ICH Q1s/5C Revision - Opportunities in Science and Risk-based Testing Approaches for Biologics

CMC Strategy Forum Japan, Dec 9, 2025

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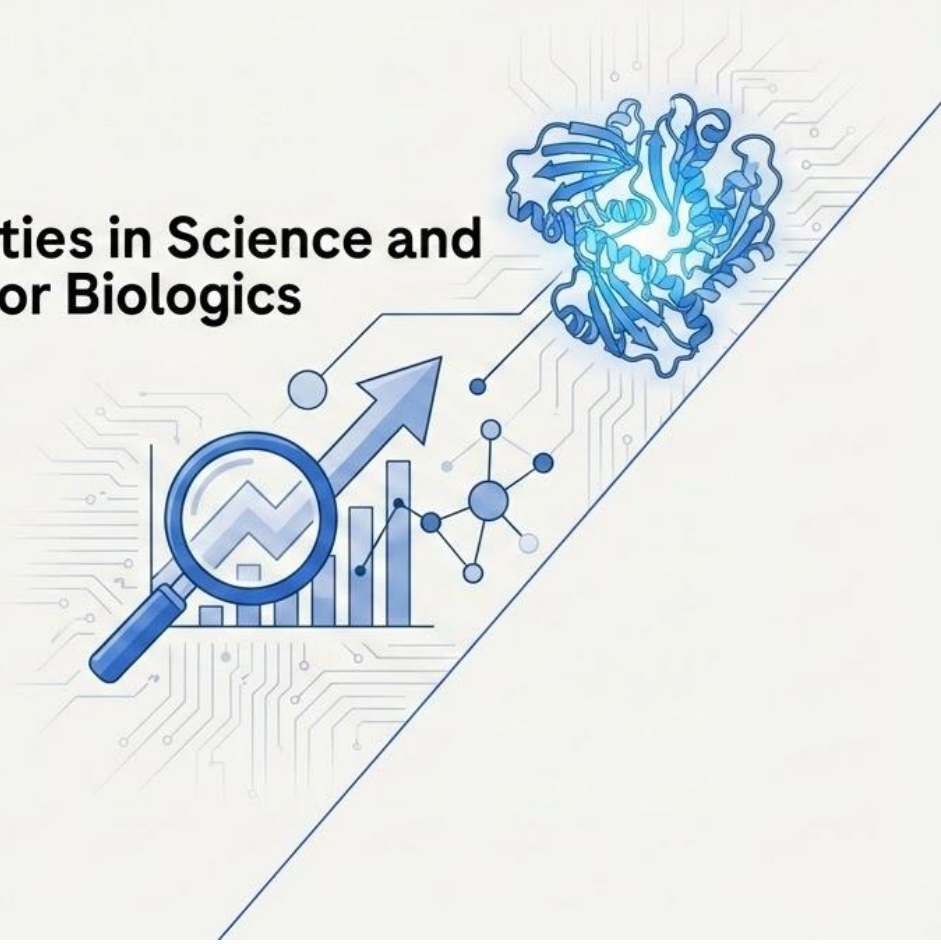

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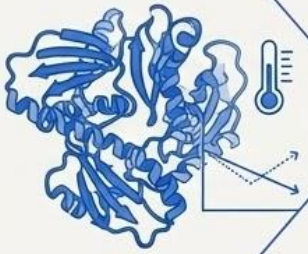

Science and risked-based approaches: Progress in ICH Q1

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times “science and risk-based” / “risk based”

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

Endorsed by the Management Committee on 15 November 2022

- Clarify applicability of requirements across development and lifecycle:
  - Application of an **integrated, science and risk-based approach** to stability.
  - 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.

ICH Q1 step 2 technical document - science and risk-based opportunities

*** 1: INTRODUCTION** [2]

Outline the stability data expectations, scope (synthetic and biological products), and general principles, including how stability testing establishes a re-test period or shelf life.

*** 2: DEVELOPMENT STABILITY STUDIES UNDER STRESS AND FORCED CONDITIONS** [1]

Describes studies used to gain product knowledge, characterize physical/chemical/biological changes, establish intrinsic stability, confirm analytical procedure validation, and inform specifications.

