Predictive Stability for Biopharmaceuticals & Vaccines

Accelerating Patient Access through Industry Recommendations and Stakeholder Alignment

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on behalf of IQ Consortium Working Group for Predictive Stability of Biopharmaceuticals

CE Pharm Regulatory Session, Monday September 28, 2026

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Agenda

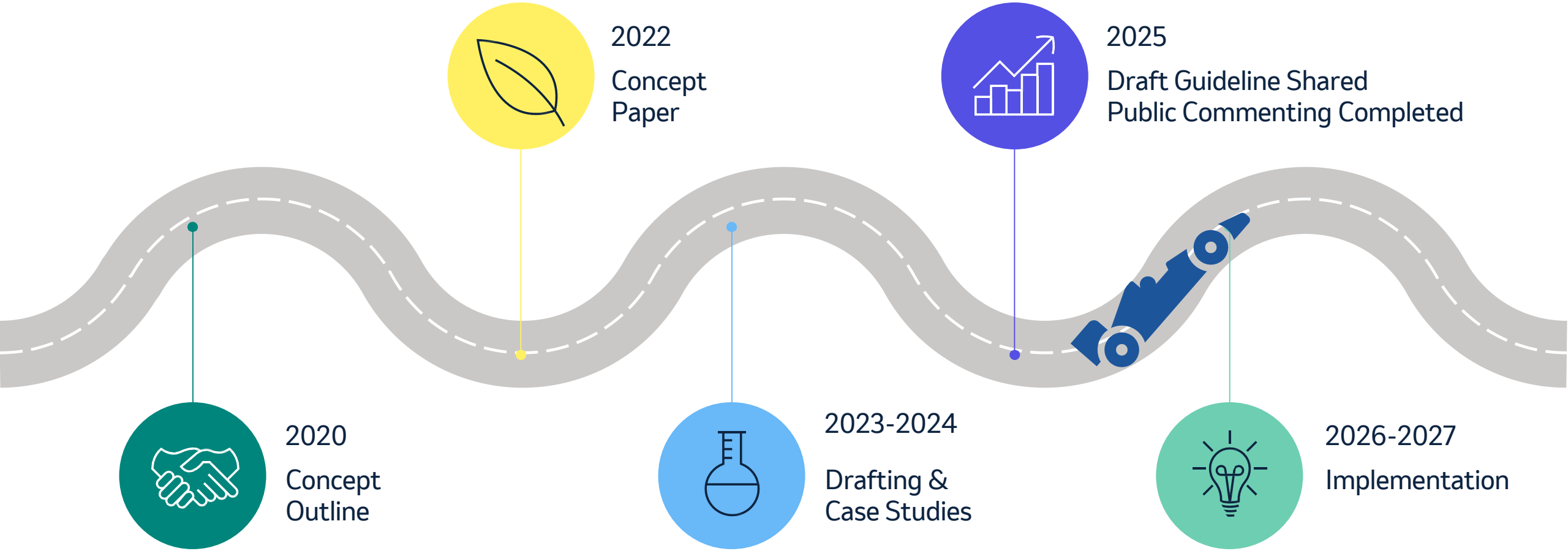
- IQ's Impact & ICH Q1 Revision
- The Toolbox: Mature Models for Biologics & Vaccines
- Proof of Concept: Success Stories Across the Industry
- The Scientific Foundation: Validation & Risk-Based Frameworks
- Overcoming Challenges & Solutions
- Key Takeaways & Conclusion

ICH Q1 Revision Timeline & IQ's Impact

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ICH Q1 Revision Annex 2 on Stability Modeling

"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 [the Stability Modeling] Annex."



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

Public



Predictive Stability Applications in Context of Use

Predictive stability is a data-informed decision-support tool that carefully considers diverse applications

Shelf-life Setting

When will DS/DP CQAs approach specification thresholds?



Comparability (Process/Lots/Devices)

Are there notable difference between groups (e.g., processes, containers, etc.) in stability?



Candidate/Formulation Selection

Are certain candidates or formulations more stable than others or carry greater risk?



Time Out of Storage/Devices

How do temperature excursions impact long-term stability?



Informing Specifications/ Internal Limits

What is a reasonable preliminary spec given the existing data?



De-risking Product Launch

Given initial release and early stability data, what is the probability of observing an out-of-specification event?



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Greater proportion of next-generation modalities and drug–device combination products for patient convenience (*e.g.* autoinjectors) → greater stability burden

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The Role of the IQ Working Group

➢ **Industry alignment**

- Set new standards for the industry and harmonize expectations
- Reduce duplication of efforts across the industry

➢ **Industry position paper**

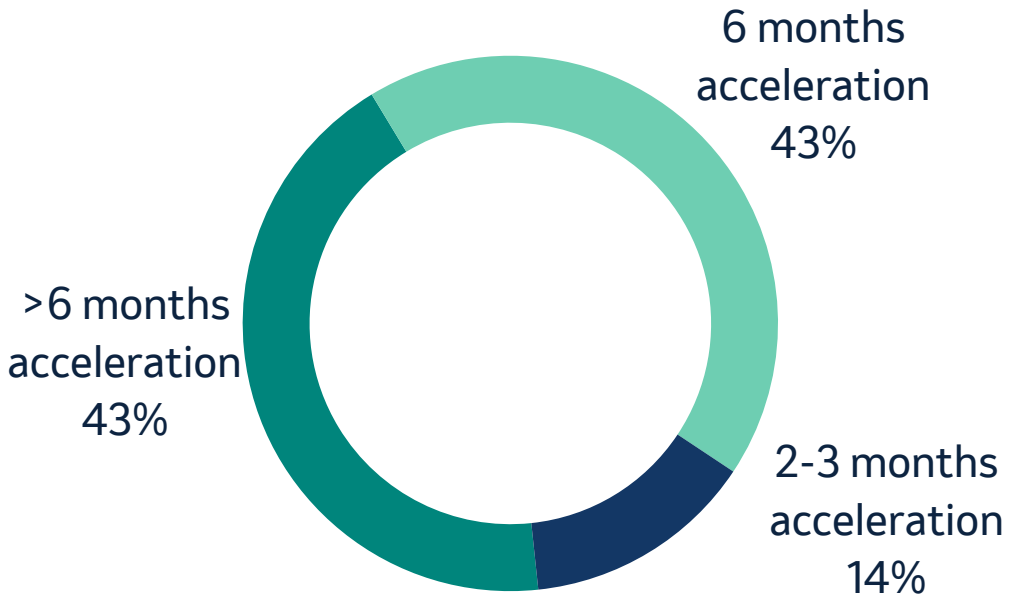
- The working group has published a comprehensive biopharmaceutical industry position paper that offers scientific and risk-based recommendations to foster collaboration with regulatory stakeholders[1]

