" introduces uncertainty. Furthermore, "alteration" could be interpreted in various ways; a clear definition would help ensure consistent application across regulated users.	ISPE suggests the following revised text: Any <del>alteration</del> <b>change</b> made to the entry on a document should be signed by the individual who made the change and dated; the <del>alteration</del> <b>change</b> should permit the reading of the original information. <del>Where appropriate,</del> the reason for the <del>alteration</del> <b>change</b> should be recorded.
USA	ISPE	391	399	4.62 Controls for issuance and reconciliation are a prime area for a risk-based approach. Master forms that directly impact the product could be controlled differently based on a risk-based approach compared with forms that have a lower quality of the product.	Controls for issuance and reconciliation are a prime area for a risk-based approach.	ISPE suggests text is revised as: 4.62 Specific controls should be implemented to ensure the integrity of raw data and results recorded on paper <b>using a risk-based approach. These may include, but are not limited to:</b> Consider deleting lines 393-399 letters i through iv as these are too detailed and prescriptive.

USA	ISPE	403	404	On Page 11, Table 1: The Data integrity principles table states, in the "Original" row, that "Information that is originally captured in a dynamic state should remain available in that state." Although this may be true in many cases, this is not always possible, feasible, or practical.	For long term archiving (for instance) conversion to a static format may be acceptable if the GxP content and meaning is preserved, the requirements of wider (predicate) GMP are met, and the ability of the regulated company to meet regulatory and statutory obligations is preserved. This is consistent with the discussion in the "Available" row of Table 1: The Data integrity principles.	ISPE proposes adding additional text to the "Original" row of the table such as in bold below: The original record can be described as the first capture of information, whether recorded on pa-per (static) or electronically (usually dynamic, depending on the complexity of the system). Information that is originally captured in a dynamic state should remain available in that state <b>or preserved by a means that ensures that content and meaning is preserved, the requirements of wider (predicate) GMP are met, and the ability of the regulated company to meet regulatory and statutory obligations is ensured.</b>
USA	ISPE	408	410	Section 4.65 The requirement to sign "with date and time" in line 409 appears to apply generally, but <b>time</b> is typically only required for electronic signatures, not for handwritten (wet) signatures.  The sentence "If signatures by initials are in use..." could benefit from further clarification regarding the scope and conditions under which initials may be used instead of full signatures.	In GMP practice, handwritten signatures are usually accompanied by the date, but not the time. Requiring both date and time for all types of signatures may lead to confusion. Clarification is needed to distinguish between electronic and wet signatures.  Clarifying the acceptable use of initials helps ensure consistent interpretation and application across different types of GMP-relevant documentation.	Original Text: 4.65. A signature represents the legally binding will of the signatory. The signatory should sign with date and time. If signatures by initials are in use a procedure defining abbreviated signatures should be in place.  <b>ISPE proposes modifying the text as follows:</b> 4.65. A signature represents the legally binding will of the signatory. The signatory should sign with date and time <b>where applicable (e.g. for electronic signatures)</b> . If signatures by initials are in use, a <b>documented</b> procedure defining abbreviated signatures should be in place, <b>including conditions for their use and the types of documents and circumstances where abbreviated signatures may be considered appropriate.</b>
USA	ISPE	422	425	Section 4.70 states that electronic records should be signed electronically and that the use of hybrid systems should be avoided. However, this does not reflect current technological practice and raises questions about the definition and handling of hybrid systems.	Avoiding hybrid systems entirely is not aligned with current practice, where hybrid systems are often necessary and accepted under controlled conditions. If electronic records must be signed electronically, it is unclear what constitutes a hybrid system, especially if wet signatures are no longer permitted on paper copies of electronic records. Clarification is needed on whether hybrid systems are prohibited or allowed under specific controls, and how signatures should be handled in such cases.	Section 4.70 should be changed to: <b>"Electronic records should be signed electronically. If hybrid systems are used, where records exist in both paper and electronic formats, the regulated user must define which signature is regulatory relevant and ensure appropriate controls are in place."</b>
USA	ISPE	473	488	Sections 4.80 and 4.81 appear repetitive and conceptually overlap with the ALCOA++ principles already outlined in section 4.63 and Table 1. Their placement may be reconsidered.	The content in 4.80–4.81 reiterates core elements of data integrity, such as lifecycle control, risk-based measures, and human factor considerations, which are already covered under ALCOA++ principles. To improve clarity and avoid redundancy, these points could be integrated into or referenced from the ALCOA++ section, which serves as the conceptual foundation for data integrity.	Consider merging the content of 4.80–4.81 with section 4.63/Table 1 on Data integrity principles, or alternatively, move it to an introductory part of the data integrity section to avoid duplication.
