Final Concept Paper

Targeted Revisions of the ICH Stability Guideline Series (Guidelines ICH Q1A-F, ICH Q5C)

Endorsed by the Management Committee on 15 November 2022

Type of Harmonisation Action Proposed

Revision of the ICH Stability Guideline Series Q1A-F and Q5C is recommended to a) streamline the series by combining the various guidelines into a single guideline focused on core stability principles; b) promote harmonised interpretation by addressing potential gaps and areas of ambiguity; c) address additional technical issues, including relevant stability strategies and innovative tools that strengthen the application of risk management; and d) consider inclusion of new topics, such as stability considerations for advanced therapies. The informal working group proposes to establish these updates through the Revision procedure. The envisioned result is a combined guideline, ICH Q1, with integrated annexes and/or appendices that address specific topics beyond the core principles on stability recommendations and to address product type[1] specific recommendations, as required. It is also recommended to update and supplement current training material.

Statement of the Perceived Problem:

Further to a comprehensive assessment of existing Quality guidelines and in consideration of potential future topics, ICH's Quality Discussion Group (QDG) issued the report to the ICH Management Committee entitled "Future Opportunities & Modernization of ICH Quality Guidelines: Implementation of the ICH Quality Vision from the ICH Quality Reflection Paper", which was subsequently published on the ICH website in October 2021. Maintenance of the Q1/Q5C Stability guideline series was determined as one of the highest priorities based on the evaluation and recommendations from the QDG.

As written, ICH Q1A-E (plus content of the withdrawn ICH Q1F currently covered by WHO) and ICH Q5C do not align with the format of more recently developed ICH guidelines that embrace a harmonised core document approach supported by topic-specific annexes/appendices. The individual guideline approach leads to interpretation of the guidelines on an individual basis, with uncertainty around how they should work together. ICH Q5C, for example, is specific to stability of biotechnological/biological products and it is often unclear which chapters of the ICH Q1 series apply to biologics as well.

Furthermore, the stability guidelines do not reflect modern analytical technologies and tools. Incorporation of guidance that addresses the use of stability modelling and risk management could enable earlier patient access to high quality medicines. Additionally, the current guidelines do not address stability considerations for advanced and emerging product types[1].

[1] Product type refers to all aspects of the drug product, including drug substance, intermediates, and devices.

Issues to be Resolved:

The Expert Working Group will aim to address the following identified issues:

- Consistency of interpretation:
    - Through reorganisation into a core guideline with topic-specific annexes/appendices, the update will clarify which parts of the guideline apply to which product types.
    - Improve harmonisation by clarifying perceived ambiguities within the current guideline.

- Clarification of technical components of current guideline and stability-related concepts; may include but not limited to:
    - Combine common/overlapping principles and expand on items specific for Drug Substances (DS)/Intermediates/Drug Products (DP).
    - Additional products not comprehensively covered by the existing ICH stability guidelines to be considered can include Cell and Gene Therapy Products / Advanced Therapy Medicinal Products (ATMPs), Oligonucleotides, Peptides, Generics, Biosimilars, New products developed from approved active substances, Vaccines, Plasma-derived products, and regulated over the counter (OTC) products. As part of this consideration, certain stability concepts (e.g., retest date) may not be applicable to all product types.
    - Data and evaluation strategies for defining the retest period/shelf-life (DS) (align with ICH Q7) and shelf-life (DP).
    - Baseline considerations in designing a stability protocol (e.g., storage temperatures/%RH/study timepoints, stability-indicating methods, Climatic Zones III and IV (former ICH Q1F guideline).
    - Container Closure System: packaging configurations on stability; related conditions for drug and drug-device combination products.
    - Photostability: testing expectations, relevant testing conditions and applicability
    - The practical use of bracketing and/or matrixing.
    - For compatibility studies, consideration for microbial testing and compatibility with drug delivery systems (e.g., infusion bags, pumps, syringes, in-line filters and tubing).
    - Clarification of how in-use stability and container closure integrity studies are conducted (i.e., in-use stability vs. open dish/worst case stability and container closure integrity (CCI) testing in lieu of sterility, including multidose containers).
    - Clarity on in-use/end user storage conditions (storage of drug product as supplied), including multidose containers.
    - Expectations for products requiring preparation prior to use (e.g., [re]constitution or dilution, mixing with other media).
    - Excipient (when applicable) and adjuvant stability considerations.
    - Clarity on application of antimicrobial effectiveness testing (AET) on stability.
    - Update of the current glossary to define the new topics and terms.
    - Clarify the difference and intent of studies under accelerated and stressed stability conditions, as well as forced degradation studies.
    - Stability profiling of reference materials/standards when applicable.
    - Acceptance criteria for stability testing versus release testing.

  - Analytical procedure validation aspects including stress testing conditions to demonstrate the stability-indicating ability of the test method, algorithms used (to align with ICH Q2 and Q14).
  - Clarity on the determination of water loss calculations when used in place of storage of the drug product at low humidity conditions for semi-permeable containers.