➢ **Workshops and trainings with health agencies**

- Help with harmonization and minimize differences in application among health authorities
- Workshops (China CDE, Brazil ANVISA/LATAM (ISPE), Egypt), early concept studies for consideration as examples to ICH Q1 EWG, multi-agency scientific advice, etc

Estimated Time-to-Market/Patient Acceleration

Predictive stability at all stages of development (pre-clinical development, clinical, market authorization), when CMC (chemistry, manufacturing, controls) is rate-limiting (n=14 IQ companies, cumulative)



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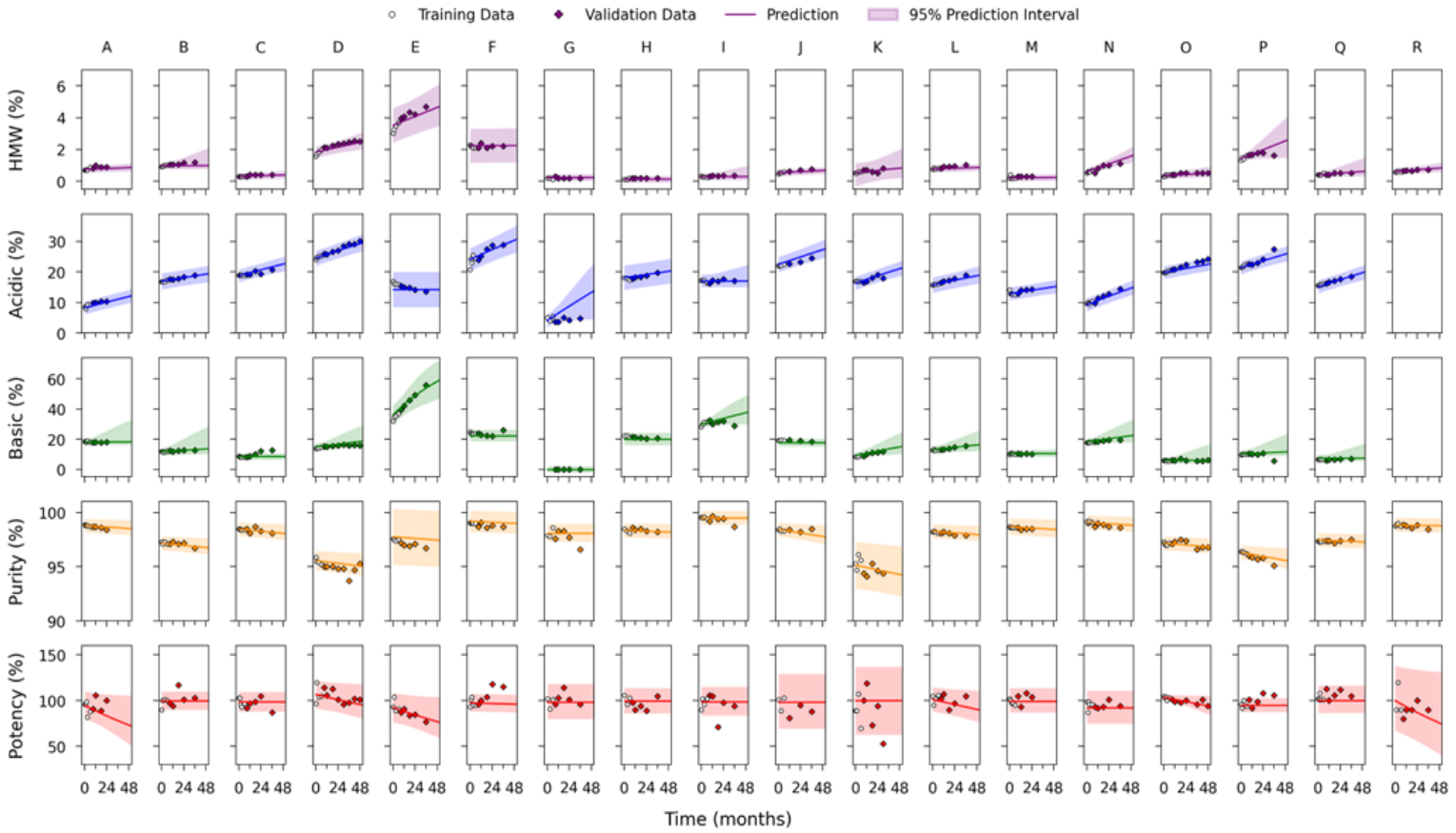
[1]Predictive stability in biopharmaceuticals and vaccines: Perspectives and recommendations towards accelerating patient access, *Journal of Pharmaceutical Sciences* 2025 https://doi.org/10.1016/j.xphs.2025.103873

Proof of Concept: Success Stories Across the Industry

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Examples from >18 Biologics Products

Broad application across different biotherapeutic modalities.



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

High: ≥ 100 mg/mL, **Medium**: **>** 25mg/mL & < 100 mg/mL, **Low:** < 25 mg/mL

Peer-reviewed journal article in *Molecular Pharmaceutics*: https://doi.org/10.1021/acs.molpharmaceut.4c00609

Models are mature as evidenced by successful applications on a broad range of biological modalities and certain types of vaccines.

