CMC Strategy Forum Japan 2025
Dec 9th

Challenges and approaches related to extrapolation and shelf life/re-test period setting in biological products

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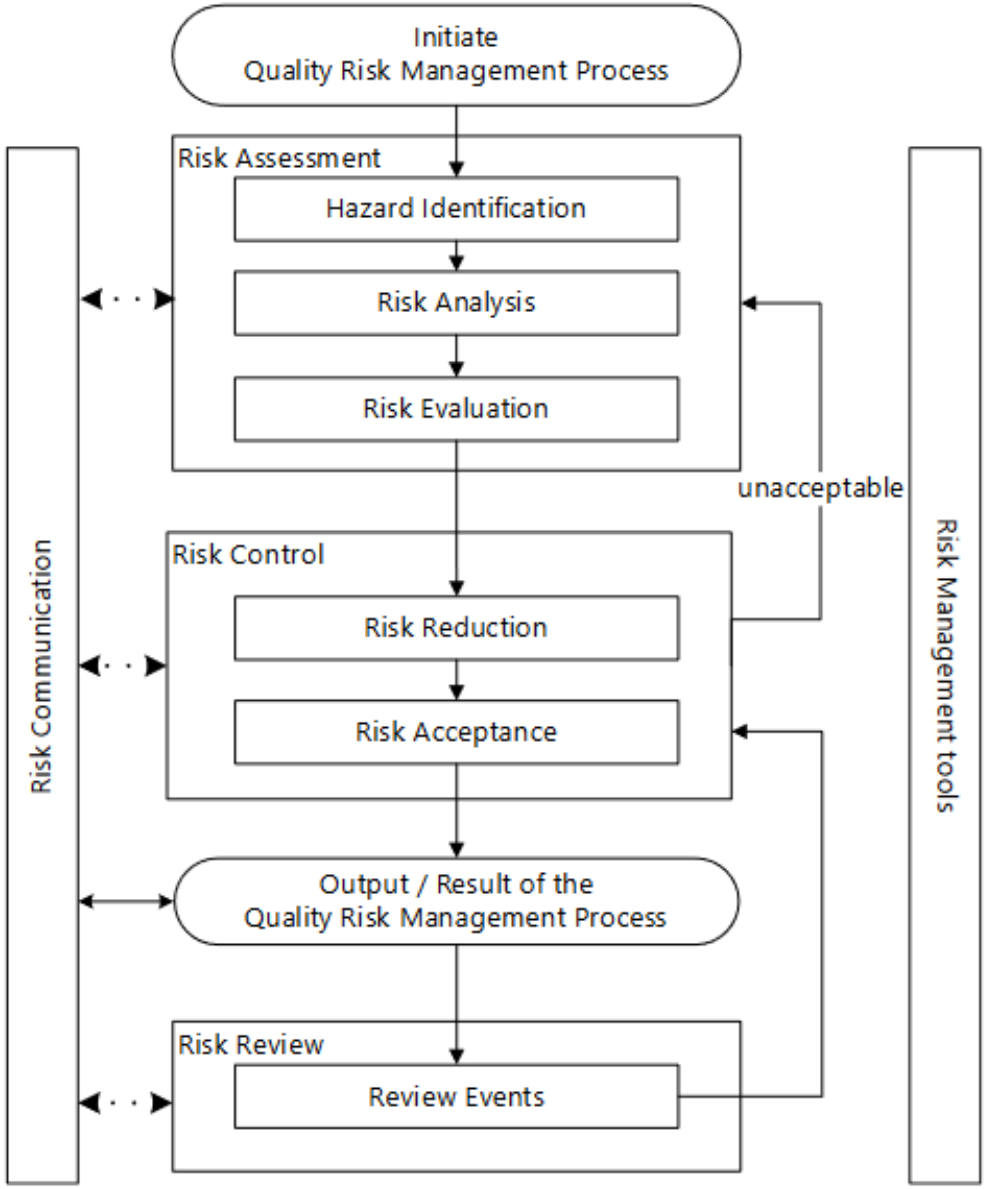
Disclaimer: The view and opinions expressed in the following presentation are those of the individual presenter, and should not be attributed to the organization with which the presenter is affiliated.

Outline

- Science and risk-based approaches proposed in ICH Q1 draft
- Extrapolation reported in scientific articles
- Japanese consortium for stability prediction of biologicals

Science and risk-based approach

ICH Q9



Incorporation of ICH Q6A/B, Q8-11

Setting QTPP

↓**Characterization**
↓Risk assessment
↓Identification of CQA
↓Setting the acceptable limit, range or distribution of each CQA
↓Establish the control strategy to make CQA
meet the acceptable limit, range, or distribution

Control Strategy

- ✓ Raw material control
- ✓ Process parameter setting
- ✓ In-process control
- ✓ Specification
- ✓ Stability testing

Prior knowledge
Development data

Stability-Indicating Critical Quality Attributes*

*Attributes that may change upon storage and may impact the functionality and/or quality of the drug substance or drug product. (Q1 draft section 3.3)

Science and risk-based approach

3. Protocol Design for Formal Stability Studies

3.3 Stability-Indicating Critical Quality Attributes

3.3.1 Recommendations for Establishing a Re-Test Period or Shelf life

- The stability protocol to establish a re-test period or shelf life should include **stability-indicating CQAs** and compile a suitable dataset to demonstrate product quality through storage and use.
- **For synthetic chemical** drug substances (DS) and drug products (DP), the stability protocol should consider appropriate, physical and chemical attributes.
- **For biological DS and DP,** the protocol should assess changes in CQAs that affect physicochemical properties, purity and impurity levels, immunochemical properties and the biological activity of the product, as appropriate.

Science and risk-based approach

Current situation for biological products

Data set required for setting shelf-life: long-term, real-time, real-condition stability studies.

Re-test period: not accepted

Extrapolation for shelf life/re-test period : not accepted

Alternative approaches proposed by Q1 draft

Applicability of a Re-Test Period to Biological Products (Q1 draft section 13.1.1)

- May also be proposed in certain cases for the **DS of biologicals with a well understood stability profile**, where justified.
- Example: a **well characterized IgG therapeutic monoclonal antibody** that is stored **frozen** and shows **little to no change** in product quality over the duration of storage.

A retest period is likely to be acceptable in certain cases of DS of biological products.

Applicability to modalities other than IgG?