*** 3: PROTOCOL DESIGN FOR FORMAL STABILITY STUDIES** [1]

Provides guidance on establishing a formal stability stability study protocol, including general principles, stability-indicating critical quality attributes (CQAs), specifications, and additional considerations for vaccines/combination products.

*** 4: SELECTION OF BATCHES** [5]

Details the requirements and considerations for selecting primary stability batches, including minimum number of batches and special considerations for multiple production sites, vaccines, and continuous manufacturing.

*** 5: CONTAINER CLOSURE SYSTEM** [0]

Discusses the considerations for the container closure system (primary and secondary packaging) used in stability studies, ensuring its protection, compatibility, and functionality over the product's shelf life.

*** 6: TESTING FREQUENCY** [0]

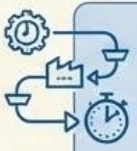
Provides recommendations on the frequency of testing for primary stability studies under long-term, accelerated, and intermediate storage conditions to establish the stability profile.

*** 7: STORAGE CONDITIONS** [0]

Specifies the long-term, intermediate, and accelerated storage conditions for different climatic zones and product types (room temperature, refrigerated, frozen) and considerations for impermeable/semi-

*** 8: PHOTOSTABILITY** [2]

Addresses the principles for evaluating photostabiiity, including forced pholodegradation and confirmatory studies, to ensure light exposure doesn't compromise product efficacy or safety.



*** 9: STABILITY CONSIDERATIONS FOR PROCESSING AND HOLDING TIMES FOR INTERMEDIATES** [1]

Details how to establish maximum processing and holding times for drug substance and drug product intermediates to ensure their quality and prevent deleterious effects on subsequent processing.

ICH Q1 step 2 technical document - science and risk-based opportunities (continued)

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*** 10: SHORT-TERM STORAGE CONDITIONS [0]**

Discusses stability studies to support a specified short-term storage condition on the label, different from long-term storage or in-use periods, for patient convenience.

*** 11: IN-USE STABILITY [2]**

Describes the principles for establishing the in-use period and storage conditions after the primary container is breached, mimicking the intended use for single-dose or multi-dose products.

*** 12: REFERENCE MATERIALS, NOVEL EXCIPIENTS AND ADJUVANTS [1]**

Covers stability considerations for reference materials, novel excipients, and vaccine adjuvants due to their potential impact on drug product quality.

*** 13: DATA EVALUATION [0]**

Focuses on the systematic evaluation of stability data, including statistical methods and extrapolation principles, to establish a re-test period or shelf life.

*** 14: LABELLING [1]**

Provides guidance on establishing storage statements and expiration/re-test dates on the product labelling, including considerations for excursions outside the labelled storage conditions.

*** 15: STABILITY CONSIDERATIONS FOR COMMITMENTS AND PRODUCT LIFECYCLE MANAGEMENT [1]**

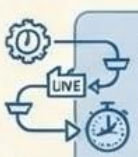
Addresses stability studies conducted to confirm initial proposals (commitment studies), monitor marketed products (ongoing studies), and support post-approval changes and new dosage forms.

*** ANNEX 1: REDUCED STABILITY PROTOCOL DESIGN [4]**

Addresses recommendations for applying reduced stability protocol designs, such as bracketing and matrixing, when warranted by product stability knowledge.

*** ANNEX 2: STABILITY MODELLING [1]**

Provides additional and specific recommendations on statistical tools and models (e.g., linear models, mixed effects models, enhanced modelling) for supporting extrapolation and enhanced stability modelling approaches.



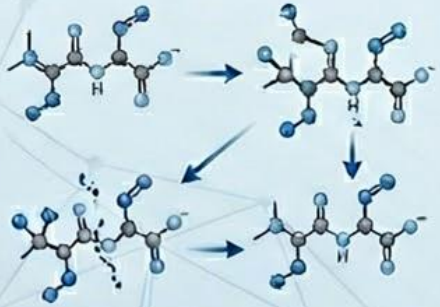
*** ANNEX 3: STABILITY OF ADVANCED THERAPY MEDICINAL PRODUCTS (ATMPs) [5]**

Provides unique recommendations for designing stability studies for ATMPs, accounting for their complex nature, small batch size challenges, and general reliance on real-time data.

