Overview of the ICH-Q1 guideline revision draft and prospects for stability assessment of biologics from the regulatory perspective
DEC. 2025

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Office of Vaccines and Blood Products
PMDA

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

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Background and activities of the ICH stability guideline revision

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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Q1F	Stability Data Package for Registration in Climatic Zones III and IV	Withdrawn on Jun-1-2006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

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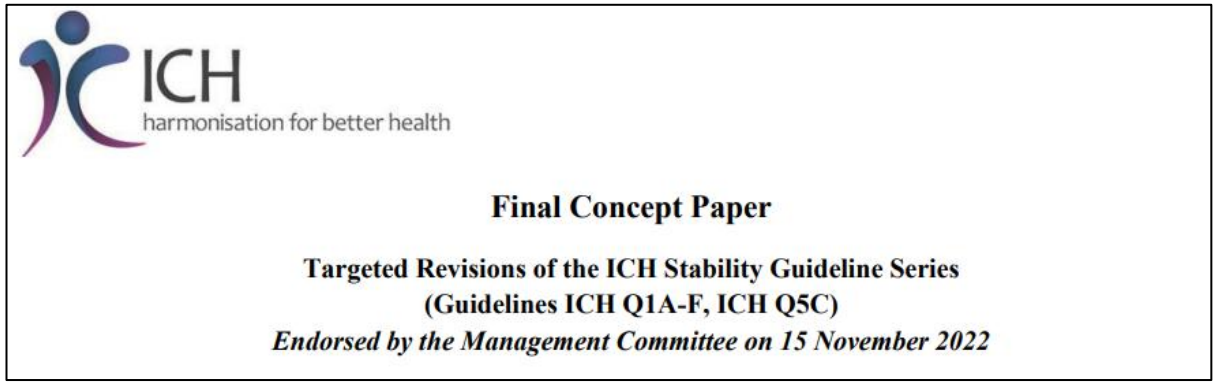
Purpose and expected deliverables of revision

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;
d) Consider inclusion of new topics, such as stability considerations for advanced therapies.

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 specific recommendations, as required.

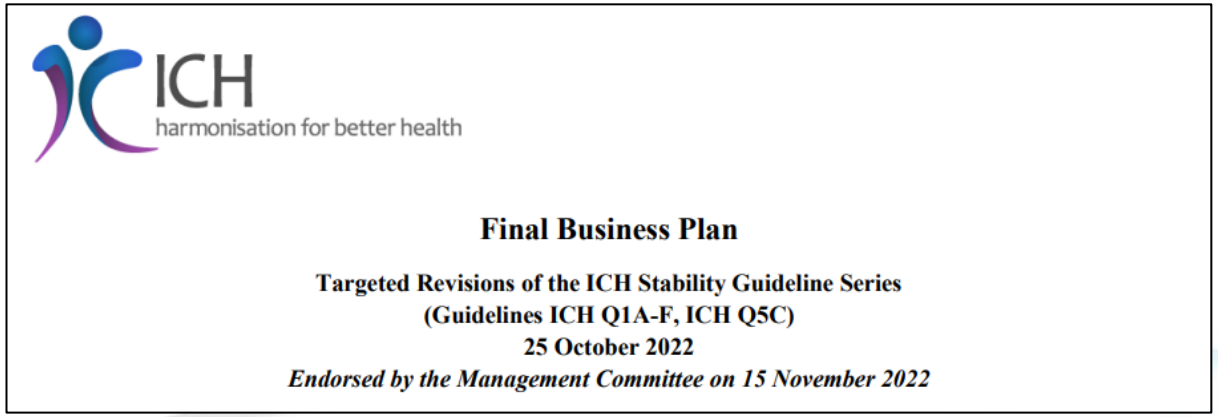
It is also recommended to update and supplement current training material.


ICH
harmonisation for better health

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

https://database.ich.org/sites/default/files/ICH_Q1Q5C_ConceptPaper_Final_2022_1114.pdf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Final Business Plan

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

https://database.ich.org/sites/default/files/ICH_Q1Q5C_BusinessPaper_Final_2022_1028.pdf

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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.
  - Data and evaluation strategies for defining the retest period/shelf-life of DS and shelf-life of 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).
  - 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.
- 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

etc.