Science and risk-based approach

Alternative approaches proposed by Q1 draft

[Applicability of extrapolation or stability modeling to establish a Shelf Life of Biological Products]

Extrapolation and Stability Modelling (Q1 draft section 13.2.4)

- A practice of using a known data set to infer information about future data.
- **A form of stability modeling** that, under certain conditions, may be **applicable to** synthetic and **biologicals**.
- **Decision tree approach would not be recommended for biological products** because biological and immunological attributes are generally not amenable to extrapolation, as they cannot be assumed to follow zero order kinetics.
- Possible example: certain **well characterized biologicals** that have no statistically significant or meaningful change over time, using the **risk assessment criteria and supporting long term development data**

Biological Products

Extrapolation using decision tree approach used for synthetics

Not be recommended

Extrapolation of well characterized biologicals

May be applicable
In certain conditions

Science and risk-based approach

Alternative approaches proposed by Q1 draft

Possibility of Setting a Shelf Life of Biological Products Using Extrapolation

Extrapolation for Biologicals (Q1 draft section 13.2.9)

- May be considered for a **well characterized biological drug substance stored frozen**, for which the **quality attributes are known, and their corresponding criticality and residual risks evaluated to ensure patient safety**.
- 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.
- **Justification**: a **risk-based approach** (including a long-term data of analytically comparable batches) to support the proposed extrapolation, and a **statistical analysis** of available long-term data to show no statistically significant or meaningful change over time.
- **Risk assessment for extrapolation**: knowledge of the molecule and its degradation profile, et al.
- **Alternative approaches** can be proposed and justified for extrapolation and/or shelf life prediction **based on appropriate prior knowledge and enhanced stability modelling**.
- Principle for DS **may be applicable to DP extrapolation**, however, applicants are encouraged to seek **agreement with regulatory authorities** and to **consider enhanced modeling techniques**.

Science and risk-based approach

<table>
<tr><th></th><th>Bio DS</th><th>Bio DP</th></tr>
<tr><td>Re-test period</td><td>● May be applicable biologicals with a well understood stability profile
e.g., well characterized IgG therapeutic monoclonal antibody  </td><td></td></tr>
<tr><td rowspan="2">Extrapolation or Stability Modeling</td><td colspan="2">Extrapolation using decision tree: Not be recommended</td></tr>
<tr><td>● May be applicable to well characterized biological DS that are stored frozen using risk-based approach (prior knowledge, statistical analysis) 
● Alternative approaches using prior knowledge and enhanced stability modeling can be proposed</td><td>● May be applicable, but encouraging to seek an agreement with regulatory authorities, and consider enhanced stability modeling</td></tr>
</table>

*Justification using risk-based approach would be required for applying all approaches

Outline

- Science and risk-based approaches proposed in ICH Q1 draft
- **Extrapolation reported in scientific articles**
- Japanese consortium for stability prediction of biologicals

Scientific reports related to extralopation

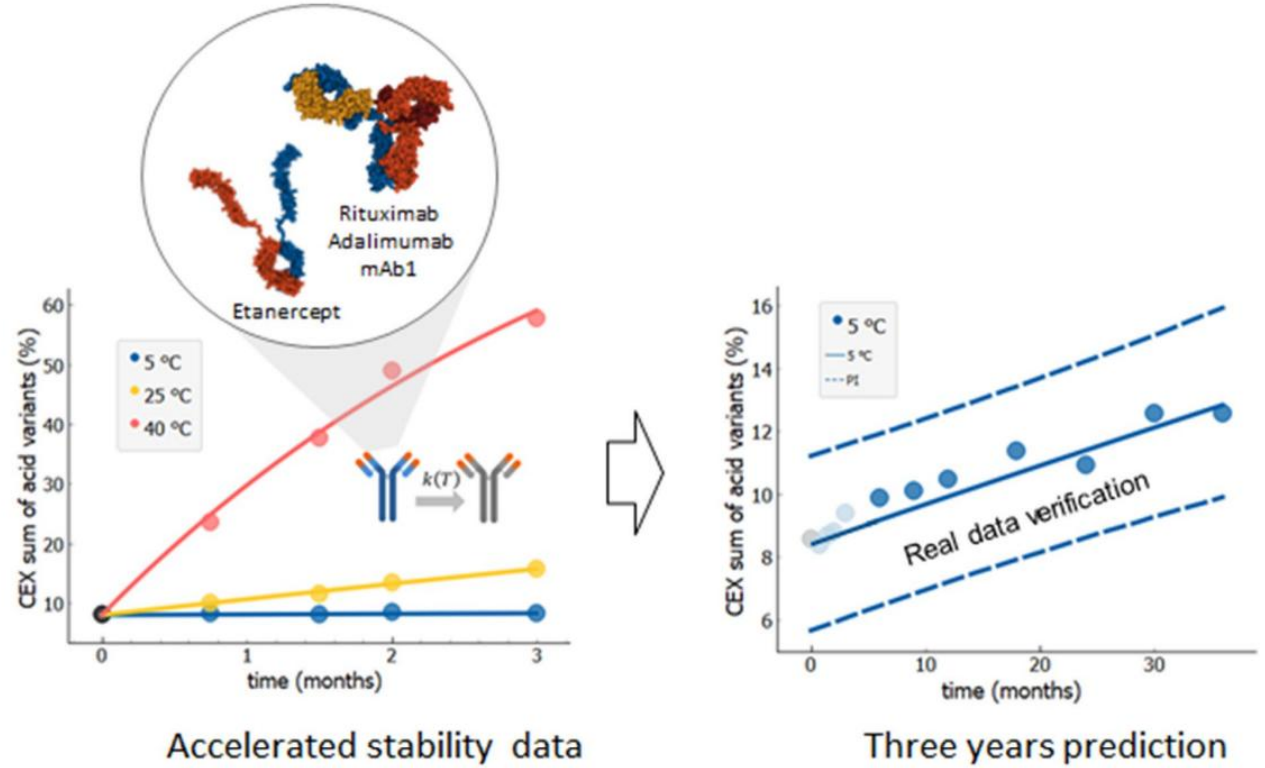
2021

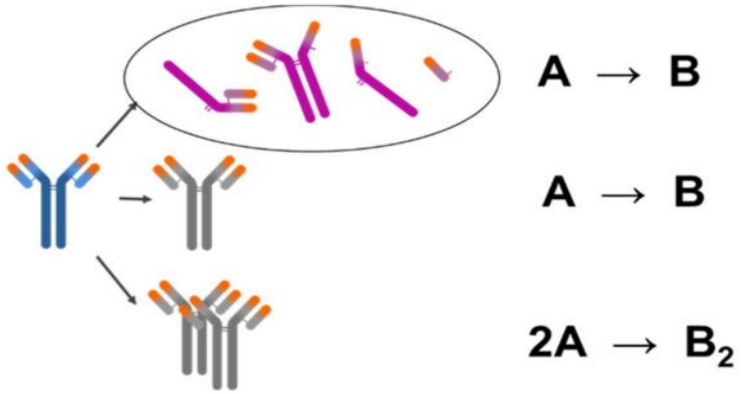
scientific reports

OPEN

Long-term stability predictions of therapeutic monoclonal antibodies in solution using Arrhenius-based kinetics

Drago Kuzman[1], Marko Bunc[1], Miha Ravnik[2,3], Fritz Reiter[4], Lan Žagar[5] & Matjaž Bončina[1]✉