- Address new technologies and modern tools/strategies used as part of enhanced product understanding:
  - Modelling techniques, criteria for selection of batches, applicability, and caveats/limitations.
  - Expectations for statistical approaches and potential for Artificial Intelligence modelling methodologies.
  - Expectations for the justification of appropriate studies to determine shelf life for drug products and retest date/shelf life for drug substances.
  - Advances in understanding accelerated stability conditions and prior knowledge which may support extrapolation.
  - Use of risk management to define appropriate stability strategies.
  - Importance of justifying the product-specific stability test conditions and methods in the stability protocol.
  - Ensure consistency with (or refer to) the ICH Q13 discussion of stability considerations for continuous manufacturing.

- Pharmaceutical Quality System (PQS) related stability topics:
  - Stability related considerations through the product supply chain (e.g., excursions during storage and transportation, freeze-thaw cycle stability).
  - Stability related considerations related to processing and hold-time studies during manufacture.
  - Stability approaches for manufacturing of DS and/or DP at multiple manufacturing sites.
  - Considerations of Out of Specification (OOS), Out of Trend (OOT) and significant change for stability data, and expectations for trending within the PQS.

- Clarify applicability of requirements across development and lifecycle:
  - Application of an integrated, science and risk-based approach to stability.
  - Labelled storage statements/recommendations (e.g., in-use periods, temperature conditions).
  - Common filing considerations, e.g., stability protocol/report; minimum data sets.
  - Consider and clarify applicability of phase specific stability throughout the different stages of product development.
  - Address how concepts should be applied to address product lifecycle/post-approval. changes (risk-based approaches based on change) and ensure consistency with ICH Q12 principles.

- Training strategies and alignment with other guidelines
  - Development of training materials related to the guideline updates with a focus on new content.
  - Development of case studies.

Background to the Proposal:

The original Q1A guideline (reaching Step 4 in 1993) was one of the first guidelines to be finalised at ICH. In the early 2000s, the parent Stability guideline had undergone a revision process and several further guidelines were developed and finalised. Multiple ICH guidelines in the Q1 series had been endorsed as 'supplementing guidance' and were given the sub-letters, i.e., Q1B, Q1C etc. These individual guidelines were intended as 'subchapters' of the "parent" Q1A(R2) stability guideline. This was done in the 1990s and in the early 2000s to build on initial achievements of harmonisation and avoid potentially reopening a section or a guideline where consensus was already achieved. ICH Q5C was later written to address the biotech/biological aspects of stability. ICH Q1F was later withdrawn in June 2006 and the aspects of stability testing in Climatic Zones III and IV were referenced to the WHO guideline 'Annex 10, Technical Report Series, 1010, 2018' since at that time the ICH Regions resided in Climatic Zones I and II. With more recently developed ICH guidelines, beginning with ICH Q7 and through Q14, ICH guidelines typically bear a single number and incorporate a broader array of topics as structured annexes/addenda.

The ICH Q1 series (Q1A-Q1E) as a Tier 1 guideline, ICH Q5C, and the WHO stability guidance covering Climatic Zones III and IV (i.e., content of the withdrawn ICH Q1F) are implemented successfully in the regulatory framework by most regulatory authorities. However, experience gained with the implementation since the finalisation of these guidelines shows uncertainties related to the interpretation of the individual guidelines and how they fit together. Furthermore, it is recognized that innovation in analytical testing including approaches as described in ICH Q2 and ICH Q14 along with the development of control strategies (ICH Q8 and Q11), Quality Risk Management principles (ICH Q9) and lifecycle approaches (as addressed in ICH Q10 and ICH Q12) create additional uncertainty for industry and regulatory agencies regarding how these pieces contribute to the assessment of product stability. This results in technical issues regarding stability that should be addressed to harmonise approaches and expectations during product development and regulatory review and inspections.

Type of Expert Working Group Recommended:

The EWG should include regulators and industry representatives with background and expertise in either (or both) the technical and regulatory aspects of pharmaceutical stability. Representatives should comprise expertise in Chemistry, Manufacturing and Controls (CMC), Good Manufacturing Practices (GMP), API/drug substance, drug product, small and large molecules, statistics, and predictive modelling. The EWG should also include experts in Cell and Gene Therapy/ATMP product types to help add this topic in the revised guidance.

Timing:

It is proposed that this work is initiated in Q4 calendar year 2022, following finalisation of the Concept Paper and Business Plan and establishment of an Expert Working Group. It is anticipated that the development of an ICH Q1 guideline using the concepts outlined in ICH Q1A-Q1E, WHO-Stability (Q1F) and ICH Q5C guideline could reach *Step 1* two years after initiation of an EWG and *Step 4* in the year after that. Training materials will be initiated during *Step 3* and available after *Step 4*.

- Q4 calendar year 2022 - Final Concept Paper, Business Plan
- Q4 calendar year 2024 – Complete *Step 1*
- Q4 calendar year 2025 – Complete *Step 4*