Please refer concept paper in detail

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Composition of EWG

FDA, United States
PhRMA
EC, Europe
EFPIA
MHLW/PMDA, Japan
JPMA
Health Canada, Canada
Swissmedic, Switzerland

ANMAT, Argentinia
ANVISA, Brazil
APIC
BIO
CDSCO, India
COFEPRIS, Mexico
EDQM
Global Self-Care Federation
HSA, Singapore
IFPMA
IGBA
INVIMA, Colombia
IPEC
MFDS, Republic of Korea
NAFDAC, Nigeria
NMPA, China
SFDA, Saudi Arabia
TFDA, Chinese Taipei
TITCK, Turkey
WHO

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Project milestones and Progression

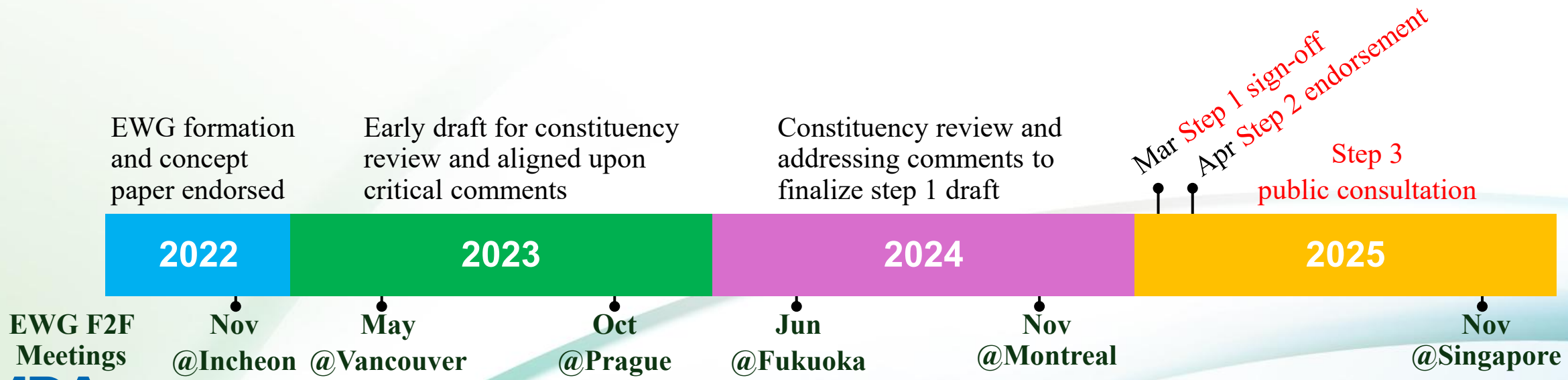

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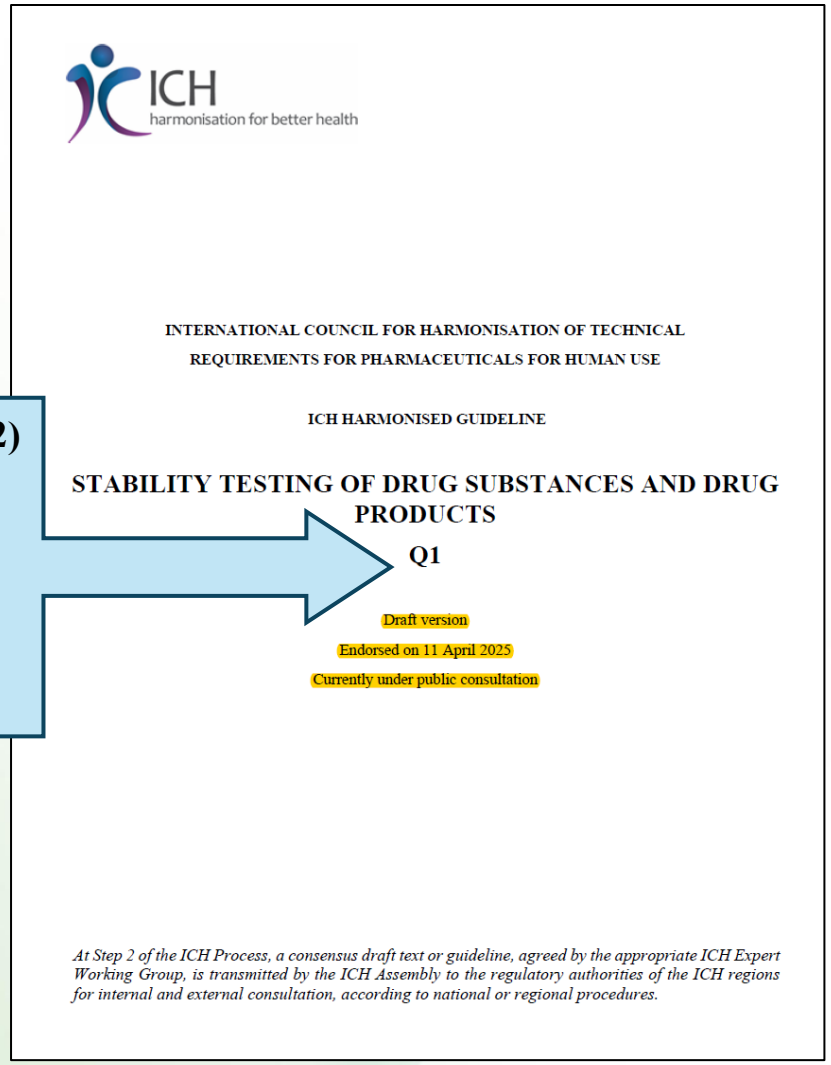
Table of Contents of new Q1 draft