First order degradation kinetic model

$$[\mathrm{A}](t,T) = [\mathrm{A}_0]e^{-k(T)t}$$

$$[\mathrm{B}](\mathrm{t},\mathrm{T}) = 1 - (1 - [\mathrm{B}_0])\mathrm{e}^{-\mathrm{k}(\mathrm{T})\mathrm{t}}$$

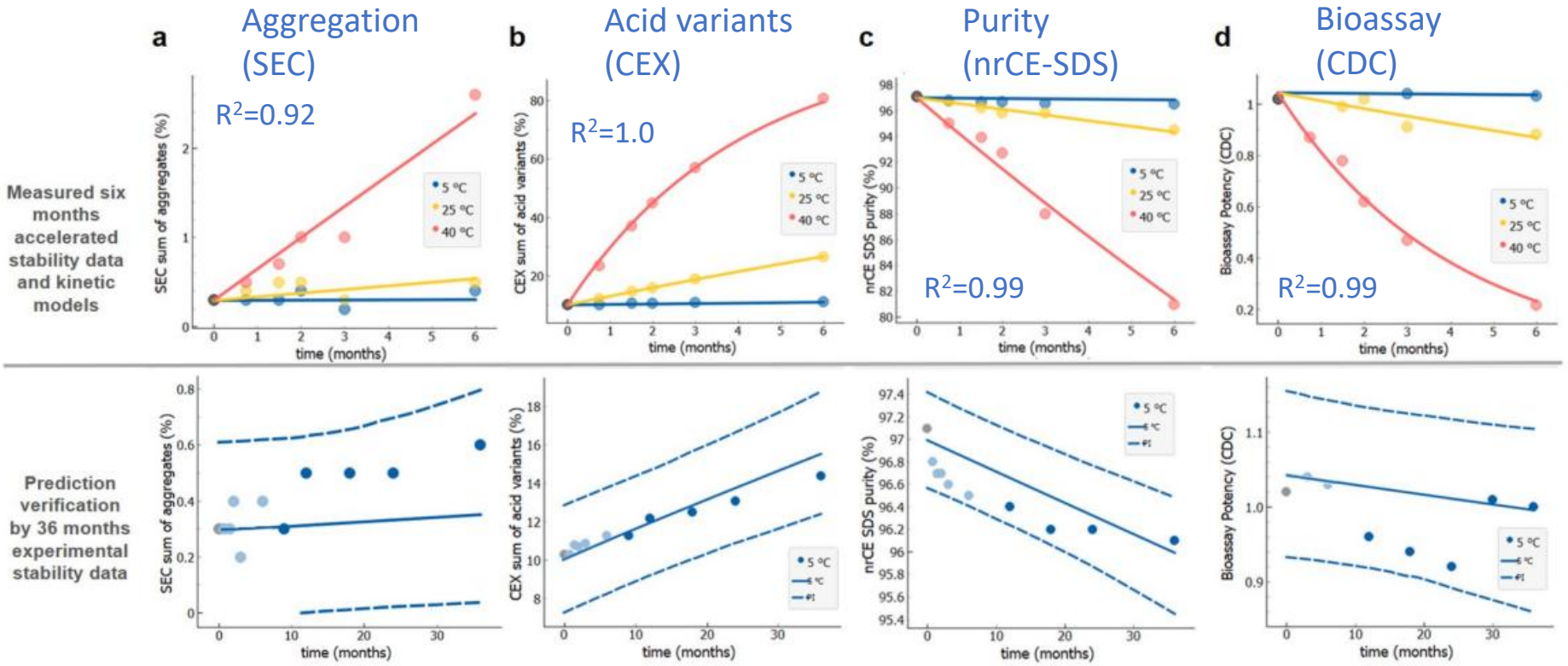
Sci Rep 11, 20534 (2021).
https://doi.org/10.1038/s41598-021-99875-9

Scientific reports related to extrapolation

2021

Actual accelerated stability data

Prediction verification



- **The predicted stability profiles from stability data up to 6 months showed high agreement with 36-month real-time data regarding acidic variants, purity, and aggregates.**

<u>Challenges or future work</u>

- ✓ **Improving prediction accuracy for quality attributes that do not follow simple kinetic behavior (e.g., basic variants)**
- ✓ **Expanding applicability to proteins with complex or multi-pathway degradation mechanisms**

Scientific reports related to extrapolation

2023

scientific reports

OPEN

A universal tool for stability predictions of biotherapeutics, vaccines and in vitro diagnostic products

M. Huelsmeyer[1], D. Kuzman[2], M. Boncina[3], J. Martinez[3], C. Steinbrugger[3], J. Wouston[4], C. Calero-Rubio[5], W. Roche[6], B. Niederhaus[7], Y. VanHaelst[8], M. Hrynyk[9], P. Ballesta[10], H. Achard[10], S. Augusto[11], M. Guillois[11], C. Pszczolinski[11], M. Gerasimov[12], C. Neyra[12], D. Ponduri[13], S. Ramesh[13] & D. Clénet[10]✉

23 products including mAbs, fusion proteins, fragments, enzymes and vaccines et al.

