Regarding revisions of ICH Q1/Q5C guidelines; Expectations and concerns for stability assessment with modeling-type extrapolation in biological products.

DEC. 2023

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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.

Revisions of ICH Q1/Q5C guidelines

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Q1F	Stability Data Package for Registration in Climatic Zones III and IV	Withdrawn on Jun-1-2006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 activities until establishment of EWG

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 Working Group (IWG) convened to draft Concept Paper and Business Plan
Nov 2022	In ICH Incheon IWG met • Concept Paper and Business Plan were endorsed • Expert Working Group (EWG) was established

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

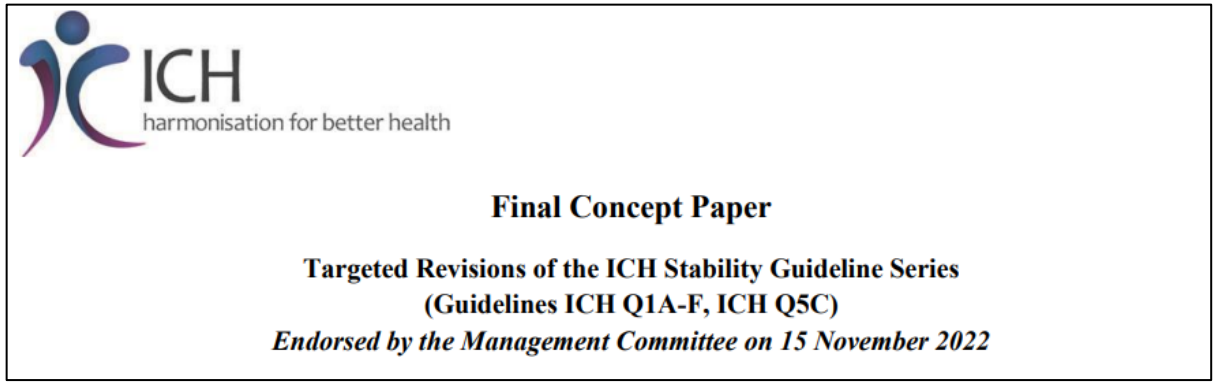
Purpose and expected deliverables of revision

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.

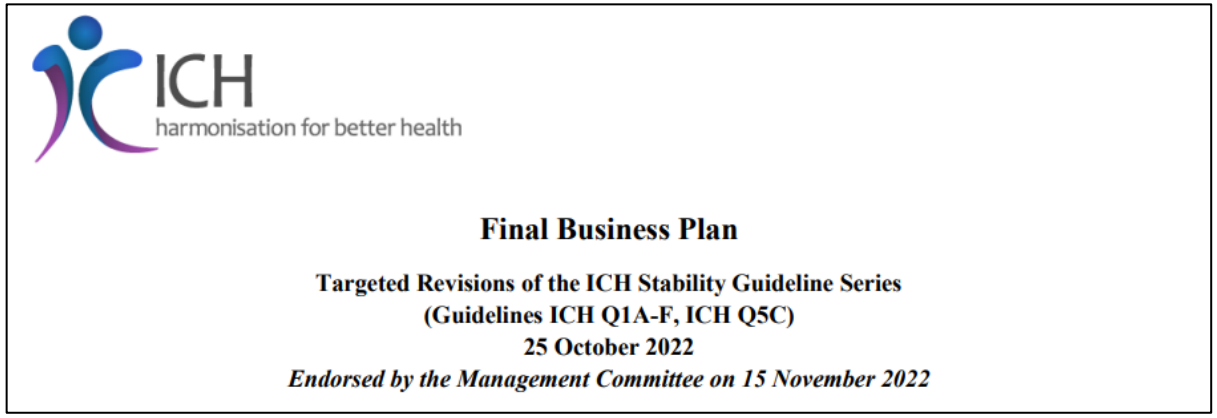
It is also recommended to update and supplement current training material.