Keep the Biologics Stable

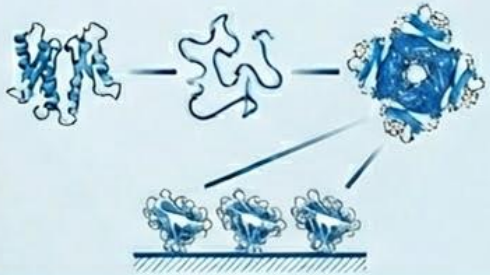
Chemical Instabilities

- **Deamidation**
- **Oxidation**: most commonly methionine tryptophan
- **Fragmentation**
- **Isomerization**: Asp to iso-Asp



Physical Instabilities

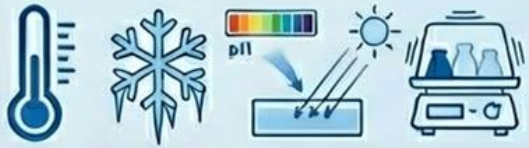
- **Aggregation:** dimers, trimers, and higher-order aggregates - major concern for immunogenicity
- **Denaturation/Unfolding**: unfavorable environmental conditions (e.g., thermal stress).
- **Adsorption**: reduces the effective concentration of the therapeutic product.
- **Precipitation:** visible, insoluble particles



Environmental Stress Factors

These instabilities are often accelerated by unfavorable storage conditions:

- **Temperature:** High temperatures accelerate both chemical degradation and physical unfolding/aggregation. Conversely, repeated freeze-thaw cycles can induce aggregation aggregation due to stresses like ice-water interfaces and solute concentration in freeze-concentrates.
- **pH and Buffer Composition**
- **Light Exposure**
- **Mechanical Stress** (Shear/Agitation)



The Stability Risks Landscape and it's Complexity

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Industry - Patient Needs, Supply & Brand Risk

Real-time data mandate is a major roadblock to market access of new products and robust and non-complex supply to patient for post-approval products.

Deficiencies may lead to risk realization:

- Product Recalls
- Patient Harm
- Reputational & Financial Loss

Product - Technical & Scientific Risk

Accelerated data alone is insufficient for complex molecules, leading to inaccurate predictions of long-term behavior.

- Inaccurate Extrapolation
- Uncertainty in CQAs like purity, aggregation level, and fragment formation under actual storage conditions.
- Process/Package Failure

Health Authorities - Patient Concerns & Efficacy Risk

The absence of real-time data leads to an inability to confirm that the product remains safe and effective throughout its proposed shelf life.

- Loss of Potency
- Safety Hazards
- Incorrect Dosing

Evolution of Biologics Stability Strategy: From Risk to Knowledge

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1.

2.

Risk reduction options

- Enhanced development approach
- Additional data
- Platform knowledge

Risk Reduction Options (Enhanced Approach)

development approach | Additional data | Platform knowledge

"Tribal knowledge" Biologics

3. Acceptable risks for stability?

- ❑ Limited data
- ❑ Reduced study design
- ❑ Both

Limited data; commit to generate foundational stability data post approval - VERIFY SCIENCE

Limited data + reduced design; based on foundational stability data - FULLY BENEFIT FROM SCIENCE

Case Study: IgG1 Monoclonal Antibody in Pre-filled Syringe

Stability Data Available at Initial Market Authorization (IMA) Submission

Product: IgG1 Monoclonal Antibody

Container: Pre-filled Syringe

Proposed Shelf Life: 24 Months

Storage Condition: 2 to 8C (Refrigerated)

The Regulatory Challenge

The submission includes data from three pivotal commercial-scale batches (primary batches) manufactured processes representative for the final process (compatibility according Q5E demonstrated).

Initial Problem: The data technically only supports a 12-month shelf life for Batches 2 and 3.

Claim/Justification Required: The manufacturer must provide a strong, science and risk-based justification to claim the full 24-month shelf life based on the success of Batch 1 and the predictive power of supplementary data and platform knowledge.

Batch Status vs. Proposed Shelf Life (24M)

Claim: Grant the 24-month shelf life.

Justification:

1. Favorable Real-Time Data & Extrapolation

- **Batch 1 Success:** Meets all CQAs (Potency, Aggregation, Purity) at 24 months.
- **Consistent Rate of Change:** Batches 2 & 3 (12M) show statistically consistent degradation rates.
- **Predictive Accelerated Data:** All 3 batches show slow, consistent degradation, supporting 24M extrapolation (low risk of non-linear failure).