Type of product	Name/company	Format, presentation	Stability attributes	Comments
Biotherapeutics	B1/Abbvie	Liquid, mAb, IgG @ 150 mg/ml	Acidic isoforms	Supporting information for stability evaluation
Biotherapeutics	B2/Novartis	Liquid, mAb, IgG @ 10 mg/ml	Acidic variants, aggregates	Supporting information for stability evaluation
Biotherapeutics	B3/Sanofi	Liquid, mAb @ 1 mg/ml	Aspartate isomerization	Stability evaluation and commercial benchmarking
Biotherapeutics	B4/Sanofi	Liquid, mAb @ 150 mg/ml	Charged isoforms	Phase III product, modeling supporting dossier
Biotherapeutics	B5/Sanofi	Freeze-dried product, enzyme @ 4.2 mg/ml	Glass transition temperature (Tg), residual moisture content (RMC)	Supporting information for stability evaluation
Biotherapeutics	B6/Abbvie	Liquid, mAb @ 40 g/L	Monomer content (SEC)	Temperature excursion at end of shelf life
Biotherapeutics	B7/Sanofi	Liquid, single variable domain @ up to 150 g/L	HMW % (SEC)	Concentration dependent shelf-life estimation
Biotherapeutics	B8/MSD	Liquid, mAb @ 25 g/L	The emergence of impurity %	Shelf-life estimation
Biotherapeutics	B9/Novartis	Liquid, fusion protein, @ 40 mg/ml	Purity (rCE-SDS)	Supporting information for stability evaluation
Biotherapeutics	B10/Novartis	Liquid, fusion protein, @ 50 g/L	Aggregates HMW(SEC)	Supporting information for stability evaluation
Biotherapeutics	B11/Novartis	Liquid, mAb @ 50 mg/mL	Aggregates HMW (SEC)	Supporting information for stability evaluation
Bulk vaccine	V1/Sanofi	Frozen liquid, bacteria-based working seed lot, commercial product	Cell viability	Supporting information for shelf-life evaluation
Multivalent vaccine	V2/Sanofi	Full liquid	Depolymerization (%)	Shelf-life estimation
Inactivated vaccine	V3/Sanofi	Liquid, splitted virus	Antigen content	Shelf-life estimation
Polysaccharide-Protein conjugate vaccine (MenQuadfi)	V4/Sanofi	Multivalent polysaccharide, liquid	Free polysaccharide (%)	Impact of successive excursions of temperature. Batch-to-batch comparison
Live-attenuated virus	V5/Sanofi	Freeze-dried product	Infectious titer (CCID50)	Impact of successive excursions of temperature
Quadrivalent vaccine	V6/Sanofi	Liquid, adjuvanted, commercial product	Antigenicity of antigen A and antigen B (ELISA)	Impact of successive excursions of temperature
Live-attenuated virus	V7/Sanofi	Freeze-dried commercial product	Infectious titer (CCID50)	Impact of successive excursions of temperature
Live-attenuated virus	V8/Sanofi	Freeze-dried product	Infectious titer (CCID50)	Impact of successive excursions of temperature
In vitro diagnostic—VIDAS PTH (1–84)	D1/bioMérieux	Full kit (i.e., standard vial S1, control vial C1, coated SPR, strips, except 4-MUP fluorescent substrate)	VIDAS relative fluorescent value on Control C1 vial	Shelf-life estimation
In vitro diagnostic—VIDAS Cortisol S	D2/bioMérieux	Full kit (i.e., standard vial S1, control vial C1, coated SPR, strips, except 4-MUP fluorescent substrate)	VIDAS relative fluorescent value on Standard S1 vial	Shelf-life estimation
In vitro diagnostic—VIDAS NEPHROCHECK	D3/bioMérieux	Control vial C1 (IGFBP7), liquid	VIDAS relative fluorescent value on Control C1 vial	Shelf-life estimation
In vitro diagnostic—VIDAS NEPHROCHECK	D4/bioMérieux	Control vial C1 (TIMP-2), liquid	VIDAS relative fluorescent value on Control C1 vial	Shelf-life estimation

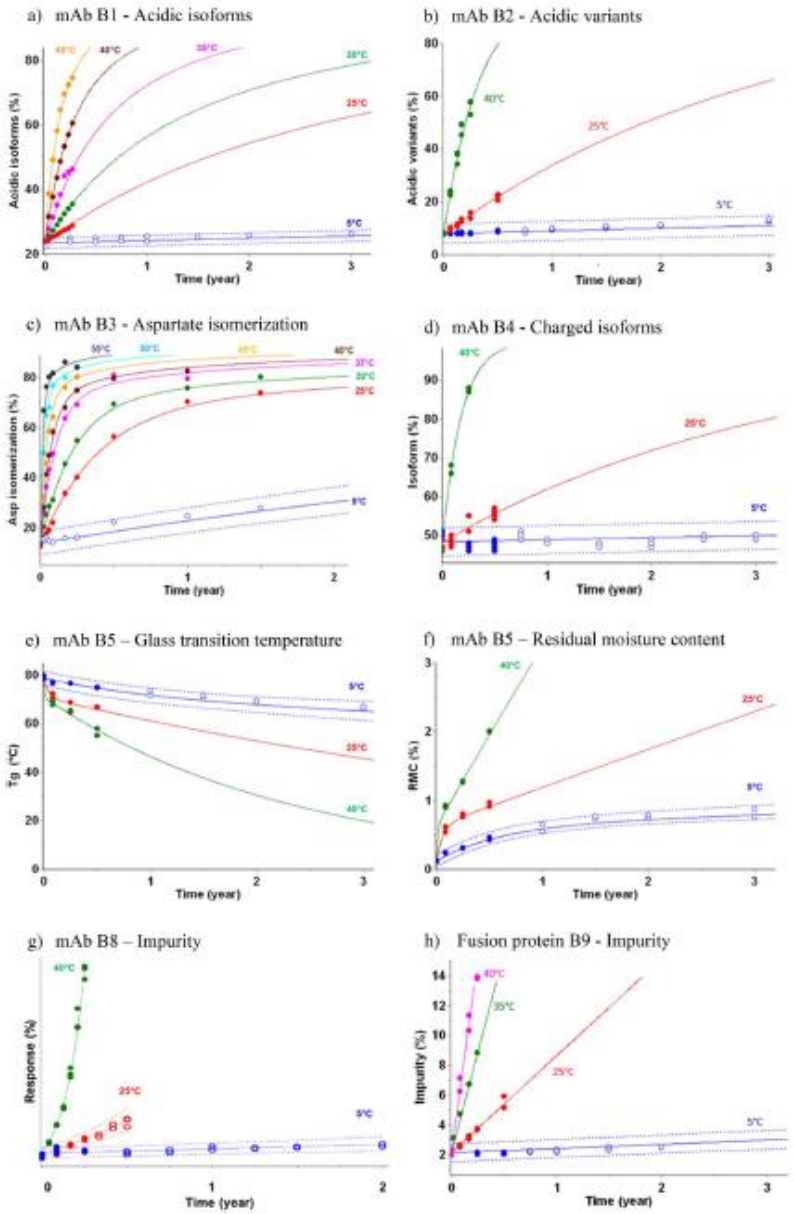
Sci Rep 13, 10077 (2023).
https://doi.org/10.1038/s41598-023-35870-6

Scientific reports related to extrapolation

2023

More measurement points than regular accelerated testing required?

One quality attribute was shown for a product.



- The study introduced a universal predictive modeling approach—Advanced Kinetic Modeling (AKM)—applicable not only to monoclonal antibodies but also to vaccines, diagnostic proteins, and other biologics.

Challenges or future work

- ✓ Extending the model to handle non-Arrhenius behavior often seen in complex biological systems
- ✓ Addressing variability originating from different manufacturing processes or raw material lots
- ✓ Establishing regulatory frameworks for accepting model-based shelf-life justification.