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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harmonisation for better health

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

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

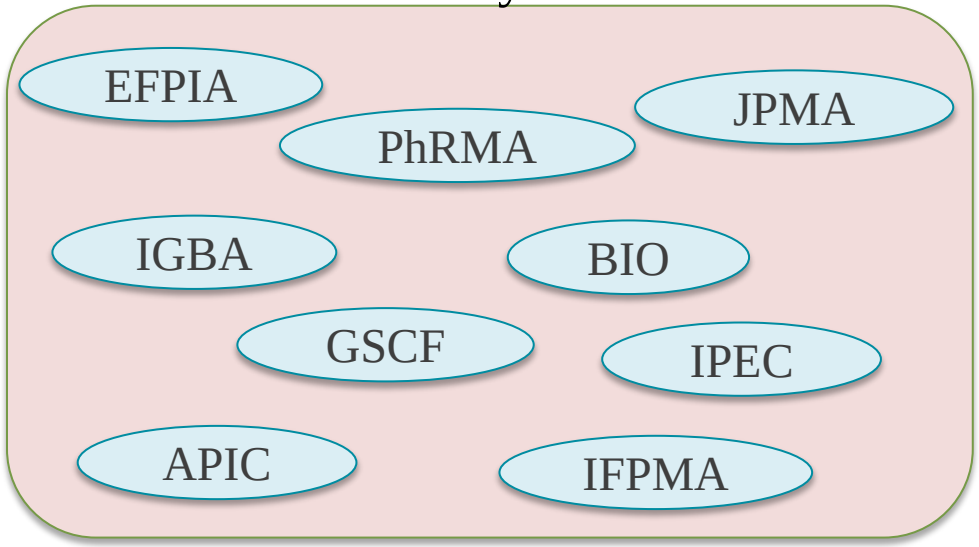
ICH activities of EWG

Dec 2022	Started EWG discussion for revisions
May 2023	Completed ‘early draft’ of guideline for early constituency (internal) review
Jun 2023	In Vancouver EWG met • Reviewed priority comments from constituency review and established work plan to have a working draft by the end of Q1 2024
Oct/Nov 2023	In Prague EWG met • Addressed issues to have a step 1 draft by the end of Q1 2024

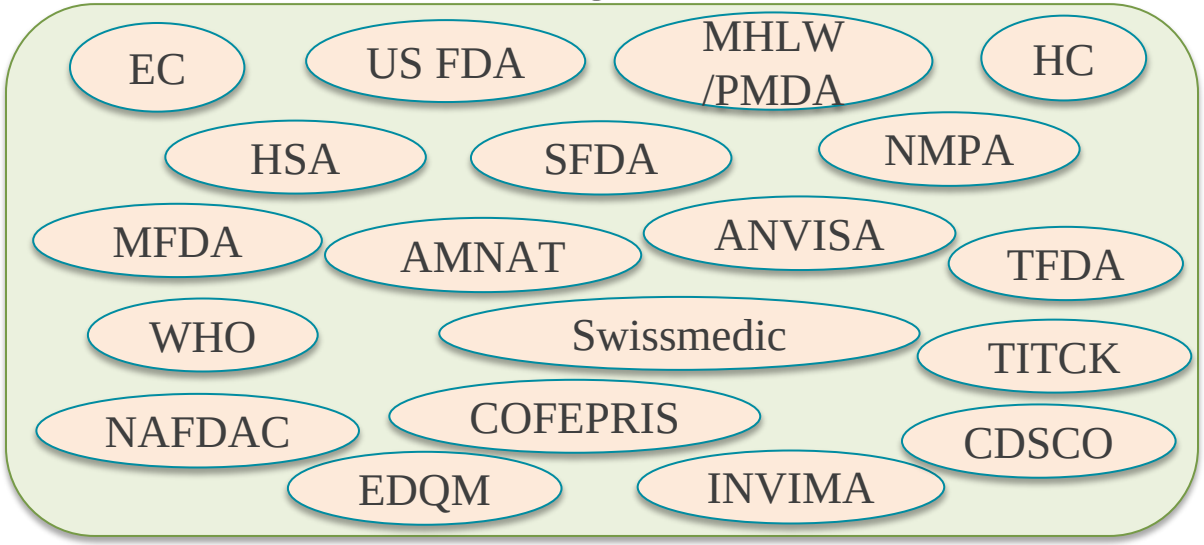
Representation in EWG

Rapporteur: Megan McMahon (PhRMA)
Regulatory Chair: Ashutosh Rao (US FDA)