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INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

STABILITY TESTING OF DRUG SUBSTANCES AND DRUG PRODUCTS

Q1

Draft version

Endorsed on 11 April 2025

Currently under public consultation

At Step 2 of the ICH Process, a consensus draft text or guideline, agreed by the appropriate ICH Expert Working Group, is transmitted by the ICH Assembly to the regulatory authorities of the ICH regions for internal and external consultation, according to national or regional procedures.

Q1A(R2)
Q1B
Q1C
Q1D
Q1E
Q1F
Q5C

Scope target

Stress conditions & Forced degradation conditions

Primary stability batches

Applicability of more severe climatic zone data

Optional light source

New guidance

Major Updates on decision tree type extrapolation

New guidance

Worst-case analysis strategies

Various type stability modeling

New guidance

https://database.ich.org/sites/default/files/ICH_Q1EWG_Step2_Draft_Guideline_2025_0411.pdf

New contents
Major updates

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Basic concepts regarding biologics stability assessment from the current Q1/Q5C

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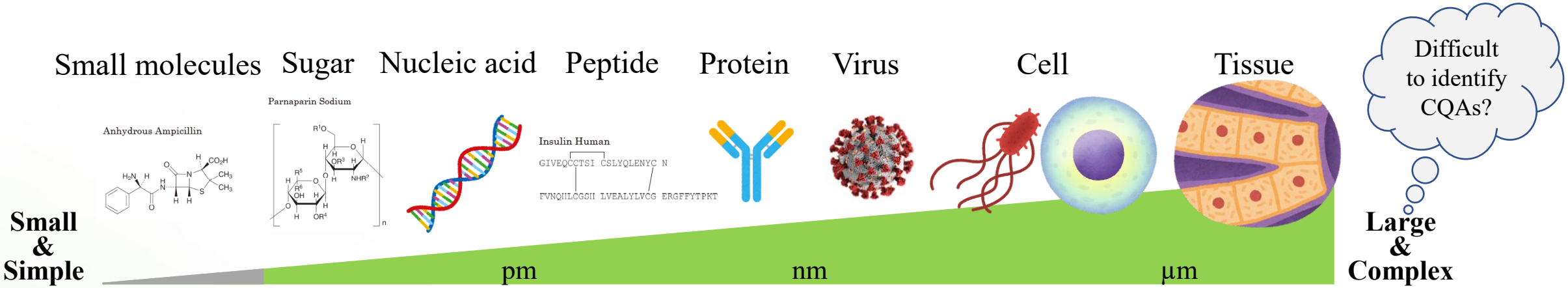
“Biologics” is a vague category for products with huge-variety of quality characteristics



Classical modality

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

Accumulation of knowledge & experience

New modality

- ATMPs
- mRNA vaccine
- recombinant viral vaccine etc.

Note for vaccine

- “Vaccine” is also not a category by quality characteristics, so there are diverse-varieties of quality characteristics.
- Most vaccines
  - ✓ Indicated to prevent infectious disease, not for cure/treatment.
  - ✓ Intended for healthy person & huge population, including infants, elderly, and vulnerable in health.

Quality assurance may require more than usual.

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Biologics type coverage on Q5C scope

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

Biologics is diverse, but the scope of Q5C is limited.

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Cautious stability evaluation stance regarding biologics in current Q1/Q5C

Basic evaluation stance 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

Typical not applicable evaluation concepts for biologics

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

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Proposal in the Q1 draft regarding Biologics Stability Assessment

Note: The content presented here is the public draft version, which may be subject to change in revisions following public comments etc..

