



Navigating the Updates Related to the ICH Q1 Stability Guideline Revision

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Disclaimer

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Background on Revision

Revision of the ICH Stability Guideline Series Q1A-F and Q5C was recommended to:

- Streamline the series by combining the various guidelines into a single guideline focused on core stability principles;
- Promote harmonised interpretation by addressing potential gaps and areas of ambiguity;
- Address additional technical issues, including relevant stability strategies and innovative tools that strengthen the application of risk management;
- Consider inclusion of new topics, such as stability considerations for advanced therapies.

The result will be a combined guideline, ICH Q1, with integrated annexes that address specific topics beyond the core principles on stability recommendations and to address product type specific recommendations.

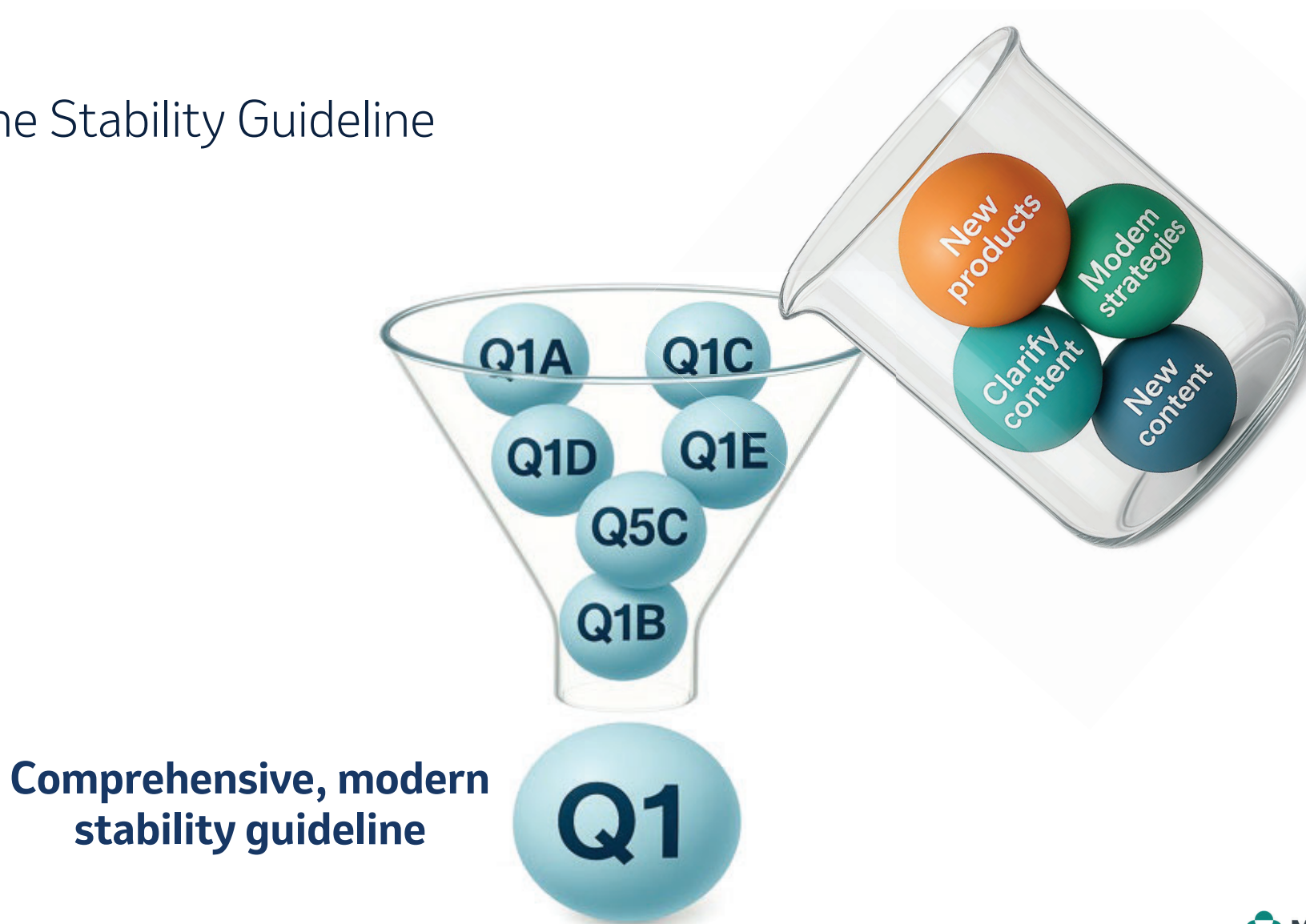
Final Concept Paper
Targeted Revisions of the ICH Stability Guideline Series
(Guidelines ICH Q1A-F, ICH Q5C)
Endorsed by the Management Committee on 15 November 2022