Industry



Regulators

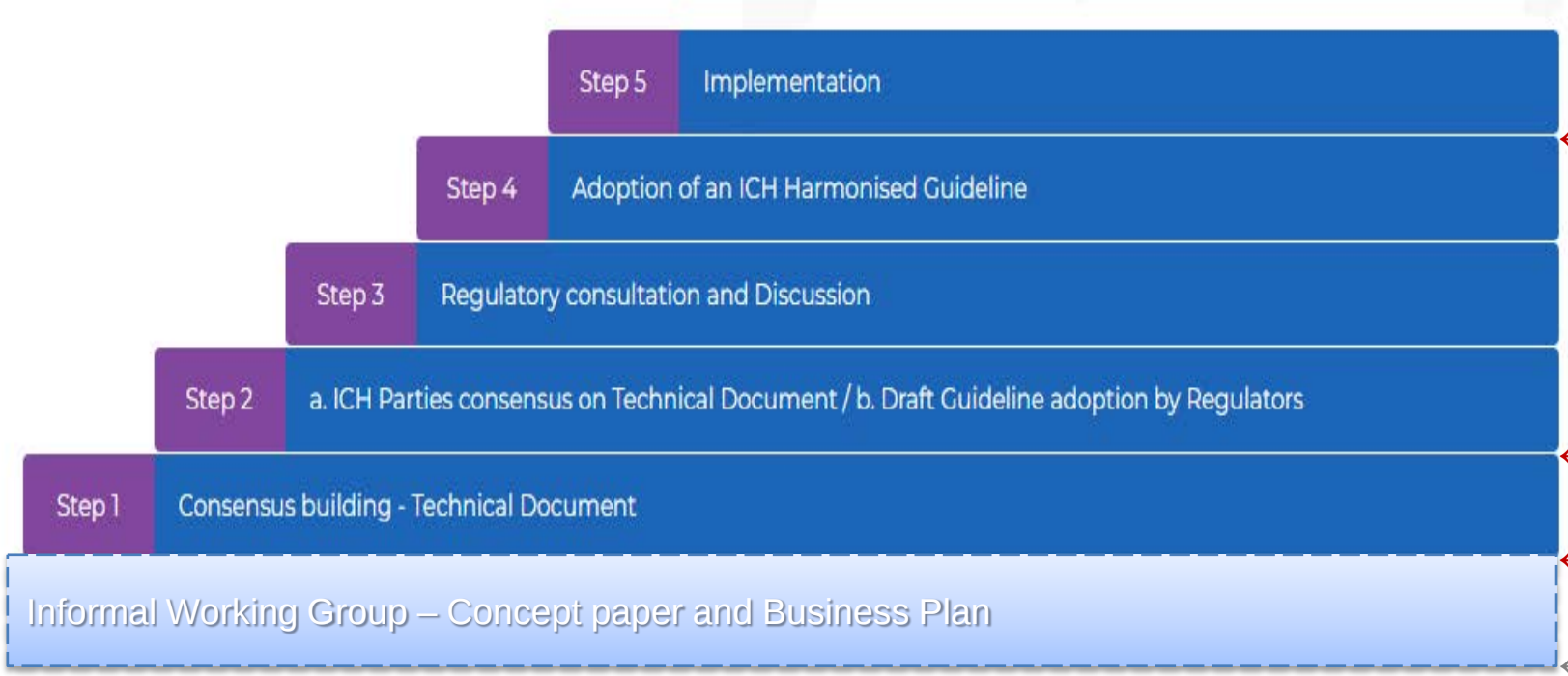


Over 50 participants

EWG discussions per topics	
Structure of Guideline	Reference Standards., Excipients, Adjuvants
Protocol Design	Holding Times during Manufacture
Batch Selection	In Use Stability
Container Closure System	Labeling
Test & Acceptance Criteria	Lifecycle
Testing Frequency	Bracketing and Matrixing
Storage Conditions	Modeling
Photostability/Excursions/Stress Testing	Vaccines
Evaluation of Data	ATMP