2. Comprehensive Prior Knowledge & Early Development Data

- **Product-Specific Knowledge**
  Formulation Screening Studies confirm IgG1 configuration is most stable.
  Stress Degradation studies show Aggregation is the only major, well-understood pathway.
- **Platform Knowledge**
  Extensive data for similar IgG1 molecules on the same manufacturing platform confirms robust stability.
  Aggregation rates are typically slow & predictable over 3-5 years.

3. Low Risk of Failure & Regulatory Commitment (Mitigation)

- **Consistent CQA Margins:** Batches 2 & 3 show large safety margin at 12M (e.g., Aggregation ~1.0% vs. 3.0% spec), suggesting sufficient buffer.
- **Commitment Stability Protocol:** Formal commitment to test Batches 2 & 3 at 18 and 24 months.
- **Action Plan:** Immediate agency notification and corrective action (e.g., sheif life reduction) upon any spec failure.

Case Study: Switch from IV to SC Formulation (Two Doses)

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Original Product: Vial, IV infusion

New SC Product: Subcutaneous (SC) Injection | Pre-filled Syringe | 2 to 8C (Refrigerated)

Proposed Shelf Life and Data Status at IMA Submission (36 Months Claim)

The manufacturer is claiming a 36-month shelf life for both the Low Dose (LD) and High Dose (HD) SC presentations.

The Combined Regulatory Challenge

1. Extrapolation Risk (HD): Justifying a 36-month shelf life with only 24 months of real-time data.

2. Major Data Gap (LD): Justifying a 36-month shelf life with only 12 months of real-time data—a 24-month extrapolation.

3. Formulation Differences: The SC formulation is inherently different from the IV formulation, limiting direct prior knowledge use.

Deficient: Missing 12 months of real-time data.

Highly Deficient: Missing 24 months of real-time data.

Scientific Justification using Prior Knowledge & Comparability

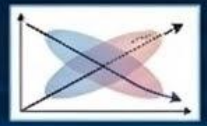
Claim: Grant the 36-month shelf life for both SC presentations

1. Product-Specific Knowledge & Comparative Stability

HD Extrapolation (24M → 36M)

Low Dose (LD) Comparability Bridge

Chemically Identical (Differ in Concentration)



Same Degradation Pathways (e.g., Aggregation)

2. Platform Prior Knowledge (Bridging from IV Product)

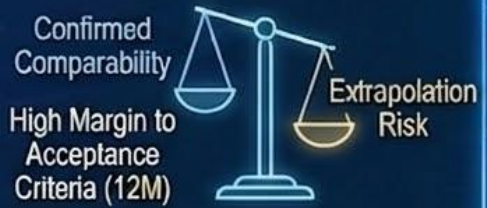
IV Product (Infusion) — **SC Product** (Injection)

IgG1 Scaffold & Disulfide Bond Integrity Robust >3+ Years

Known Stabilizing Platform (High-Concentration IgG1s)

3. Risk Mitigation & Regulatory Commitment

LD Extrapolation Justification (12M → 36M)



Commitment Protocol

- ☑ Submit 36M Data (HD)
- ☑ Submit 18M, 24M, 36M Data (LD)

Contingency: Reduce Shelf Life to 24M if Failure at 36M

Summary and Conclusion

Key takeaways

- New ICH Q1 accelerates science and risk-based approaches.
- A risk framework is crucial for biologics stability testing
- Early investment in stability knowledge drives lifecycle benefits
- Successful cases exist (limited but to build on), IMA shelf life claim, switch from IV to SC formulation
- The required approach is flexible and case-by-case

Promoting science and risk-based stability

- What is the true risk for biologics?
- Frontloading opportunity to gain earlier knowledge and profit at IMA and post-approval
- Tribal/Platform knowledge Biologics to be acknowledged
- End of shelf life specification safety margin for stability CQA
- Opportunity to balance manufacturing convenience <-> long-term storage covincience
- Lifecycle considerations and significant lower risk post-approval

A change is needed

- Science- and risk based framework exists and to be better utilized for stability
- It will be case by case (no standard approach)
- Mindset shift for both regulators and industry - we need accelerated product approval timelines with a meaningful shelf life for predictable global patient supply

Doing now what patients need next