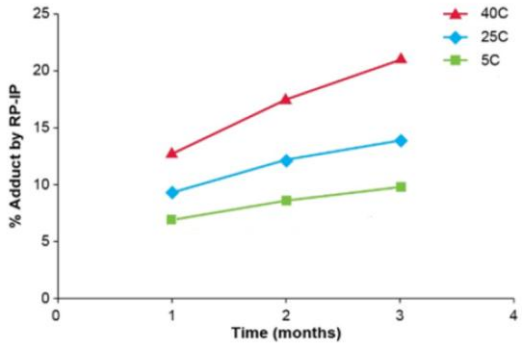
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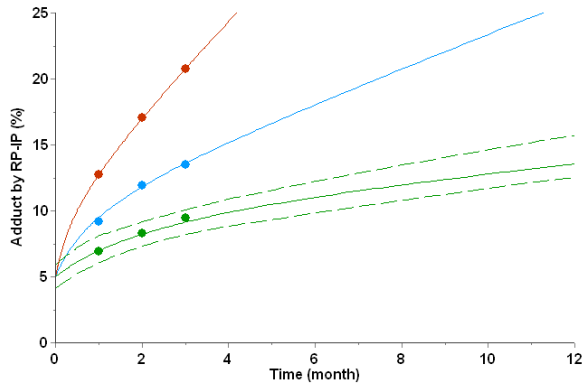
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Examples from >5 Vaccine Products

Broad application across various types of vaccines

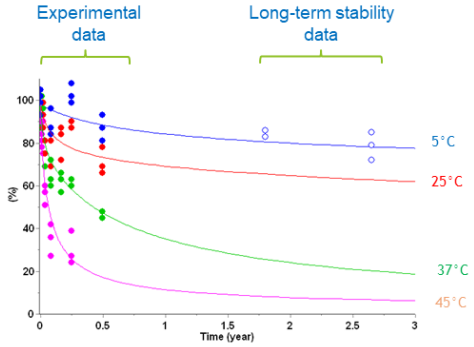
mRNA Vaccine





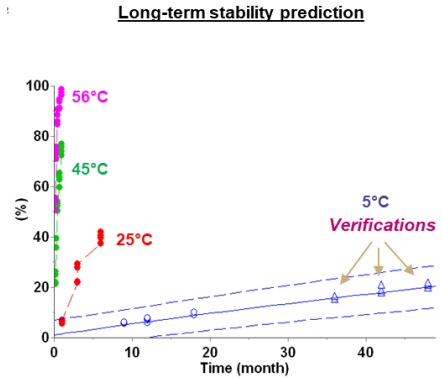
M. Packer et al., 2021

Inactivated Virus-Based Vaccine



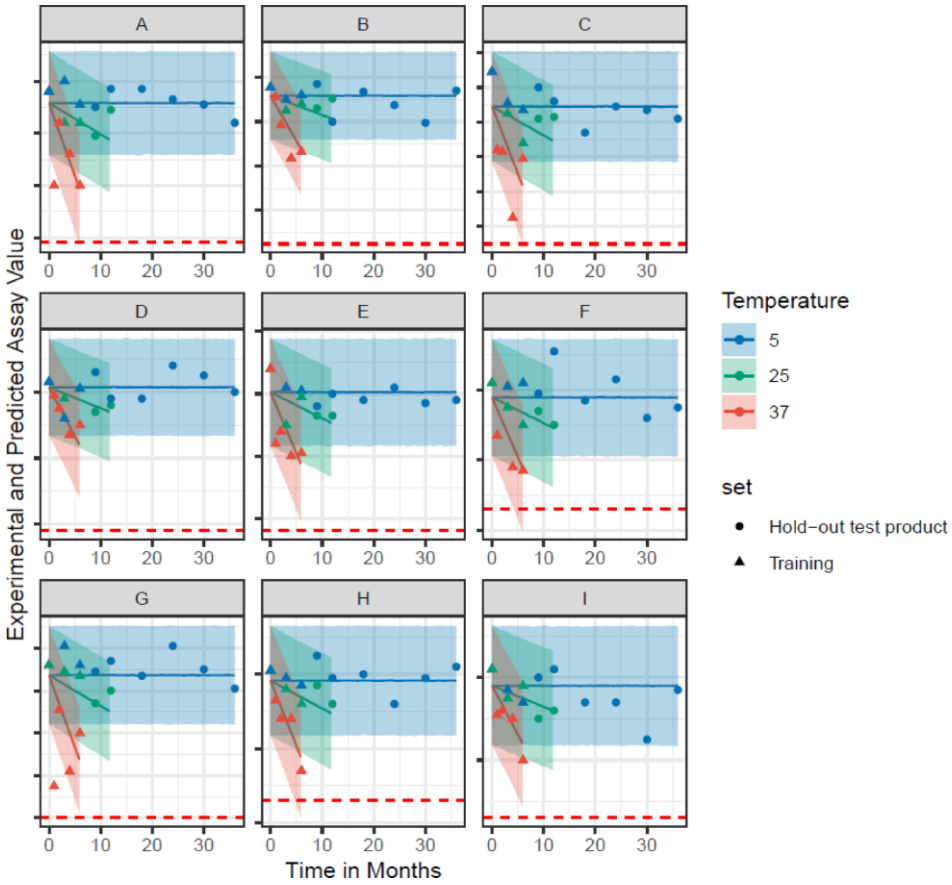
C. Campa et al., 2021

Polysaccharide-based vaccine



C. Neyra et al., 2021

VLP-based Vaccine



Ferrari, Skomski et al., 2025

Models are mature as evidenced by successful applications on a broad range of biological modalities and certain types of vaccines.