Q1 Step 2 Presentation

Note: ICH Q1 currently in Step 3 draft and may change prior to implementation.

All-in-One Stability Guideline



Enhancements in Q1 Revision

- Alignment on comprehensive scope of products
- Alignment on core principles for drug substance and drug product stability
- Sections to clarify expectations on current content in Q1 series and Q5C (photostability, data evaluation, storage conditions and testing frequency, etc.)
- Expanded guidance for various concepts, such as data evaluation, reduced protocol designs, stressed/forced degradation studies, glossary, etc.



ICH Q1: Stability Testing for Drug Substances and Drug Products

ICH Q1 Step 2 Draft Guideline - Table of Contents

1. Introduction
2. Development Stability Studies Under Stress and Forced Conditions
3. Protocol Design for Formal Stability Studies
4. Selection of Batches
5. Container Closure System
6. Testing Frequency
7. Storage Conditions
8. Photostability
9. Stability Considerations for Processing and Holding Times for Intermediates
10. Short-Term Storage Conditions
11. In-Use Stability
12. Reference Materials, Novel Excipients and Adjuvants
13. Data Evaluation
14. Labelling
15. Stability Considerations for Commitments and Product Lifecycle Management
16. Glossary
17. References
18. Annexes
 - Annex 1: Reduced Stability Protocol Design
 - Annex 2: Stability Modelling
 - Annex 3: Stability of Advanced Therapy Medicinal Products (ATMPs)

9

New Content

- Hold times for intermediates
- Short-term storage conditions (in label)
- In-use studies
- Clarify expectations for reference materials, novel excipients, and adjuvants
- Labeling and storage statements
- Stability commitments and expectations for post-approval changes (lifecycle)
- New Annex 2 for general principles and guidance on using enhanced stability modeling
- New Annex 3 for ATMPs

Short-term Storage Conditions vs In-Use Studies

Each appears on labeling, if implemented

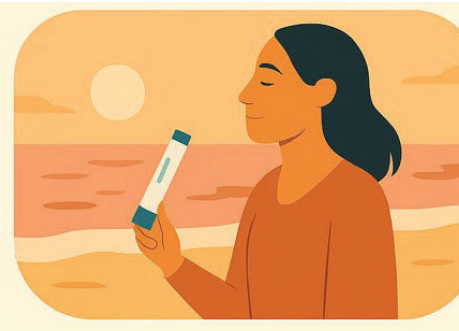
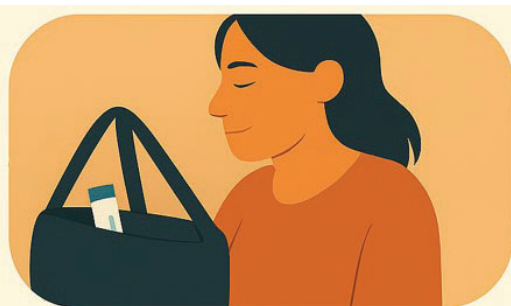
- Instructions
- Conditions
- Duration

Short-term storage- primary container closure is not breached and can be held for a prescribed duration as detailed on label

- Specific short-term storage condition stability study with considerations on number of batches, impact at end of DP shelf life, climactic zones, etc.

