



25 July 2025

**International Society for Pharmaceutical Engineering (ISPE)**

Worldwide Headquarters  
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**Submission of comments on : ICH Q1: Stability Testing of Drug Substances and Drug Products-Step 2 Document**

*STABILITY TESTING OF DRUG SUBSTANCES AND DRUG PRODUCTS*

*Q1*

*Please note that these comments and the identity of the sender will be published unless a specific justified objection is received.*

*When completed, this form should be sent to the European Medicines Agency electronically, in Excel format (not PDF), to the following address:*

[ICH@ema.europa.eu](mailto:ICH@ema.europa.eu)

*All the cells with an asterisk (\*) should be filled in prior to completing the columns "Comment and rationale" and/or "Proposed changes / recommendation".*

*For more details on how to use this template please refer to the tab "Manual for commenter".*

Name of organisation or individual*	Line from* (line Nr or 0 for general comment)	Line to* (line Nr or 0 for general comment)	Section number	Comment and rationale (to go to next line within the same cell use Alt + Enter)	Proposed changes / recommendation (if applicable - to be used if you want to propose specific text changes)
International Society for Pharmaceutical Engineering (ISPE)	0	0	General	ISPE considers that the ICH Q1 revision draft document, Stability Testing of Drug Substances and Drug Product is very well written and comprehensive document, fulfilling the consolidation of the various ICH Q1 guidelines into one guideline. It is repetitive at times, but that is expected as many readers will 'jump' to the section that they believe is applicable to their application.	None
International Society for Pharmaceutical Engineering (ISPE)	0	0	General	Throughout the document, various advisory terms such as "strongly suggested," "recommended," and "should" (including variations like "should generally") are used inconsistently and without clear definition. It would be helpful to clarify whether there is an intended hierarchy or standardized interpretation of these terms. Additionally, it is unclear whether all users would have a common understanding of these terms.	Consider including a discussion of these terms in Section 1.3, Introduction to Guideline and General Principles.

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International Society for Pharmaceutical Engineering (ISPE)	0	0	General	ISPE suggests that references to Good Manufacturing Practice (GMP) topics should be removed from this guideline. ICH Q1 should be focused on scientific and technical guidance on stability testing. Inclusion of GMP-related content may lead to confusion regarding the scope and regulatory expectations, and such topics are more appropriately addressed in GMP-specific guidelines.	References to GMP-related requirements should be removed from this guideline to maintain clarity of scope. For example, the requirement outlined in lines 599–604 regarding the maintenance and monitoring of chamber temperatures falls under GMP expectations and is more appropriately addressed in GMP-specific guidance. Alternatively, this guideline should clarify that these studies are documented in the pharmaceutical quality system (PQS) and are not included in the dossier. Similarly, hold time studies for synthetic drug substance and drug products (Section 9), especially for synthetic drug substances, are considered GMP as stated in the guideline in lines 855 to 859.
International Society for Pharmaceutical Engineering (ISPE)	0	0	General	While the intent of the revised guideline appears to be to address both standard and alternative approaches to stability, the main body of the text predominantly focuses on standard approaches. In contrast, alternative approaches are primarily discussed in the annex. To reflect the evolving landscape of stability science and to support broader implementation of innovative strategies, it may be beneficial to include at least a brief section within the main guideline that introduces and acknowledges alternative approaches. This would help reinforce their legitimacy and encourage their thoughtful application within the framework of regulatory expectations.	ISPE recommends adding a short paragraph at the end of section 1 to introduce the 'Alternative' approach. A section could also be included in Section 15 on how development batches could be used for commitments and product lifecycle management.
International Society for Pharmaceutical Engineering (ISPE)	0	0	General	To support the core objective of ICH—harmonization of technical requirements across regions—it may be beneficial to remove statements that reference region-specific requirements, such as the one noted on line 1600. Including such references within the main body of an ICH guideline can create ambiguity and potentially lead to inconsistent implementation. Instead, maintaining a focus on globally harmonized principles, while allowing regional specifics to be addressed through local regulatory channels, would help ensure clarity, reduce complexity for global development programs, and promote consistent regulatory expectations.	ISPE suggests the removal of references to regional requirements and harmonize the requirements.