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Industry Survey and Regulatory Outcomes

Description of Case Study	Phase	Modality	Territory	Regulatory Outcome
support shelf-life determination beyond the available long term stability data	Commercial (REGEN-COV)	biologics (2-antibody cocktail)	various global health agencies incl US FDA/EMA (10 agencies)	Full acceptance under emergency use
shelf-life determination without full real-time stability data	Commercial	recombinant protein vaccine	EMA, US FDA, Health Canada	Acceptance / positive feedback
extend shelf-life for a Phase 3 clinical batch [a]	clinical	inactivated virus vaccine	Thailand	Full acceptance (no follow up questions)
de-risk impact of high temperature excursions [b]	commercial	multi-valent adjuvant vaccine	EMA	Full acceptance of new model-informed acceptance criteria (no follow up questions)
de-risk temperature excursions [c]	commercial	live attenuated vaccine	Brazil	Full acceptance (no follow up questions)
Phase 1 formulation selection justification [d]	clinical	live attenuated vaccine	US FDA	Acceptable justification (no follow up questions)
understanding degradation process [e]	commercial	mRNA	EMA82	Acceptable justification
support process/site change [f]	lifecycle	biologics (monoclonal antibody)	unspecified	Full acceptance (no follow up questions)
support a drug substance site change	lifecycle	biologics (monoclonal antibody)	US FDA (BLA)	Partial acceptance (permissible as supporting information but no relief on DS/DP stability package)

a Use of a kinetic model and associated predictive bands to extend shelf-life for a clinical batch to secure the Phase III clinical development plan.
b Use of a kinetic model and associated predictive bands to predict and claim acceptable impact of several temporary high temperature excursions on a key stability indicating attribute changes. Whenever the temperature excursion occurs, prediction remains conform to the estimated acceptance criterion at 48 months at 5°C (recommended storage condition).
c Stability Modeling used for management of adverse temperature excursions during transport and distribution of drug products. Kinetic model used to argue absence of impact of short excursion of temperature.
d Use of a kinetic model in an IND PhI submitted to the CBER justifying the selection of PhI formulation to ensure drug product quality and stability.
e Data on the degradation rate was provided and shown to demonstrate Arrhenius behavior, with first order kinetics. The stability profiles were demonstrated to be predictable.
f Kinetic models of two quality attributes were provided as part of a regulatory submission package to support a process change (across three sites). Degradation profiles and stability predictions were used to demonstrated comparability of trends, before and after process changes.

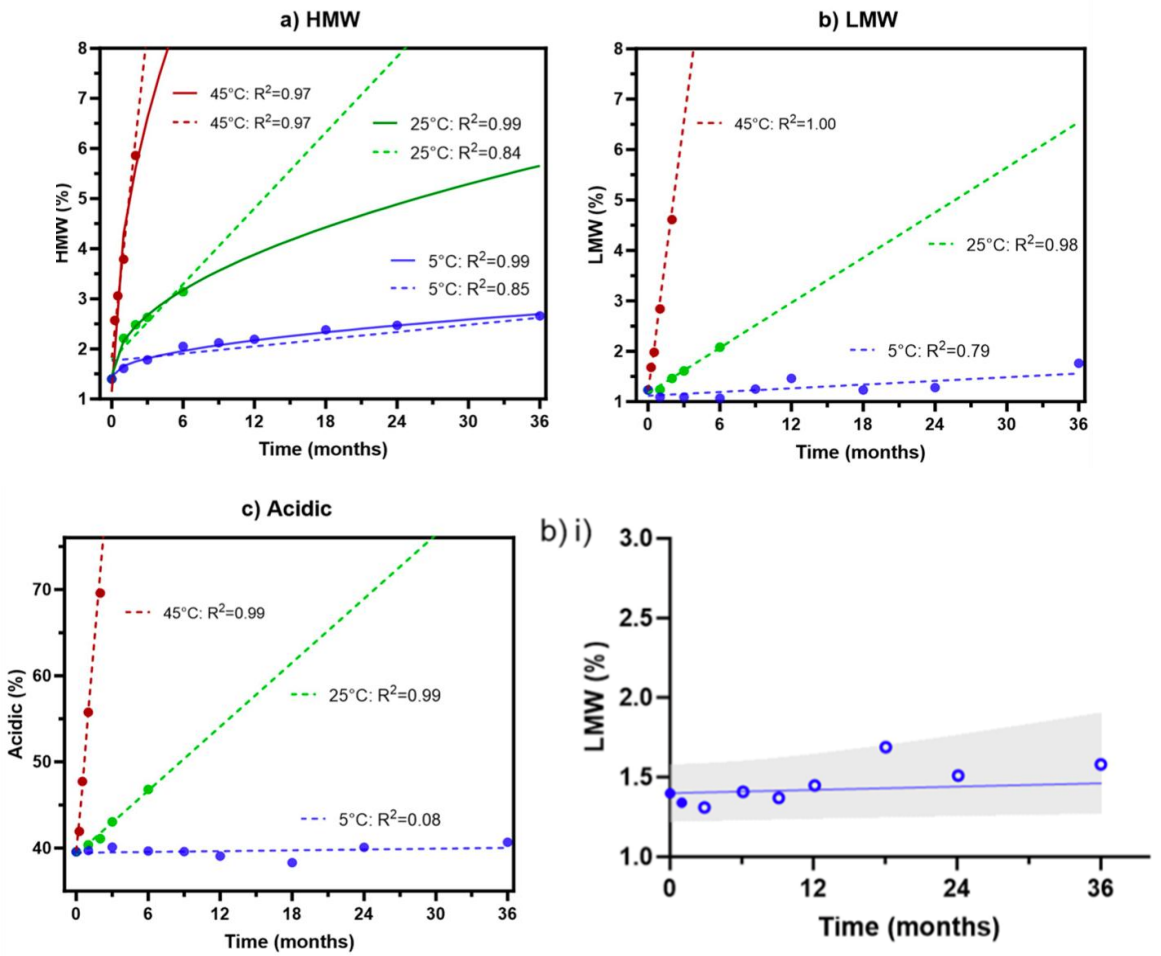
Skomski D, Ji, A., et al. Predictive Stability in Biopharmaceuticals and Vaccines: Perspectives and Recommendations Towards Accelerating Patient Access. J Pharm Sci. 2025 Jun 12:103873.