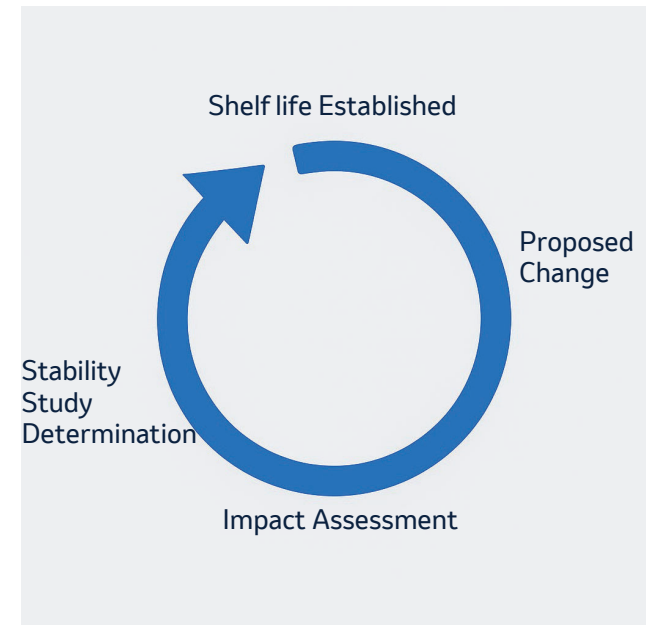
In-use storage- primary container closure is breached, prepared and stored prior to patient administration as detailed on label

- In-use stability study with considerations on handling and preparation, extent of storage prior to use, multi-dose preparations, environmental factors, etc.



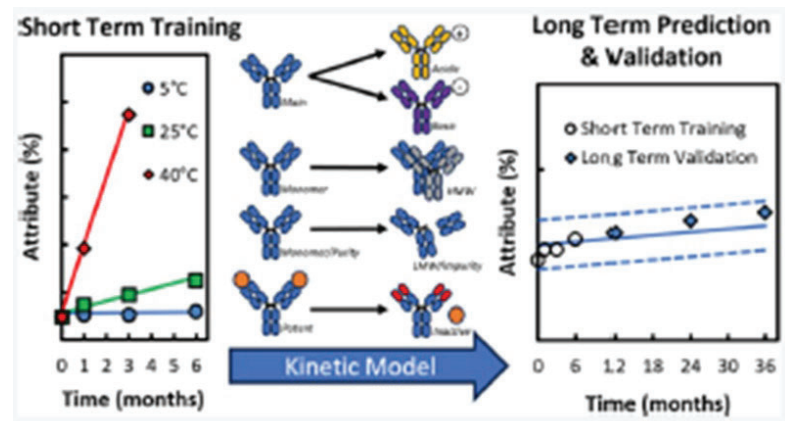
Stability Commitments for Lifecycle Management

- Commitment stability studies
 - Including ongoing stability studies (annual)
- Product Lifecycle Stability Studies
 - Post-approval change scenarios to determine if new stability studies maybe needed
- Recommendations for stability studies for new dosage forms and strengths/concentrations



New Annex 2 Stability Modeling

- General principles and core study design elements for modelling
- Part 1: Statistical tools and models commonly used to assess stability data
 - Evaluation of variability between batches in single factor and multi-factor designs
 - Linear models to assess stability profile (mixed and fixed effects models)
- Part 2: Enhanced stability models for shelf life evaluation
 - General principles for model development, selection of data and parameters for model construct, evaluation of the model, risk management and life cycle considerations



Dillon, M et al. Predicting the Long-Term Stability of Biologics with Short-Term Data. *Molecular Pharmaceutics*. 2024.