The proposed Q1/Q5C milestones

ICH Procedure for harmonization



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

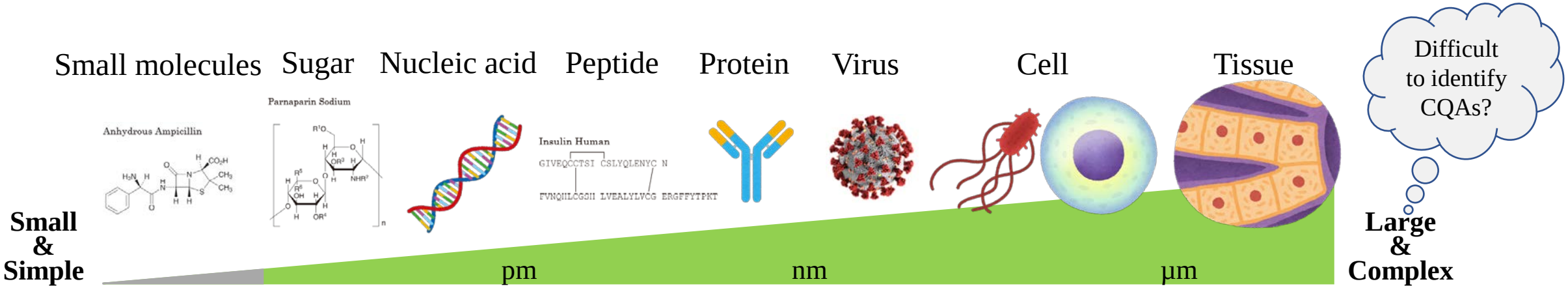
← **Q4 calendar year 2024**
Complete Step 1

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

← **August 2022**
informal WG was established

Biological products
&
Modeling-type extrapolation

“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.

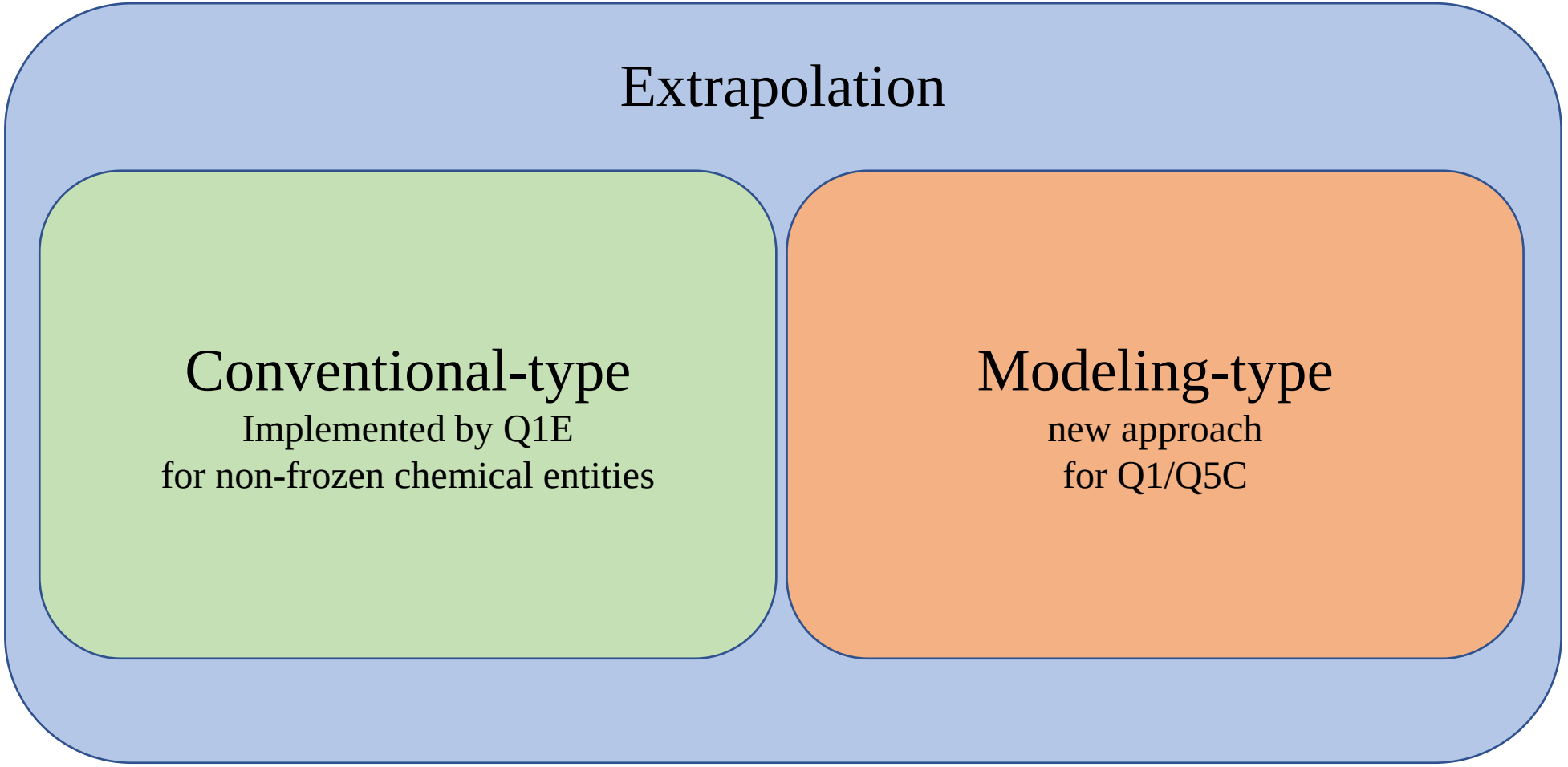
Quality assurance may require more than usual.