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Case Study: Achieving Positive Patient Outcomes with Predictive Stability during COVID

- 1 M accelerated data was used to forecast stability up to 36 M and establish 12 M shelf-life, verified with real-time data.
- Successfully applied to 7 anti-SARS-CoV-2 mAbs across multiple lots and used in regulatory filings to address the COVID global health emergency.

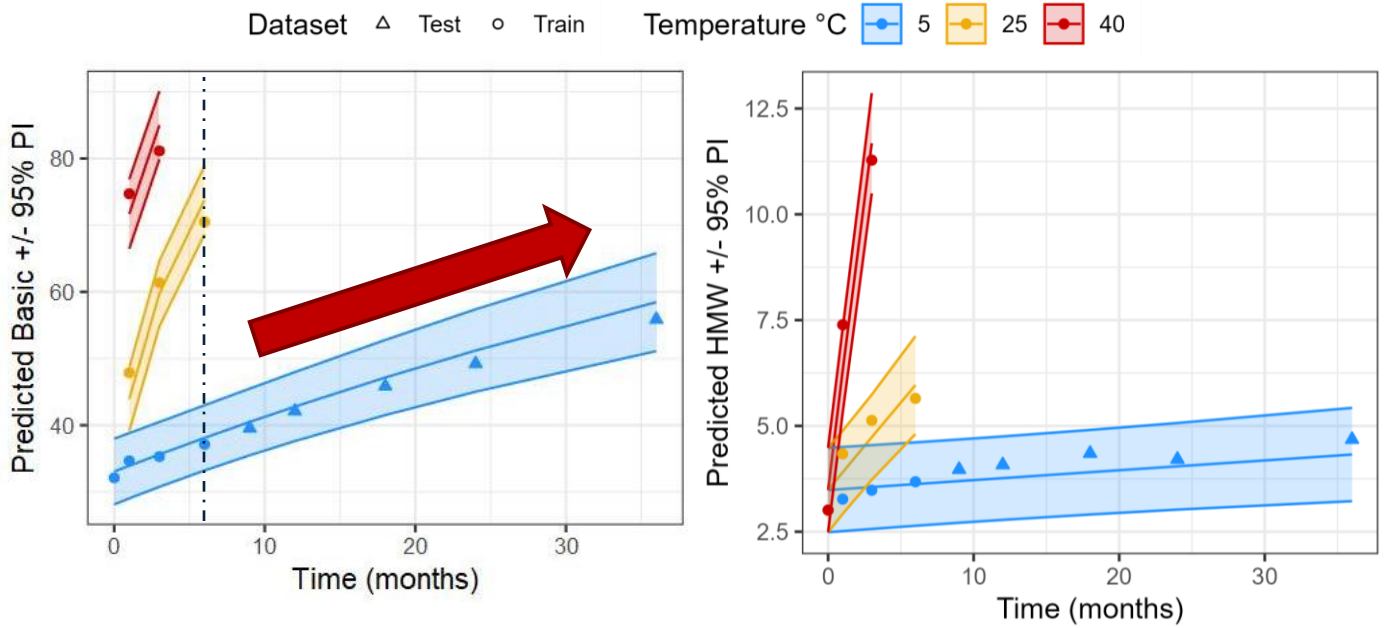


Luo, L., Meleties, M. *et al.*, MABS, 2025, 22, 3189-3197.

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Case Study: Accelerating Development of New Medicines

- biologic monoclonal antibody (mAb)
- exhibited stability issues in development
  - **significant basic variant formation**
  - some high molecular weight aggregation
  - out-of-spec for visible particulates
- **transitioned from an earlier liquid configuration to a lyophilized presentation owing to instability**
- later discontinued



