Topics regarding Revisions of ICH Q1/Q5C guidelines: focus on biological products
DEC. 2022

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Note: This presentation is not the official position of the PMDA or the EWG of Q1/Q5C, containing personal views of the speaker.

Current ICH Stability guidelines
and
Background of proposed revision

Stability related ICH guidelines

Code	Title	Step 4
Q1A（R2） Q1A（R1）	Stability Testing of New Drug Substances and Products	Feb-6-2003 (Dec-1993)
Q1B	Photostability Testing of New Drug Substances and Products	Nov-6-1996
Q1C	Stability Testing for New Dosage Forms	Nov-6-1996
Q1D	Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products	Feb-7-2002
Q1E	Evaluation for Stability Data	Feb-6-2003
Q1F	Stability Data Package for Registration in Climatic Zones III and IV	Withdrawn on Jun-1-2006
Q5C	Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products	Nov-30-1995

ICH Quality Guidelines specific to Biologicals

Code	Title	Step 4
Q5A	Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin	Sep-23-1999 Now Revising
Q5B	Analysis of the Expression Construct in Cells Used for Production of r-DNA Derived Protein Products	Nov-30-1995
Q5C	Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products	Nov-30-1995 Now Revising
Q5D	Derivation and Characteristation of Cell Substrates Used for Production of Biotechnological/Biological products	16-Jul-1997
Q5E	Comparability of Biotechnological/Biological Products Subject to Changes in their Manufacturing Process	18-Nov-2004
Q6B	Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products	10-Mar-1999 Now Revising

Activities on Q1/Q5C revision

Jun 2021	In ICH Incheon meeting, revisions of the stability guidelines was endorsed as a new topic.
May 2022	In ICH Athens meeting, the Assembly approved PhRMA's nomination of Ms. Megan McMahon as the informal WG Leader/Rapporteur of the Q1/Q5C WG.
Aug 2022	Informal WG was established.
Nov 2022	In ICH Incheon meeting, the Concept Paper was approved.

Considerations for Updates to ICH Q1 and Q5C Stability Guidelines: Embracing Current Technology and Risk Assessment Strategies

Megan E. McMahon, Alexander Abbott, Yelizaveta Babayan, Jenny Carhart, Chi-wan Chen, Elke Debie, Mingkun Fu, Cherokee Hoaglund-Hyzer, Andrew Lennard, Hanlin Li, Tony Mazzeo, Lori McCaig, Sylvine Pischel, Fenghe Qiu, Dennis Stephens, Robert Timpano, Debra Webb, Chad Wolfe, Kayla Woodlief & Yan Wu

The AAPS Journal **23**, Article number: 107 (2021) | Cite this article

In consideration of the recent ICH Quality Discussion Group (QDG) recommended revision to the ICH series of stability guidelines.
Conducted a comprehensive review of ICH Q1A, Q1B, Q1C, Q1D, Q1E, and Q5C to identify areas where the guidelines could be clarified, updated, and amended to reflect the potential knowledge gained from current risk-based predictive stability tools and to consider other science- and risk-based stability strategies in accordance with ICH Q8–12.
Propose a holistic approach to stability understanding, utilizing historical data, prior knowledge, modeling, and a risk assessment process to expand the concept of what could be included (or would be acceptable) in the core stability data package, including type and amount of stability evidence, assignment of retest period and shelf-life for a new product, and assessment of the impact of post-approval changes.

https://link.springer.com/article/10.1208/s12248-021-00641-6

Excerpt from Concept Paper

Signed by the ICH parties, publication pending

Issues to be Resolved:

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.

Issues to be Resolved:

Clarification of technical components of current guideline and stability-related concepts; may include

- Combine common/overlapping principles and expand on items specific for Drug Substances (DS)/Intermediates/Drug Products (DP).

- Additional products not 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.
  - ✓ regulated OTC products

  As part of this consideration, certain stability concepts (e.g., retest date) may not be applicable to all product types.

Issues to be Resolved:

<u>Clarification of technical components of current guideline and stability-related concepts; may include</u>

- 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.

etc.

Issues to be Resolved:

Address new technologies and modern tools/strategies used as part of enhanced product understanding

Pharmaceutical Quality System (PQS) related stability topic

Clarify applicability of requirements across development and lifecycle

Training strategies and alignment with other guidelines

ICH Guidelines to be considered for reflection in revised Q1/Q5C guidelines

Code	Title	
Q2	Validation of Analytical Procedures	
Q8	Pharmaceutical Development	Risk-based management
Q9	Quality Risk Management	
Q10	Pharmaceutical Quality System	
Q11	Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/Biological entities)	
Q12	Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management	
Q14	Analytical Procedure Development	

The proposed Q1/Q5C milestones

ICH Procedure for harmonization

← **Q4 calendar year 2025**
Complete Step 4 and training materials

← **Q4 calendar year 2024**
Complete Step 1

← **Q4 calendar year 2022**
Final Concept Paper, Business Plan

← **August 2022**
informal WG was established

ICH

International **C**ouncil for **H**armonisation of Technical Requirements for Pharmaceuticals for Human Use

Founding Regulatory Members
- EC, Europe
- FDA, United States
- MHLW/PMDA, Japan

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- EFPIA
- JPMA
- PhRMA

Standing Regulatory Members
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- Swissmedic, Switzerland