USA	ISPE	489	502	ISPE recommends that risk-based acceptance criteria and interface controls are applied to hybrid systems.	Clear criteria and validated interfaces ensure appropriate management and data integrity in hybrid environments.	ISPE suggests adding a section 4.86: <b>"Hybrid systems shall be evaluated against documented, risk-based acceptability criteria. Interfaces between manual and electronic components must be validated and controlled to ensure data integrity and compliance."</b>

USA	ISPE	503	503	We suggest including in the glossary several terms found in the document	ISPE suggests consideration should be given to developing definitions for the following terms:  Raw Data vs Initial Data. Generated data Derived data Masters Documents	none
USA	ISPE	510	510	The term "Automated script" is listed in the glossary but is not mentioned or explained in the main text of the document.	Without any reference in the main chapters, it remains unclear how automated scripts should be used, controlled, validated, or documented in a GMP environment.	Clarification is requested on how automated scripts are to be addressed within the pharmaceutical quality system and whether further guidance should be included in the main text.
USA	ISPE	513	516	The glossary definition of "Data governance" appears incomplete and should be reviewed for consistency with the ALCOA++ principles.	The definition lists several ALCOA++ attributes (e.g. attributable, legible, contemporaneous, original, accurate, complete, consistent, enduring, available), but "traceable" is missing. This may lead to confusion or misinterpretation of the full scope of data governance requirements.	Clarification and completion of the definition is requested to ensure all ALCOA++ attributes are included, including "traceable".
USA	ISPE	517	520	The glossary definition of "Data integrity" could be reviewed to ensure it includes all ALCOA++ attributes as outlined in Table 1.	The current definition mentions several ALCOA++ attributes but omits others that are listed in Table 1, such as "complete", "consistent", "enduring", "available" and "traceable". Including all attributes would improve consistency and support a harmonised understanding of data integrity expectations.	ISPE Suggests replacing the text with: <b>"Data integrity refers to the completeness, consistency, and accuracy of data. Data should be attributable, legible, contemporaneously recorded, original or a true copy, accurate, complete, consistent, enduring, available and traceable (ALCOA++)."</b>
USA	ISPE	532	536	"Data Risk Assessment" appears twice in glossary: in lines 532-536 and line 589.	The glossary includes "Data Risk Assessment" on both page 15 (lines 532-536) and again on page 17 (line 589). This redundancy may cause confusion and should be corrected for clarity and consistency.	Consider removing the second occurrence of "Data Risk Assessment" on page 17 (line 536) to avoid duplication.
USA	ISPE	550	552	Document A formatted compilation of data. Operations and activities that are memorialized in (electronic) records may consist of one or more documents that describe the activity in a moment of time.	This is a confusing and possibly inaccurate description of a document in what appears to be the context of use within the draft guideline. It is not clear whether the draft definition means a discrete electronic file or paper document or if this means records in a database - which could also be considered "formatted", or both. This would lead to misinterpretations about intent or applicability of the guideline.	ISPE has suggested some text for consideration. There are dictionary definitions of "document", which should also be considered: <b>"Unstructured compiled data in single file format e.g. PDF, .docx report, created from a master electronic template, such as a report, Instructions (directions, or requirements). A document typically reviewed/approved either via electronic signature or hand-written signature on paper."</b>
USA	ISPE	566	566	Definition states that "Information that is originally captured in a dynamic state should remain available in that state." Although this may be true in many cases, this is not always possible, feasible, or practical.	For long term archiving (for instance) conversion to a static format may be acceptable if the GxP content and meaning is preserved, the requirements of wider (predicate) GMP are met, and the ability of the regulated company to meet regulatory and statutory obligations is preserved. This is consistent with the discussion in the "Available" row of Table 1: Data integrity principles.	ISPE Proposes adding: "Information that is originally captured in a dynamic state should remain available in that state, <b>or preserved by a means that ensures that content and meaning are preserved, the requirements of wider (predicate) GMP are met, and the ability of the regulated company to meet regulatory and statutory obligations is ensured.</b> "
END						