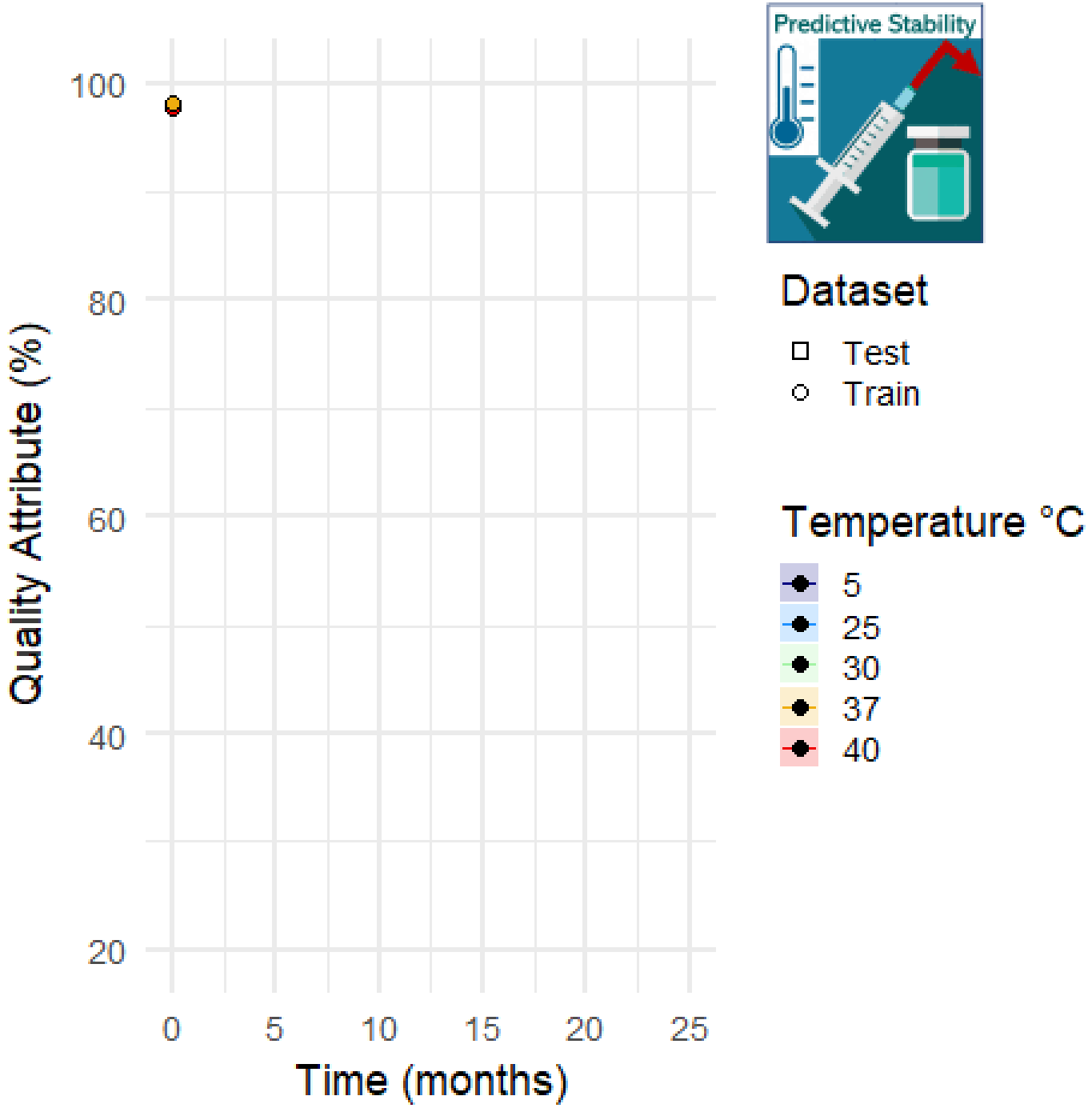
In this scenario, **predictive stability can save 3-12 months in resourcing** through prevention of reformulation, earlier alignment/initiation of workstreams, and avoidance of confirmatory/repeat stability studies.

Thank you to Sam Gleich & Mike Dillon

The Toolbox: Mature Models for Biologics & Vaccines (+Small Molecules)

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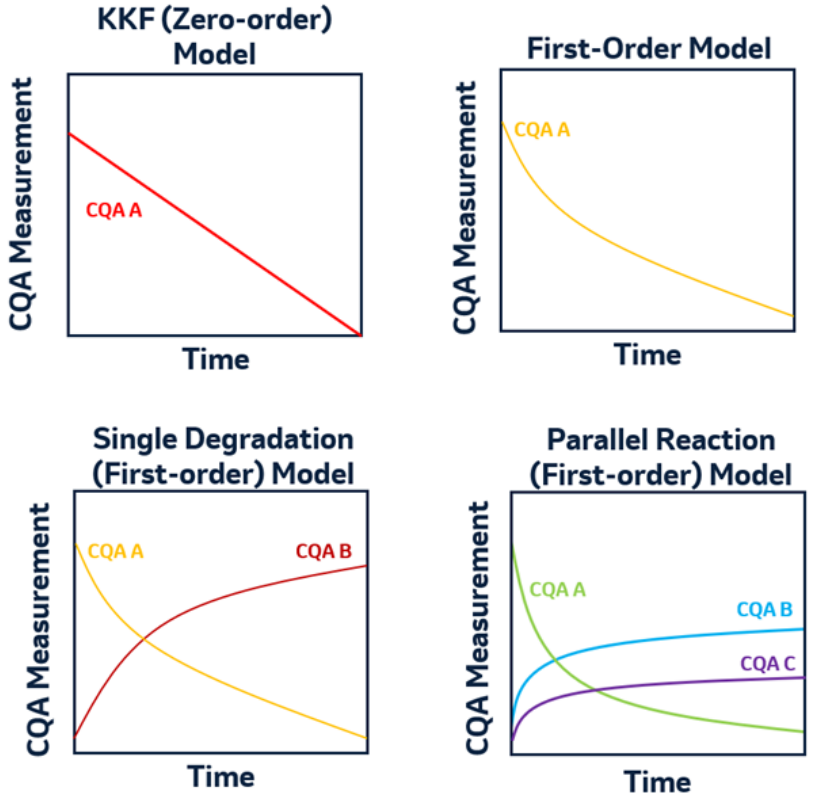
How it Works (Video)



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Overview of Fit-For-Purpose Models

Model Category	Most Common Model Type	Application	Sub-Type
Single-temperature (e.g. 5°C)	Linear and non-linear mixed regression	Well-controlled products exhibiting known behaviors or simple chemical reactions.	▪ Frequentist or Bayesian ▪ With/Without Prior Knowledge (*Qualitative/ Quantitative*) ▪ Non-Hierarchical or Hierarchical ▪ Product-Specific or Leverage Analogous Product
Multi-temperature (e.g. 5°C, 25°C, 40°C)	Advanced kinetic modeling	Complex bioproducts and physicochemical degradation mechanisms.	
Machine Learning, AI, Molecular Simulations		Discovery and early development. Emerging use cases in regulatory.	



Other complex mechanisms can be modeled e.g. autocatalytic and two-step reactions

Models consider minimum data expectations generally ranging from a dozen data points (across 3 temperatures) for platform biologics with well-understood pathways to a couple dozen data points for novel modalities

Models are robust and customized for each product. Advanced Kinetic Modeling (AKM) evaluated for wide range of product types in biotherapeutics, vaccines and biomolecules. Reliable stability predictions for ≥3 years.