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Comparison on biologics type coverage by Q5C and Q1 draft

Q5C

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

Q1 draft section 1

biologics

Applies	✓ Chemically synthesised drug substances including oligonucleotides, polysaccharides and polypeptides, semi-synthetic drug substances and fermentation-derived drug substances. ✓ Therapeutic proteins/polypeptides, polysaccharides and proteoglycans produced using recombinant DNA (rDNA) technology or isolated from human, animal or plant tissues, other natural sources, including body fluids (such as plasma-derived products), or cell cultures. ✓ Conjugated products that are made up of proteins/polypeptides linked to another moiety (e.g., antibody drug conjugate). ✓ Vaccines, allergenic products, and adjuvants. ✓ Autologous and allogenic cell-based substances, including those which may be genetically modified ex-vivo.ATMPs ✓ Gene therapy products that mediate their effect by the expression (transcription or translation) of transferred genetic materials, and genome editing products used to modify cells. ATMPs ✓ The drug constituent part of a combination of a drug product with a medical device (both integral or co-packaged). ✓ Co-packaged solvents/diluents. ✓ Natural health products that are regulated as drug product
Not applicable	device constituent parts, radiopharmaceuticals and whole blood products

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The scope of biologics covered by guidance is expanded and clarified

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Stability evaluation stance regarding biologics in current Q1/Q5C

Basic evaluation stance 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

Typical not applicable evaluation concepts for biologics

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

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Basic stance regarding biologics stability evaluation

- Biological drug substances and drug products usually require stringent conditions for their storage to ensure maintenance of biological activity and to avoid degradation, because of dependence of molecular conformation and biological activity on noncovalent as well as covalent forces, resulting their high sensitivity to environmental factors (e.g., temperature changes, oxidation, light, ionic content and shear). The evaluation of their stability may necessitate complex analytical methodologies including physicochemical, biochemical and immunochemical methods, and consideration of many external conditions which can affect the product's potency, purity and quality.

excerpt from Q1 draft section 3.2

- While shelf life for biological products is generally established based on long-term stability data, enhanced stability modelling approaches could be considered for biological drug substances and drug products using the principles in section 2 of this Annex or using extrapolation principles (refer to Section 13.2.9- Extrapolation of Biologicals) for certain well-characterised biological drug substances with a well understood stability profile.

excerpt from Q1 draft section Annex 2

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Re-test

- A re-test period is normally applicable to drug substances of synthetic chemical entities as an alternative to establishing a shelf life. This approach may also be proposed in certain cases for the drug substances of biologicals with a well understood stability profile, where justified.
- An example where a re-test period may apply for biological drug substance is a well characterised IgG therapeutic monoclonal antibody that is stored frozen and show little to no change in product quality over the duration of storage.

excerpt from Q1 draft section 13.1.1

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Extrapolation

- 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.

excerpt from Q1 draft section 13.2.4

- Extrapolation beyond the period covered by available long-term primary stability data may be considered for a well characterised biological drug substance stored frozen, for which the quality attributes are known, and their corresponding criticality and residual risks evaluated to ensure patient safety. Extrapolation of drug substance shelf life should be limited to one and a half times the available long-term data from the primary stability batches to a maximum of 12 months beyond available long-term data, when justified.

excerpt from Q1 draft section 13.2.9

- While shelf life for biological products is generally established based on long-term stability data, enhanced stability modelling approaches could be considered for biological drug substances and drug products using the principles in section 2 of this Annex or using extrapolation principles (refer to Section 13.2.9- Extrapolation of Biologicals) for certain well-characterised biological drug substances with a well understood stability profile.

excerpt from Q1 draft section Annex 2

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Stability evaluation stance regarding biologics on Q1 draft in comparison from current Q1/Q5C

Basic evaluation stance 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
- 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.

excerpt from Q5C PREAMBLE

Q1 draft
- The basic stability evaluation stance should be carried over from Q5C.
- Science and risk-based approach is applicable while it needs justification.

Typical not applicable evaluation concepts for biologics

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 stored under
- A batc a different portio ues to compl
- 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

Q1 draft
- Re-test approach may also be proposed in certain cases for the drug substances of biologicals with a well understood stability profile.

Extrapolation

Extrapolation is the practice of using a known data set to infer information abou beyo appl acce
- Relevant supporting data

excerpt from Q1E 2.3

Q1 draft
- A limited extrapolation protocol would be applicable for a well characterised biological drug substance stored frozen.
- Possibility to apply enhanced modelling approach is paved, but careful consideration should be required.