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International Society for Pharmaceutical Engineering (ISPE)	222	224	2.3	The current wording may be interpreted as suggesting that data not supporting the proposed label claim should be excluded from the submission. If that is not the intended message, it may be helpful to clarify the intent to avoid potential misinterpretation and ensure transparency in data reporting.	<p>ISPE suggests removing the sentence <i>"Data from development studies under stress condition should be included in regulatory submissions if they support a claim on the product labelling."</i></p> <p>and amend the previous sentence as follows:</p> <p><b>"Although forced degradation and stress studies are not part of the formal stability studies, results from the forced degradation and stress studies are an integral part of the information provided to regulatory authorities (e.g., support analytical procedure validation, product characterisation, specifications or packaging considerations)."</b></p>

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International Society for Pharmaceutical Engineering (ISPE)	304	308	3.2	<p>The current language stating that “for biological drug substances and drug products, data from three primary batches that cover the duration of the proposed shelf life should be submitted unless an alternative approach is justified” may be interpreted as requiring real-time data covering the full proposed shelf life. This appears to be inconsistent with the information in Table 1 and principles outlined in Section 13.2.9 (line 1453), which allows for limited shelf-life extrapolation for biologics under certain conditions.</p> <p>The language on lines 306–308 appears to imply a requirement to submit six months of stability data from commercial-scale batches when the primary stability batches are not at production scale. This interpretation may introduce a new expectation for biologics, as current ICH Q1A(R2) guidance allows for such data to be provided post-approval as a commitment. Requiring this data at the time of initial submission could have significant implications for registration timelines.</p> <p>Furthermore, this expectation seems to be inconsistent with Section 4, “Selection of Batches” (lines 445–449), which states that primary stability batches should be representative or comparable, rather than strictly produced at commercial scale. Clarification on this point would help ensure alignment across the guideline and avoid unintended shifts in regulatory expectations. To avoid potential misinterpretation, it may be helpful to simplify this statement. This would support clearer alignment across the guideline and facilitate consistent interpretation of the expectations for stability data submission in an application.</p>	<p>ISPE suggests deleting "that cover the duration of the shelf life: as given below:</p> <p>For biological drug substances and drug products, data from three primary batches <del>that cover the duration of the proposed shelf life</del> should be submitted unless an alternative approach is justified. When these primary batches are not production scale, a minimum of 6 months of data from production batches should also be submitted to support the evaluation of the regulatory submission.</p>
International Society for Pharmaceutical Engineering (ISPE)	324	326	3.2	<p>Table 1 contains a significant amount of detail, including numerous footnotes, which may make it challenging to interpret at a glance. Consider simplifying the presentation or streamlining the footnotes to enhance clarity and usability for readers. <del>See comments on Lines 304–308 and footnote 6. These should be aligned.</del></p> <p>Table 1 footnote 3 should also be applied to biologics.</p> <p>In summary, the text in lines 304 to 308 (see the comment above) should be aligned with Table 1.</p>	<p>Please add footnote 3 to bottom right cell before footnote 7.</p>