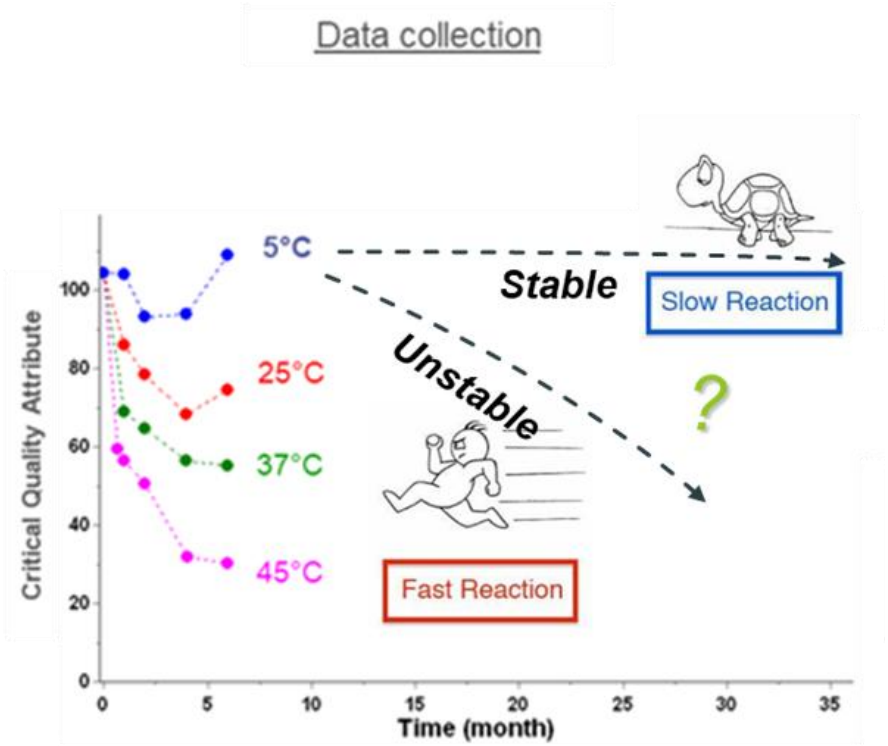
Dillon *et al*, Predicting the Long-Term Stability of Biologics with Short-Term Data, *Molecular Pharmaceutics* 2024, https://doi.org/10.1021/acs.molpharmaceut.4c00609
M. Matu Huelsmeyer, *et al*. Nature, *Scientific Reports 13*, Article number: 10077 (2023)

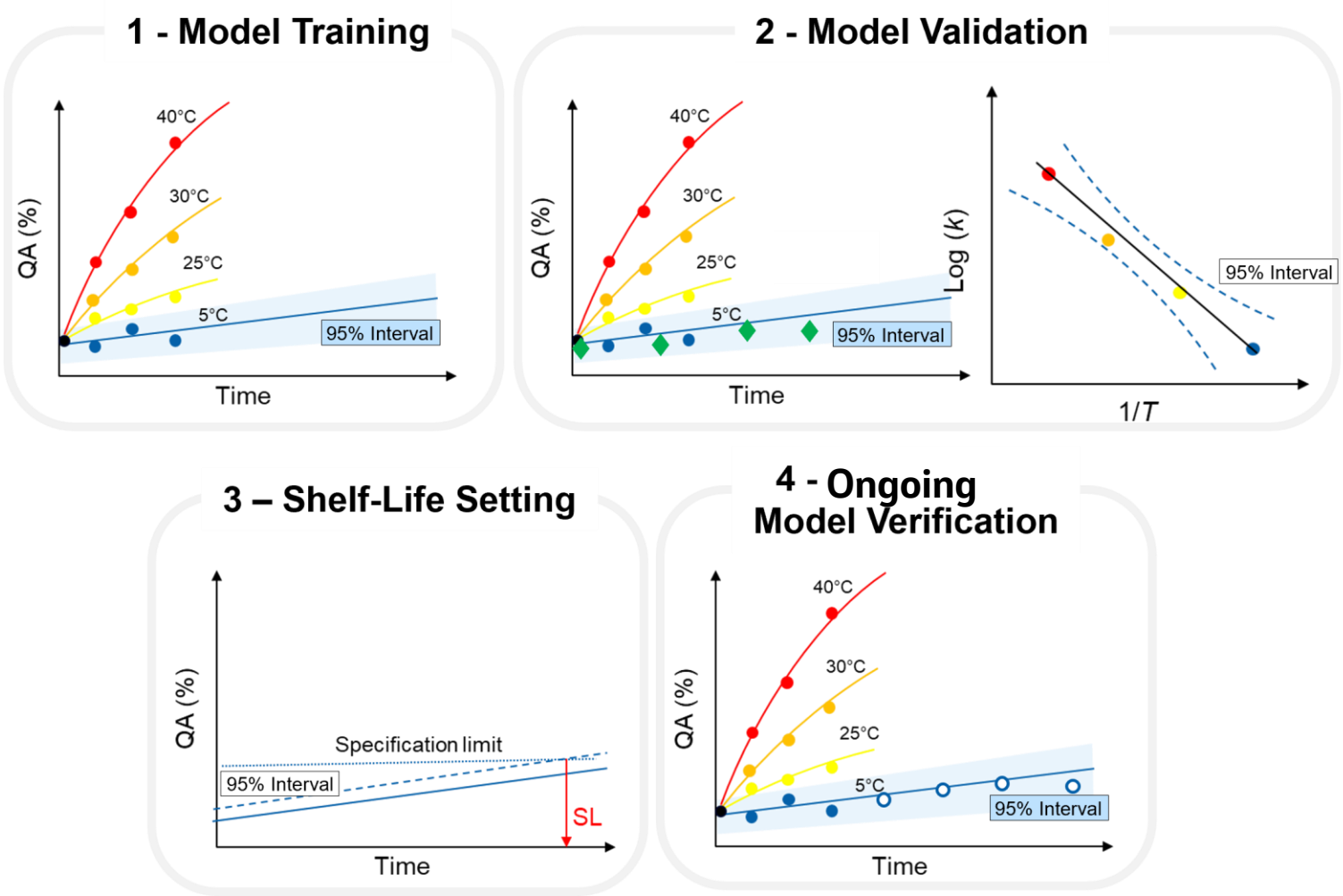
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General Model Approach