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Recommended minimum core stability data at submission in Q1 draft section 3

Table 1 Recommended Minimum Core Stability Data for the Standard Approach at Submission to Support the Initial Re-test Period or Shelf Life[1]

Product Type	Batch Type	Number of Batches[2]	Long-term storage condition	Accelerated storage condition
New synthetic chemical entity drug substances and/or drug products for which a new drug regulatory submission is required[4]	Primary[5]	3	12 months	6 months[3]
Existing synthetic chemical entity drug substances and/or related drug products for which an abbreviated/ abridged regulatory submission is required	Primary[5]	3	6 months	6 months[3]
Biological drug substances and/or drug products	Primary, Production[5]	3	6 months[6]	6 months[7]

[1] For testing frequency guidance refer to Section 6 – Testing Frequency

[2] For a full design, 3 batches of each strength or fill covering the proposed container closure systems. Reduced designs may be applied where justified (refer to Annex 1 – Reduced Stability Protocol Design)

[3] If a significant change (refer to Section 13 - Data Evaluation) or an out of specification result occurs at accelerated conditions within the first 3 months, it is considered unnecessary to continue to test through 6 months.

[4] In principle, stability protocols for new dosage forms and new strengths/concentrations should follow the guidance for a new drug. However, a reduced stability dataset at submission time (e.g., 6 months accelerated and 6 months long term data) may be acceptable in certain justified cases (refer to Section 15.3 - Stability Studies to Support New Dosage Forms and New Strengths/Concentrations).

[5] **There should be a commitment to continue stability studies for production batches corresponding to the proposed re-test period or shelf life.**

[6] **A primary batch can be a production batch but does not need to be a production batch. If the re-test period or shelf life proposed from non-production primary batch data is greater than 6 months, stability data from production batches should be a minimum of 6 months. The shelf life would generally be supported by three primary batches having stability data through to shelf life.**

[7] Testing under accelerated storage conditions is strongly suggested when appropriate for the storage condition and product type and the minimum time period should be justified by the applicant in accordance with the selected storage conditions. A minimum of three time points, including the initial and final, is recommended.

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The Minimum Core batch data recommended for biologics approval application is clarified

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Primary Stability Batches of Drug Substance and Drug Product in Q1 draft section 4

Table 2 Considerations for Primary Stability Batches of Drug Substance and Drug Product

	Synthetic Chemical Entities	Biologicals
Drug Substance	• Same chemical synthetic route • Similar manufacturing process (differences justified) • At minimum, all batches manufactured at pilot scale[2] • Meet proposed registration specification • Containers constructed of the same material and type of container closure system as production batches.	• Same cell production system, if applicable • Similar manufacturing process (differences justified) • Meet proposed registration release specification • Containers constructed of the same material and type of container closure system as production batches. • Comparable to production batches (ICH Q5E)
Drug Product	• Same formulation[1] and dosage form • Minimum of 2 batches manufactured to at least pilot scale[2], other batch(es) can be smaller if justified • Same manufacturing process with equipment with the same operating principles. • Meet the proposed registration release specification • Same fill unless a reduced protocol design is applied[1] • Same container closure system as proposed for marketing	• Same formulation and dosage form • Comparable to production batches (e.g., ICH Q5E) • Meet proposed registration release specification • Same fill volume unless a reduced protocol design is applied[1] • Same container closure system as proposed for marketing.

In general, production scale batches are expected to be used to set shelf life of vaccines. If non-production scale batches are used as primary batches, a justification should be based on product knowledge, comparability studies and risk. The remaining recommendations for primary batches for biologicals in Table 2 are also applicable to vaccines.

Requirement for "Primary Stability Batches" in Biologics is outlined with specific caution to vaccines

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Other noteworthy biologics related recommendations in Q1 draft

Section 9: Stability Considerations for Processing and Holding Times for Intermediates

- Provides stability recommendations for processing and holding times for intermediates.
- A holding time study for a biological will typically consider two elements: (a) physicochemical stability and (b) microbial control strategy.

Section 12: Reference Materials, Novel Excipients and Adjuvants

- Provides guidance on reference materials, novel excipients and adjuvants.
  - Considerations for Biological Reference Materials
  - Considerations for Vaccine Adjuvants

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

- Points to note regarding stability assessment that take into account the unique characteristics of ATMP are presented, in addition to the core guidance recommendations .

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Expectations on the revise of Q1 guideline

Current issues to be addressed in potential or apparent

Mature and traditional approach
- Solid foundation for rigid evaluation
- Accumulated track record

Too conservative?
Just because it feels trustworthy?

Science and risk-based new approach
- How to apply prior knowledge?
- What is "the well-characterized"?
- How to justify and confirm?
- How to mitigate the impact of misjudgment?

Commonly acceptable?
Unexpected defects?

Q1/Q5C revision and new Q1 implementation

Optimization of stability evaluation

Steady assurance of efficacy and safety through total shelf life

Reasonable evaluation
- Time and cost balance
- Response to Emergency

Flexibility to not stick to traditional methods

Continuous accumulation of knowledge and experience

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