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International Society for Pharmaceutical Engineering (ISPE)	423	425	3.6	The statement that the shelf life for integrated drug-device combination products should be based on the shorter of either the constituent part or the final assembled product may benefit from further clarification. This approach appears inconsistent with how drug substances are typically managed in small molecule drug products, where the drug substance can be used up to the end of its retest period prior to incorporation into the final product. Clarifying the intent and scope of this requirement—particularly in relation to established practices for drug substance use—would help ensure consistent interpretation and application across product types. Suggested text is in the field to the right.	ISPE suggests modifying the text as given below:  <b>For integrated device-drug products, the shelf life should be based on the final combination of a drug product with a medical device.</b>
International Society for Pharmaceutical Engineering (ISPE)	473	473	4.1	In Table 2, under considerations for drug product primary batches, it may be helpful to allow for greater flexibility in container closure system requirements. Specifically, minor differences—such as the use of bulk stoppers versus ready-to-sterilize stoppers, or variations in supplier where there is no change to the contact material—could be considered acceptable without impacting the representativeness of the batch. Including this clarification would support practical implementation while maintaining product quality and comparability.	ISPE suggests the addition in bold: "Same container closure system as proposed for marketing <b>or comparable.</b> "
International Society for Pharmaceutical Engineering (ISPE)	485	486		The expectation to include a comparison of batch data—understood to refer to batch release data rather than stability data—between primary batches and those from each production site in the initial regulatory submission appears to represent a new requirement for non-sterile synthetic chemical entity drug substances. Clarification on this point would be helpful to ensure consistent interpretation and alignment with established regulatory practices. ISPE proposes rationale for selection of stability batches is given in the stability discussion section of a dossier. The current text creates impression that comparison data should be stability rather than release data.	ISPE suggests deleting "For synthetic chemical entities, a comparison of batch data of the primary batches with data from each production site should be provided in the regulatory submission."

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International Society for Pharmaceutical Engineering (ISPE)	547	557		The language in line 550 suggests a requirement for monthly testing for the first 3 months, which may not be scientifically justified or operationally necessary in all cases. We recommend revising this to allow for a risk-based, product-specific approach.	ISPE recommends amending the first sentence to: <b>"For primary stability studies, the frequency of testing should be scientifically justified and sufficient to establish the stability profile of the drug substance or drug product, taking into account the nature of the product and its intended storage conditions"</b> .
International Society for Pharmaceutical Engineering (ISPE)	854	913	9.1-9.2	Section 9 is intended to clarify when data should be included in a regulatory submission versus when it may be managed within the Pharmaceutical Quality System (PQS). However, this distinction is not clearly articulated in the current draft guidance.	Specifically, for synthetic chemical entity drug substance intermediates, ISPE strongly recommends that the text explicitly state that holding times may be fully managed within the PQS and do not require inclusion in the regulatory submission. Clear guidance on this point would support consistent interpretation and efficient regulatory submissions.
International Society for Pharmaceutical Engineering (ISPE)	892	892	Introduction	Consider including a sentence in line 892. Example to the right.	ISPE recommends including a sentence in line 892 after the introductory sentence <b>"Data from and design of stability studies for synthetic drug substance intermediates are managed in the pharmaceutical quality system and not included in a submission."</b>
International Society for Pharmaceutical Engineering (ISPE)	900	904	9.2	Clarification is requested regarding how/when these data are managed. ISPE recommends amending the text, example to the right.	ISPE recommends that these data are held in the pharmaceutical quality system. ISPE recommends amending the text to: <b>"..... that is representative of that for marketing, the storage period or transportation arrangements, should be included in the pharmaceutical quality system."</b>