Scientific reports related to extrapolation

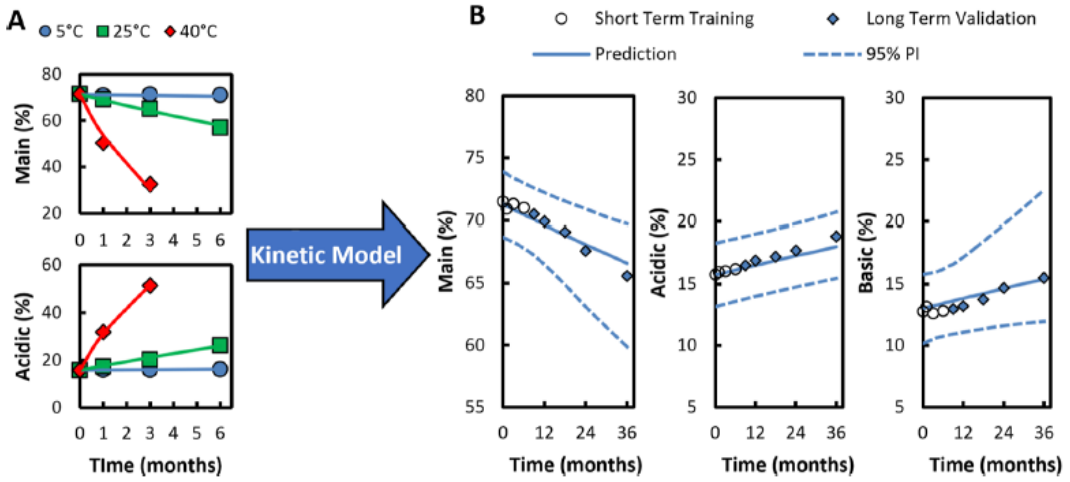
2024

molecular pharmaceutics

pubs.acs.org/molecularpharmaceutics Article

Predicting the Long-Term Stability of Biologics with Short-Term Data

Michael Dillon,* Jun Xu, Geetha Thiagarajan, Daniel Skomski, and Adam Procopio



Mol. Pharmaceutics 2024, 21, 4673−4687
https://doi.org/10.1021/acs.molpharmaceut.4c00609

Table 1. Tested Drug Products[a]

drug product	state	modality	subtype	concentration (mg/mL)
A	liquid	mAb	IgG4	medium
B	liquid	mAb	IgG1	medium
C	liquid	mAb coform	IgG1 + IgG4	low
D	liquid	mAb	IgG1	high
E	liquid	mAb	IgG4	high
F	liquid	ADC	IgG1	low
G	lyophilized	ADC	IgG1	low
H	liquid	mAb	IgG4	low
I	lyophilized	mAb	IgG4	low
J	liquid	mAb	IgG4	high
K	liquid	mAb	IgG1	high
L	liquid	mAb	IgG4	low
M	liquid	mAb coform	IgG4 + IgG4	low
N	liquid	mAb	IgG4	medium
O	liquid	mAb	IgG1	medium
P	liquid	mAb	IgG1	medium
Q	liquid	mAb coform	IgG1 + IgG4	low
R	lyophilized	fusion protein	N/A	medium

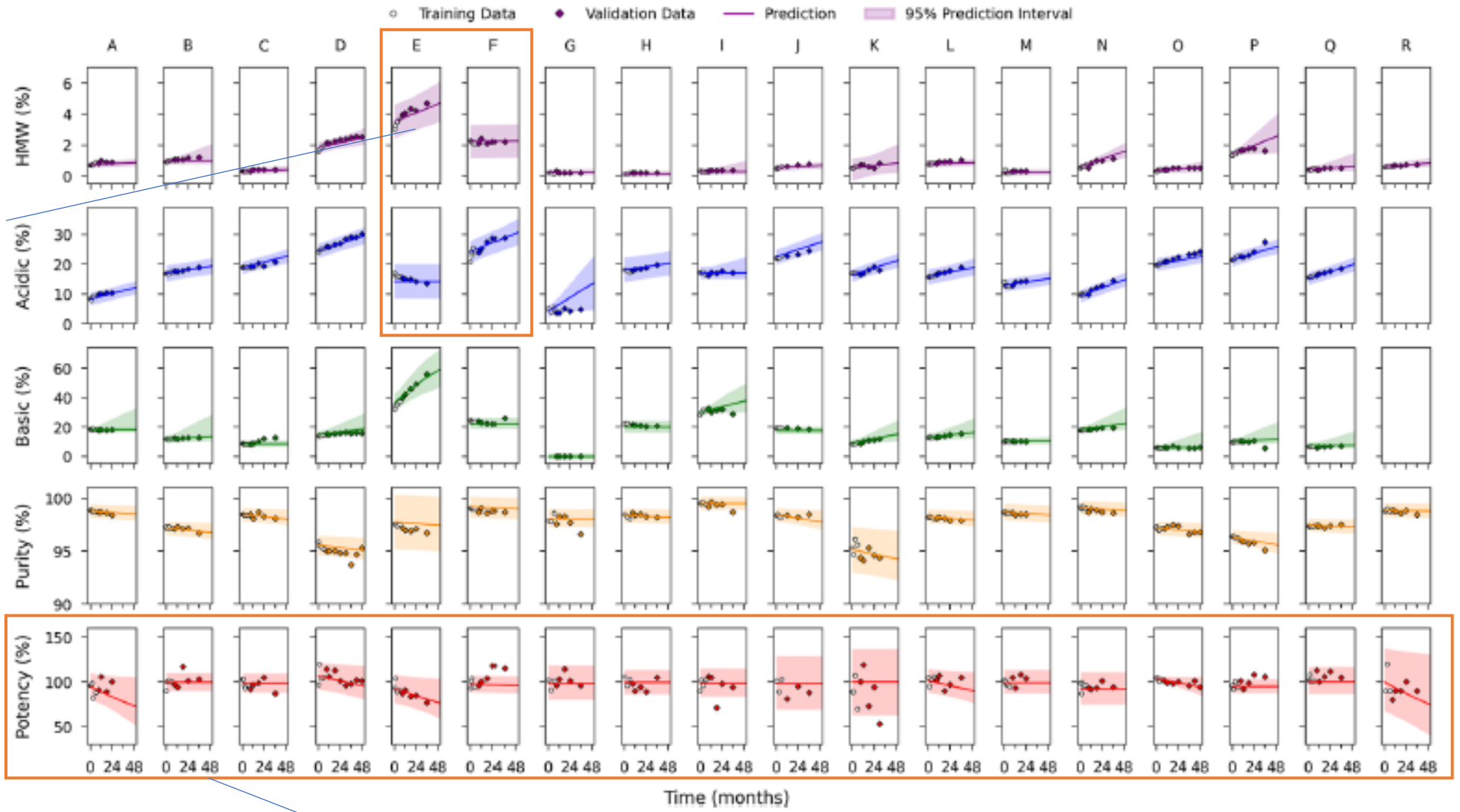
[a]High: ≥100 mg/mL, medium: >25 and <100 mg/mL, low: <25 mg/mL.