Stance of current Q1/Q5C guideline on stability assessment of biologics

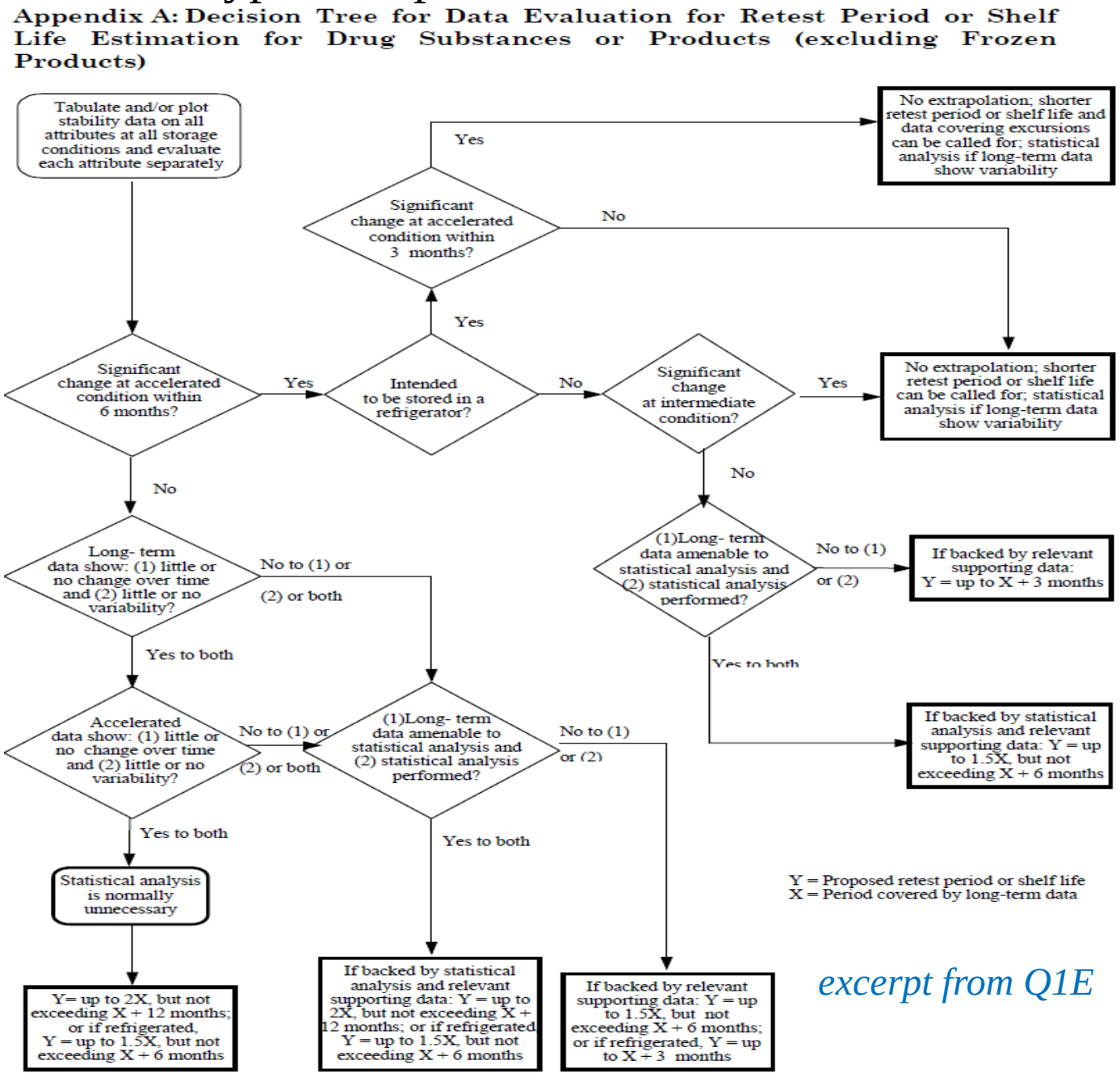
Basic evaluation stance for biologics	Typical not applicable evaluation concepts for biologics
The guidance stated in this annex **applies to well-characterised proteins and polypeptides** *excerpts from Q5C SCOPE OF THE ANNEX*	**Extrapolation** Extrapolation is the practice of using a known data set 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*
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*