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International Society for Pharmaceutical Engineering (ISPE)	1087	1088	12.1	<p>The statement that stability data for biological reference materials are “generally provided with the regulatory submission” may not reflect current practices for vaccines and other biopharmaceuticals, where such data are typically managed within the control strategy and not routinely included in the initial submission.</p> <p>As currently worded, this statement could be interpreted as establishing a new expectation, potentially leading to a requirement for inclusion of this data in future registrations. Clarification would be helpful to ensure alignment with established regulatory practices and avoid unintended implications.</p>	<p>ISPE recommends that the statement "These data are generally provided with the regulatory submission for biologicals and managed within the pharmaceutical quality system (PQS) for synthetics."</p> <p>is changed to <b>"These data are generally managed within the pharmaceutical quality system (PQS)".</b></p>
International Society for Pharmaceutical Engineering (ISPE)	1153	1160	13.1	<p>The statement suggesting that biologics are precluded from modeling using accelerated conditions due to “inherent differences” may unintentionally imply that biologics are excluded from all forms of enhanced modeling, including approaches based on prior knowledge or Bayesian methods. Given the current structure of the section, this could lead to misinterpretation. It may be helpful to clarify that while certain accelerated conditions may not be appropriate for biologics, other scientifically justified modeling approaches remain applicable and should not be excluded. ISPE considers that all modalities could be suitable for modeling.</p>	<p>ISPE recommends the following deletion of the sentence starting in line 1157 "For biologicals, the decision tree approach, which is based on the extent of attribute change at accelerated storage conditions, is not considered suitable due to the inherent differences in degradation mechanisms and other structure/function differences within biologicals."</p> <p>and replacing with a new bullet</p> <p><b>" * For biologicals, while certain accelerated conditions may not be appropriate, other scientifically justified modeling approaches remain applicable and should not be excluded"</b></p>
International Society for Pharmaceutical Engineering (ISPE)	1546	1547	13.3.2	<p>The current wording may be interpreted to suggest that stability models are expected to be maintained after regulatory submission. However, this is not standard practice, nor is it typically required. The sentence may benefit from further clarification. ISPE recommends referring to Annex 2 - Stability Modelling, Section 2.7 – Risk Management and Model Lifecycle Considerations and allow flexible approaches to model management based on need.</p>	<p>ISPE recommends amending the sentence in lines 1546 to 1547 to:</p> <p><b>"After model selection and implementation, Annex 2 - Stability Modelling, Section 2.7 – Risk Management and Model Lifecycle Considerations provides guidance on management of the lifecycle on the model, if required."</b></p>

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International Society for Pharmaceutical Engineering (ISPE)	2171	2173	A1-3.3.3	ISPE suggests updating this sentence to clarify that reductions in stability protocols may also be applicable to primary stability studies (for initial shelf-life setting), in cases where an enhanced stability understanding can be demonstrated based on a science- and risk-based approach.	ISPE suggests changing "Primary" to "Formal" as : ' <u>Reductions from the Formal Stability Protocol:</u> Based on overall product knowledge.....'
International Society for Pharmaceutical Engineering (ISPE)	2294	2295	A2-1.1	<p>It appears that the wrong graph is presented in line 2294 to 2295 and this should be replaced by the one sided acceptance criteria.</p> <p>Example, Figure 2.2, The text 'Shelf Life Estimation with Upper and Lower Acceptance Criteria' on line 2294 and the Figure on line 2295 (which is a duplicate of Figure A2-1) should be removed and replaced by reference to Figure A2.2 since the text refers to impurity degradation.</p>	ISPE recommends removing the text "Shelf Life Estimation with Upper and Lower Acceptance Criteria' on line 2294, and remove the Figure on line 2295. It should be replaced by reference to " Figure: A2- 2: Shelf Life Estimation with Upper Acceptance Criterion"
International Society for Pharmaceutical Engineering (ISPE)	2451	2453	A2-2.2.1	<p>The reference to "prior knowledge" in lines 2451–2453 may benefit from further clarification, as the term currently appears broad and could be interpreted to include data from both prior batches of the same product and from analogous products. This level of ambiguity may place a significant burden on sponsors to justify the relevance and acceptability of the data submitted as prior knowledge, potentially leading to inconsistent expectations across regulatory agencies.</p> <p>To support consistent interpretation and implementation, it may be helpful to include a few illustrative examples that clarify the types and sources of prior knowledge considered acceptable, as well as the level of supporting evidence expected. This would also help mitigate the risk of divergent regulatory decisions, which could complicate global stability strategies for sponsors.</p>	<p>ISPE recommends that the sentence in line 2451 to 2453 is modified as follows:</p> <p>"Prior knowledge, <b>which from a statistical perspective could include historical data based on similar compounds, modeling using Bayesian techniques and Frequentist 'pool-and-test' strategies, dataset and knowledge from previous filings</b> may be incorporated into the stability model evaluation in different ways, for example, to establish an acceptable range for the attribute stability profile, or by using Bayesian statistics."</p>