18 products:
mAb×15, ADC×2, Fusion protein ×1

Scientific reports related to extrapolation

2024

Discrepancy around zero

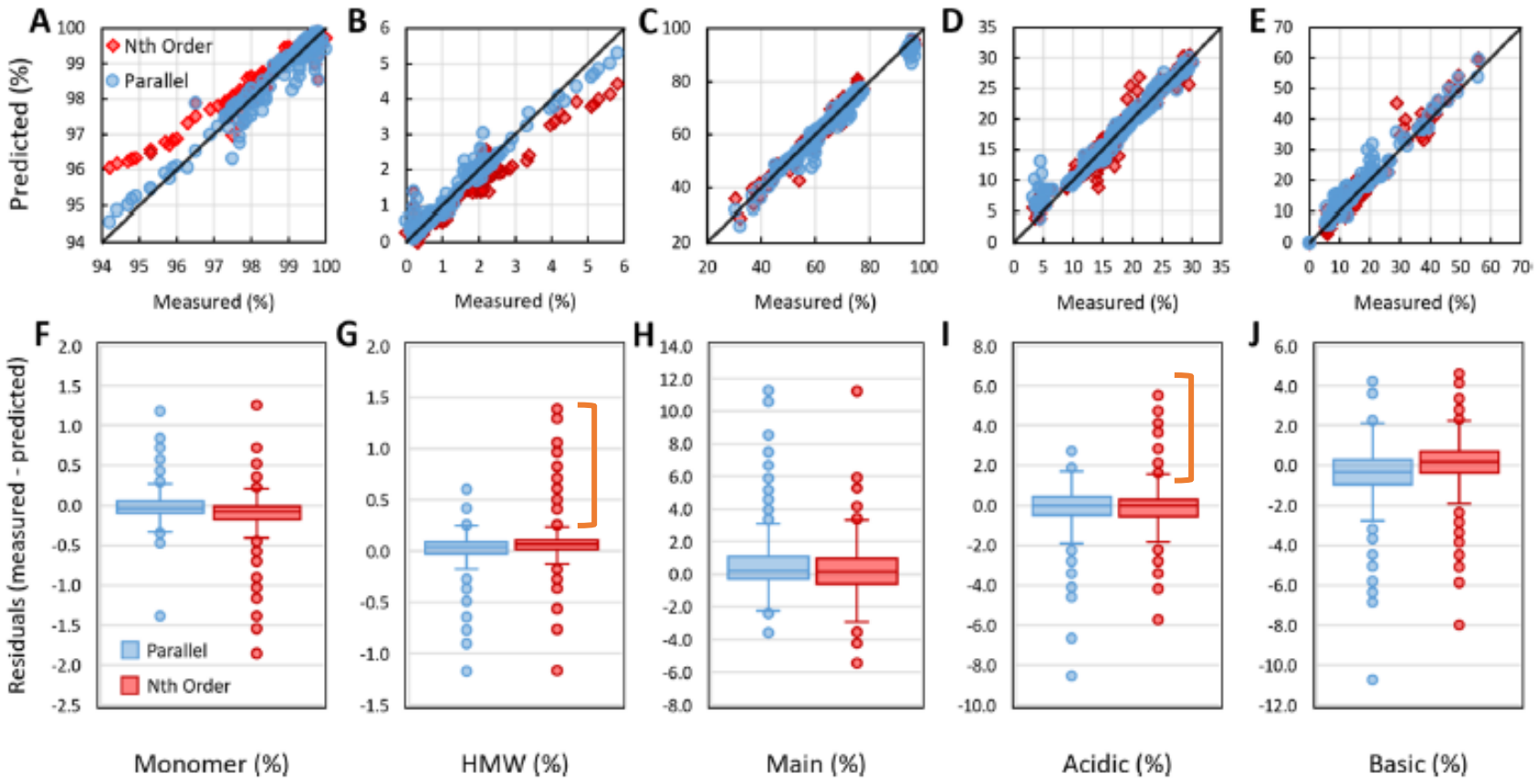


The prediction interval for potency being wider than for other properties due to the variability in methods.

Scientific reports related to extrapolation

2024

- ✓ The parallel pathway model can obtain the predicted values closer to the actual measured values.
- ✓ In the single pathway model, there is a high rate of underprediction, which increases the risk of OOS.
- ✓ The parallel pathway models can reduce the risk of underprediction.



Challenges or future work

- ✓ Modeling complex, multi-pathway degradation networks more accurately
- ✓ Capturing the impact of protein-protein interactions in high-concentration formulations
- ✓ Integrating physical degradation (e.g., aggregation) with chemical degradation pathways in a single model