Most regulators and companies do not have sufficient knowledge, experience and expertise in the application of extrapolation and re-test period in biologics.

Two types of Extrapolation



Conventional-type extrapolation



excerpt from Q1E

Determine extrapolatable shelf life/retest period from long-term storage data and accelerated condition data, according to the defined decision tree.

Modeling-type extrapolation

Study data of limited period

Input

$$k = Ae^{\frac{-E_a}{RT}}$$

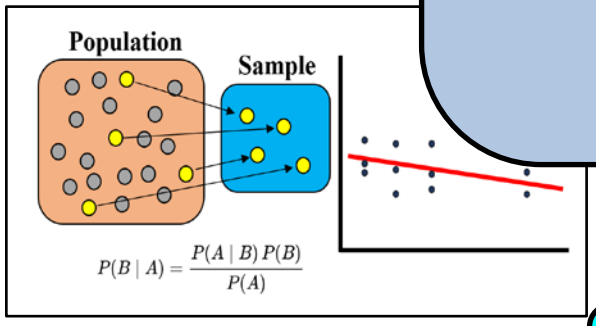
k: rate constant
T: absolute temperature
A: pre-exponential or frequency factor
Ea: activation energy for the reaction
R: universal gas constant

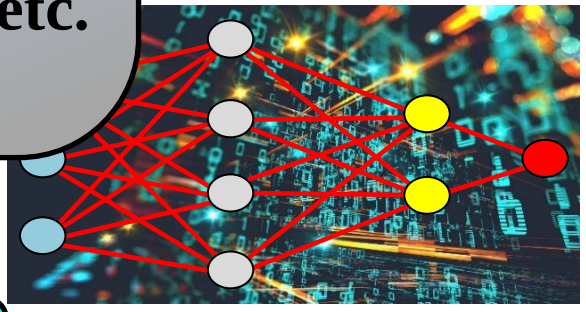
Stability model

- **Prior knowledge**
- **Chemical-kinetics**
- **Risk management**
- **Statistics**
  Bayesian inference
- **Digital technology**
  AI

etc.