Considerations for Enhanced Stability Modelling



Statistical and Scientific Justifications for setting shelf life based on the model output



Well-characterized biological drug substances and drug products with a well understood stability profile



Model Validation to determine the suitability of a model by challenging it with independent test data and comparing the results against predetermined performance criteria



Model Verification to ensure the model is implemented as intended. Confirmation that the modelled data for the initially proposed shelf life or re-test period are comparable to on-going primary stability study data



Post-approval on-going stability studies to verify shelf life and model

New For Biologicals

- Start of shelf-life definition
- Process hold times/Intermediates
- Primary stability batch considerations (representative of production)
 - Same cell production system
 - Comparable to production (ICH Q5E)
 - Same container closure system
 - Same fill volume (unless reduced protocol design- Annex 1)



New For Well-Characterized Biologicals

- Well-characterized and well understood stability profile:
 - Retest period for frozen DS
 - Little or no change over time
 - Establish retest period and then test and immediately use
- Extrapolation
 - Frozen DS- 1.5x long term PSS data (not more than 12 months)
 - DP- justification with potential impact patient safety and efficacy
- Modeling to extend shelf life beyond real-time data (predictive modeling)

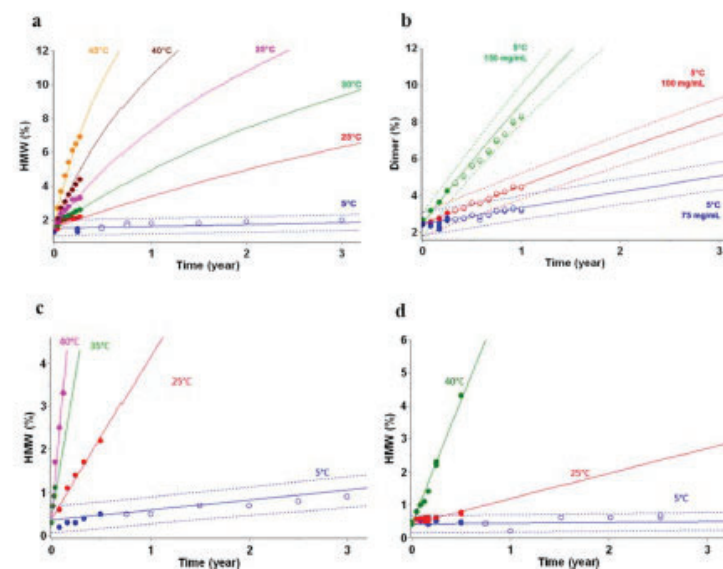


Figure 2. Kinetic modeling of aggregation of biopharmaceuticals—Stability predictions for several bioproducts—(a) HMW (mAb B1), (b) dimer (Single variable domain B7), (c) HMW (Fusion protein B10), (d) HMW (mAb B11). Data points (filled circles) from 5 °C to 45 °C used to build kinetic models overlaid with predictions (solid lines). The prediction is shown as predictive band representing the 95% PB (dotted lines). Additional stability data (open circles), not used to build the models, are displayed as verification of the stability predictions.

M. Huelsmeyer *et al.* A universal tool for stability predictions of biopharmaceuticals, vaccines, and in vitro diagnostic products. *Scientific Reports*. 13 (2023)

New Annex 3 Stability of Advanced Therapy Medicinal Products (ATMPs)

- ATMPs- complex biological products, including somatic cell therapies, gene therapies, tissue-engineered products, etc.
- Additional information specific for ATMPs (used in conjunction with core)
- Study design considerations:
 - Short-term stability (days/months)
 - Patient-specific and/or small batch size
 - Unique temperatures (cryopreserved or warm)
 - Physical force effects
 - Product-specific stability attributes
 - Starting material impact



Summary

- Harmonization of requirements across global health authorities
- Clear guidance on a comprehensive approach to stability studies for global submissions
- One ICH Q1 core guideline applicable to most types of marketed products
- Enables science- and risk-based approaches to potentially shorten time to submission and time to market
- Updated content for clarity on requirements for biologicals and ATMP products





Thank you