Scientific reports related to extrapolation

2025

scientific reports

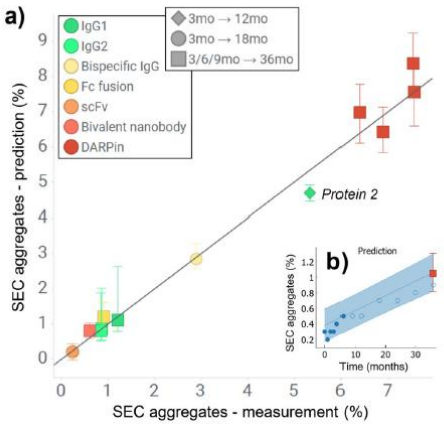
Check for updates

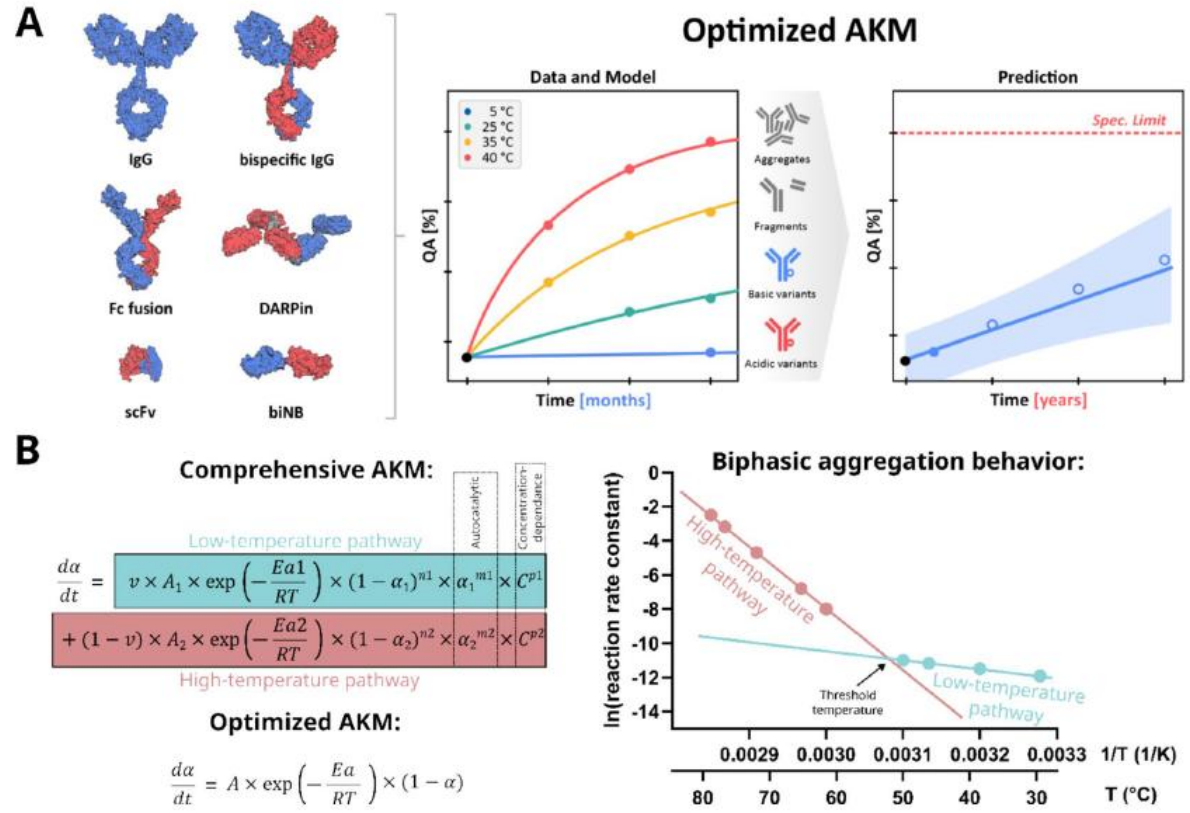
OPEN

Simplified kinetic modeling for predicting the stability of complex biotherapeutics

Mitja Zidar[1], Stefano Cucuzza[2], Matjaž Bončina[1] & Drago Kuzman[1]✉

- Effective modeling of aggregate predictions for diverse protein modalities.
- Significance of temperature selection in stability studies
- Note: A continuous validation with the long-term data is crucial in cases where the measured change at the lowest temperature is comparable to the method variability.





Scientific reports related to long-term stability prediction

Shelf life determination: Long-term stability studies at actual storage conditions for three years

Publication year	Title	Samples	Quality (Stability) Attributes	Data sets	Model
2021	Long-term stability predictions of therapeutic monoclonal antibodies in solution using Arrhenius-based kinetics	Rituximab Adalimumab Etanercept mAb1	Aggregation (SEC) Purity(CE-SDS) Charge variants (CEX) Bioactivity	up to 6 months at 5, 25, and 40 °C	First order degradation kinetic model + Arrhenius equation
2023	A universal tool for stability predictions of biotherapeutics, vaccines and in vitro diagnostic products	23 products **mAb ×7** Fusion protein×2 Fragment ×1 Enzyme ×1 Vaccines ×7	For mAbs and fusion proteins, Acidic variants Aspartate isomerization Aggregates/HMW Purity (CE-SDS)	Typically, at 5, 25, 40 °C (5-55 °C for mAbs)	Advanced kinetic modeling (AKM)
2024	Predicting the Long-Term Stability of Biologics with Short-Term Data	18 products **mAb×15** ADC×2 Fusion protein ×1	Size variants Charge variants Purity Potency	up to 6 months at 5, 25, and 40 °C	First order reaction (single, parallel), Nth-order reaction Monte Carlo simulation
2025	Simplified kinetic modeling for predicting the stability of complex biotherapeutics	8 products IgG×4, Fc fusion, scFv, nanobody, DARPin	Aggregation (SEC)	up to 9 months between 5 to 40 °C	Optimized AKM

Increasing utility of extrapolation

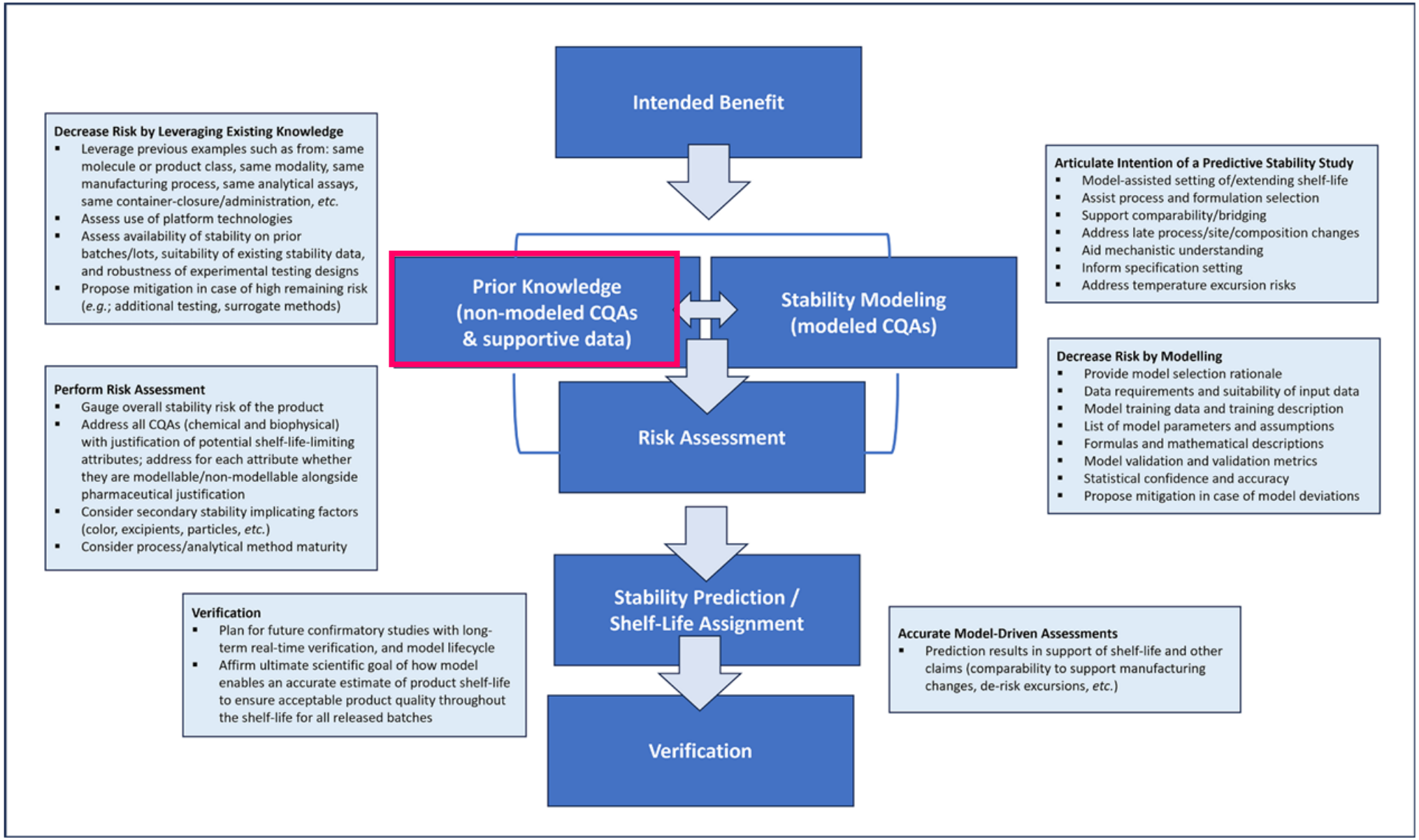
More applicability to complex and diverse modalities and future expansion of application scope

Is it not necessary to predict other quality characteristics specified in the specification?