Select/Construct proper Model
Verification & Validation for Credibility





Output

Prediction of long-term future quality attribute

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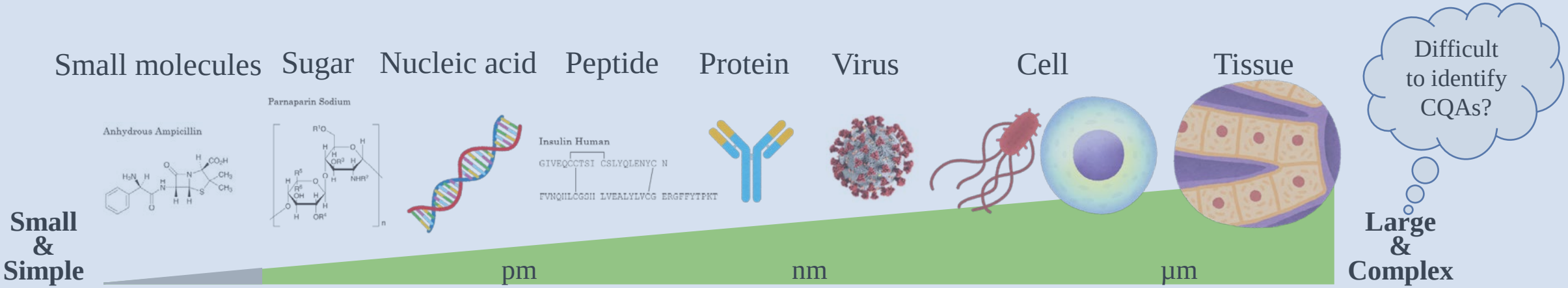

Applicability of Modeling-type extrapolation on Biologics ?

Classical modality

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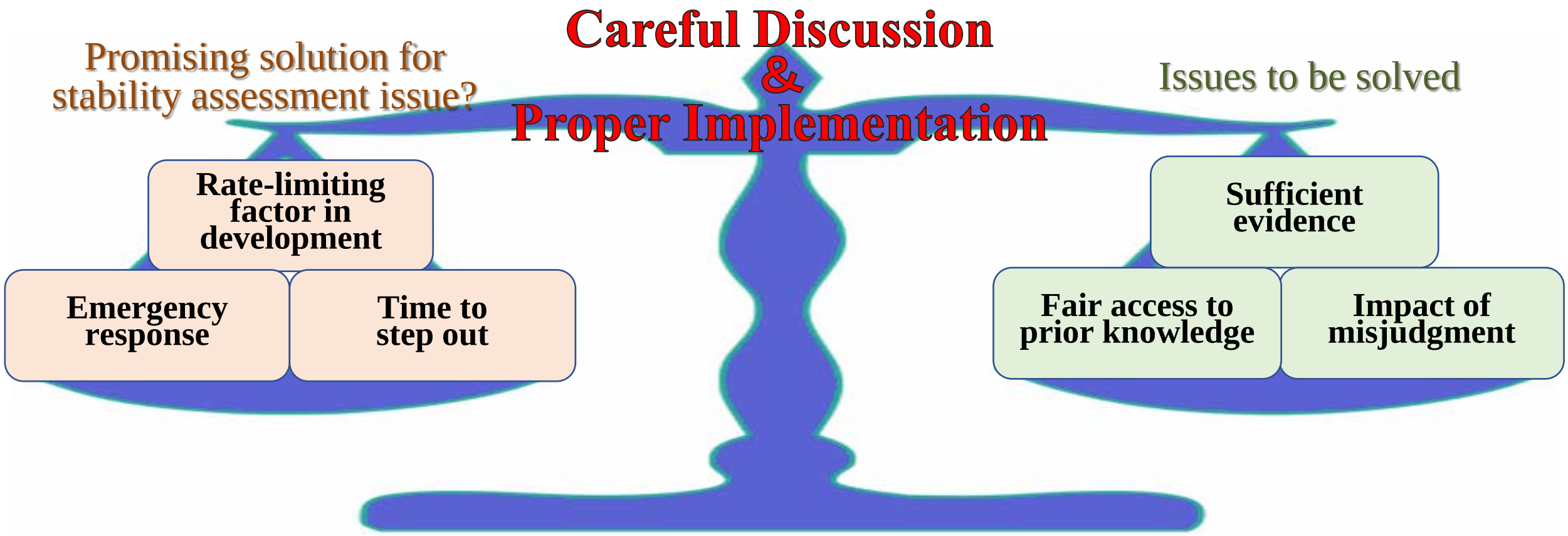
Quality assurance may require more than usual.

Balance regarding modeling-type extrapolation



Product character	Model type	Prior knowledge	Real data	Social situation	Risk mitigation /Commitment
Source material MW Purity Composition Degradation profile etc.	Credibility	Evidence level Public/Private	Sufficiency	Emergency?	Sufficiency

Thank you for your attention.

ありがとう

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