Regulatory Members
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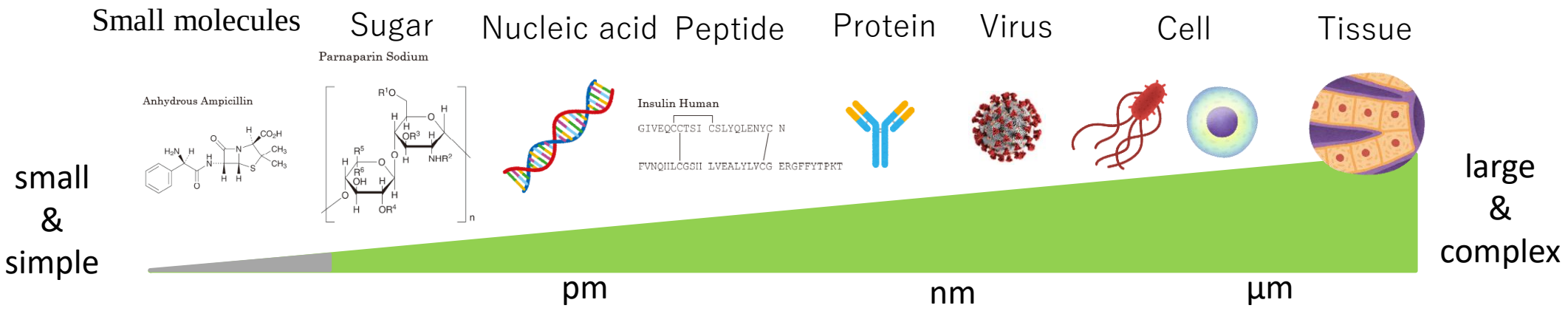
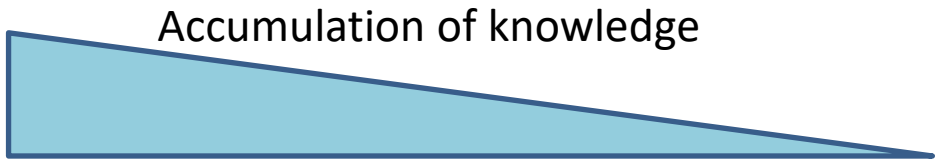
- COFEPRIS, Mexico
- HSA, Singapore
- MFDS, Republic of Korea
- MHRA, UK
- NMPA, China
- SFDA, Saudi Arabia
- TFDA, Chinese Taipei
- TITCK, Turkey

Industry Members
- BIO
- Global Self-Care Federation
- IGBA

Specific considerations assumed for biological products in the revision of Q1/Q5C guidelines

Variety of biological products





Classical modality

- Proteins or peptides, isolated from plasma or produced by recombinant technology etc.

New modality

- ATMPs
- mRNA vaccine
- recombinant viral vector vaccine etc.

Current Q5C

Scope	Product type
Cover	well-characterised proteins and polypeptides, their derivatives and products of which they are components, and which are isolated from tissues, body fluids, cell cultures, or produced using rDNA technology e.g. • cytokines, erythropoietins, plasminogen activators • blood plasma factors • growth hormones and growth factors, insulins • monoclonal antibodies • vaccines consisting of well-characterised proteins or polypeptides
May cover	conventional vaccines, after consultation with the appropriate regulatory authorities
Not cover	antibiotics, allergenic extracts, heparins, vitamins, whole blood, or cellular blood components

How to cover biological products in new guidelines

Basic evaluation stance for biologics	Typical not applicable evaluation concepts for biologics
Q1 guideline applies in general to biotechnological/biological products. However Biotechnological/biological products do have distinguishing characteristics. • Active components are typically proteins and/or polypeptides • Maintenance of molecular conformation and, hence of biological activity, is dependent on noncovalent as well as covalent forces. • The products are particularly sensitive to environmental factors such as temperature changes, oxidation, light, ionic content, and shear. • To ensure maintenance of biological activity and to avoid degradation, stringent conditions for their storage are usually necessary. Primary data to support a requested storage period for either drug substance or drug product should be based on long-term, real-time, real-condition stability studies. *excerpts from Q5C PREAMBLE*	Re-test period • The period of time during which the drug substance is expected to remain within its specification and, therefore, can be used in the manufacture of a given drug product, provided that the drug substance has been stored under the defined conditions. • A batch of drug substance can be re-tested multiple times and a different portion of the batch used after each re-test, as long as it continues to comply with the specification. • For most biotechnological/biological substances known to be labile, it is more appropriate to establish a shelf life than a re-test period. The same may be true for certain antibiotics. *excerpt from Q1A Glossary* Extrapolation Extrapolation is the practice of using a known data set to infer information about future data. Extrapolation to extend the retest period or shelf life beyond the period covered by long-term data can be proposed in the application, particularly if no significant change is observed at the accelerated condition. • Knowledge of change pattern • Fit of mathematical model • Relevant supporting data *excerpt from Q1E 2.3*

Applicability of new technologies and modern tools/strategies

Societal demand for urgent development such as pandemic response

Thank you for your attention.

ありがとう

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