Shelf life determination: Extrapolation using accelerated studies + stability modeling (kinetic models)

Predictive stability in biopharmaceuticals and vaccines: Perspectives and recommendations towards accelerating patient access

Review from IQ consortium



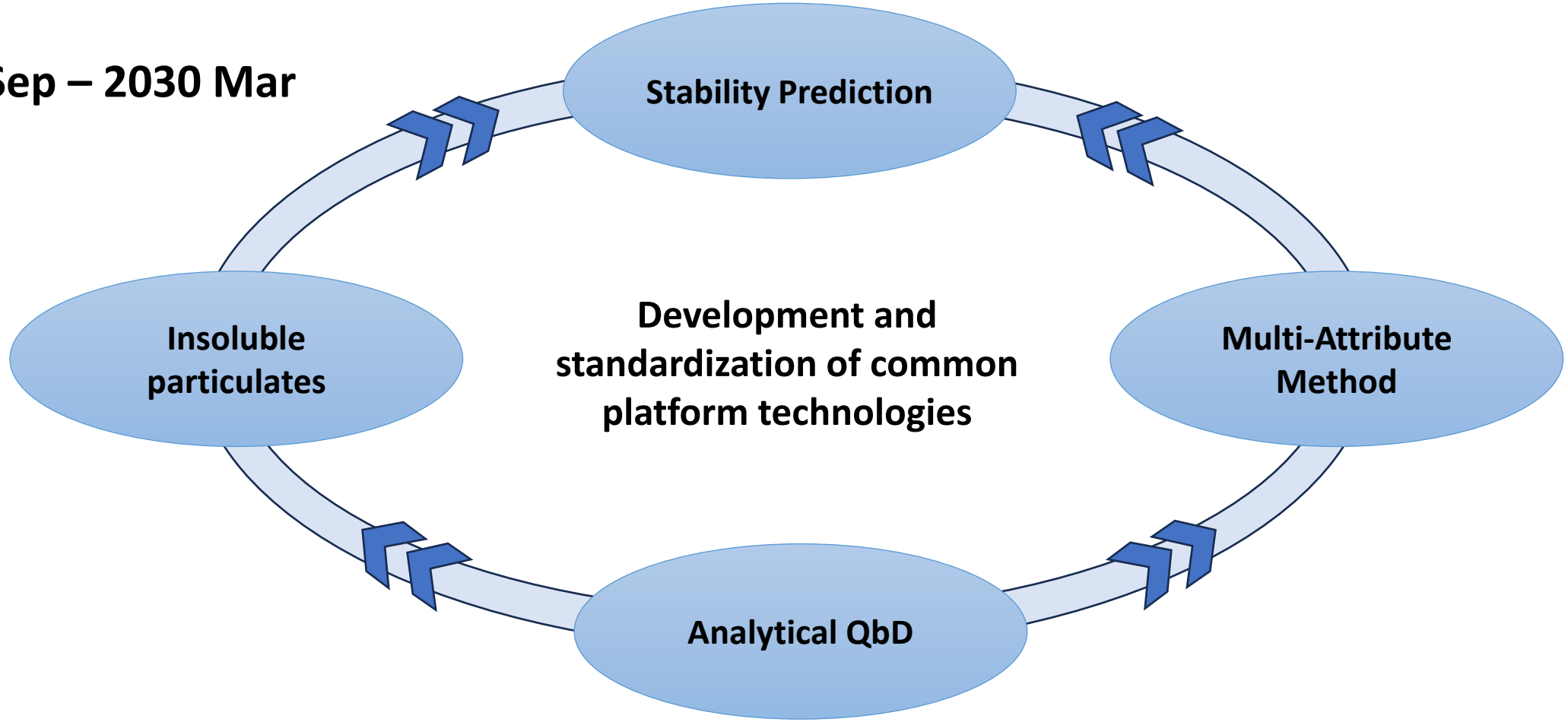
https://doi.org/10.1016/j.xphs.2025.103873
Journal of Pharmaceutical Sciences 114 (2025) 103873

Outline

- Science and risk-based approaches proposed in ICH Q1 draft
- Extrapolation reported in scientific articles
- **Japanese consortium for stability prediction of biologicals**

AMED research project
Japanese biopharmaceuticals consortium

2025 Sep – 2030 Mar



Academia

NIHS, Osaka Uni., Toyo Univ.

Industry (27 companies)

17 pharmaceutical companies, 6 equipment manufacturers, 2 CRO, and others

Research on Stability Prediction

Current research plan

Collecting stability data sets from participants

Verification of the feasibility of existing models

Evaluation of the predictive accuracy for each modality and quality attribute

- Applicable modality
- Acceptance predictive accuracy
- Extraction of issues or points to be considered

Development of a new predictive model

- The model that can be compliment to the existing models
- The models that can predict formation of aggregates and insoluble particles

Considerations for extrapolation using stability models based on case studies

Research on Stability Prediction

Issues regarding extrapolation raised by participating institutions

General Comment

- ✓ Aligning Regulatory and Industry Perspectives on Stability Prediction
- ✓ What validation results would enable both regulators and industry to use extrapolation for setting shelf life of final products?
- ✓ Documentation of white papers
- ✓ Cross-company analysis common model data for shelf life determination
- ✓ Establishing standard method/approach for shelf life determination based on accelerated test results
- ✓ Principles for screening products capable of long-term stability prediction versus those that are not, given varying quality characteristics across products

Research on Stability Prediction

Issues regarding extrapolation raised by participating institutions

Extrapolation

- ✓ Enabling the establishment of methods for extrapolating shelf life using existing data, since the EMA guidelines permit extrapolation of biopharmaceuticals during the clinical trial phase.
- ✓ The scope of similar products when utilizing existing knowledge such as similar products.

Stability modeling

- ✓ Which prediction methods (e.g., Arrhenius, Prior Knowledge such as Bayesian estimation) are appropriate?
- ✓ What level of prediction accuracy is required?
- ✓ Which analytical tools (software, etc.) are best?
- ✓ Approaches to Advanced Kinetic Modeling
- ✓ Setting criteria for validity period (extrapolation)
- ✓ Methods for determining appropriate accelerated test temperatures based on storage temperatures for each formulation
- ✓ Distinguishing between Arrhenius-type degradation and non-Arrhenius-type degradation
- ✓ Extrapolation/modeling of aggregation, predicting aggregate formation

Future Perspective

Academia

Industry

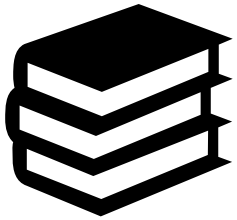
Consortium

ICH Q1

- ✓ Main Document
- ✓ Annex
- ✓ Training Materials

Scientific publications

- Case studies
- AI/ML



White paper

Points to consider

Implementation of extrapolation/stability modeling
for biologicals using science and risk-based approach

Enhancing patient access to new medicines