Workflow for Application of Predictive Stability Assessment for Shelf-Life Determination





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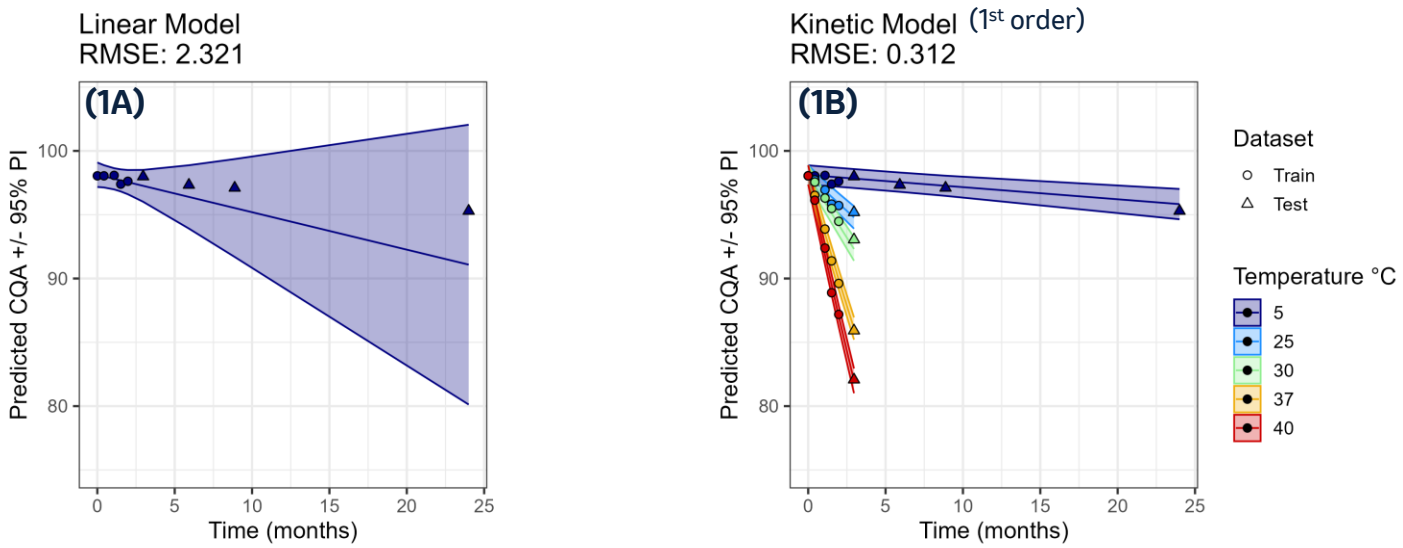
Model Selection Example of Arrhenius Model vs. Linear Regression

Linear regression single-temperature models will continue to be relevant to address simpler mechanisms and well-controlled products

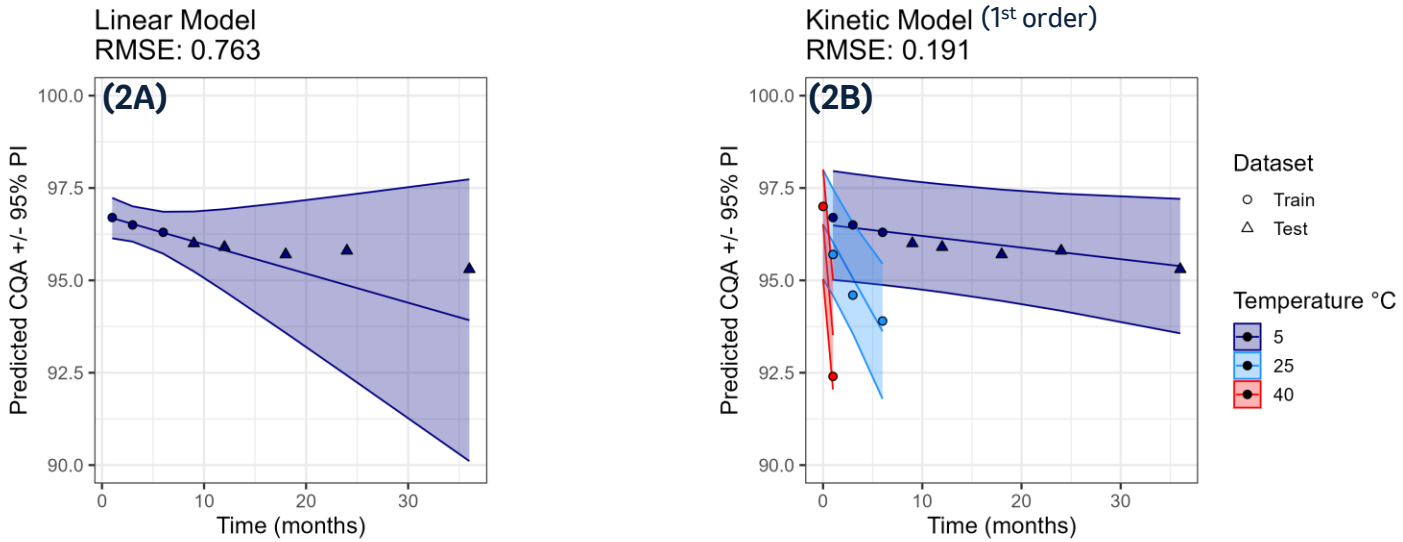
Kinetic n^{th} order models using multiple-temperature data show more accurate prediction compared to linear regression on just 5 °C when limited timepoints are available

RMSE: Root Mean Square Error
(measured vs predicted)
~ lower is better

Example #1: Therapeutic peptide



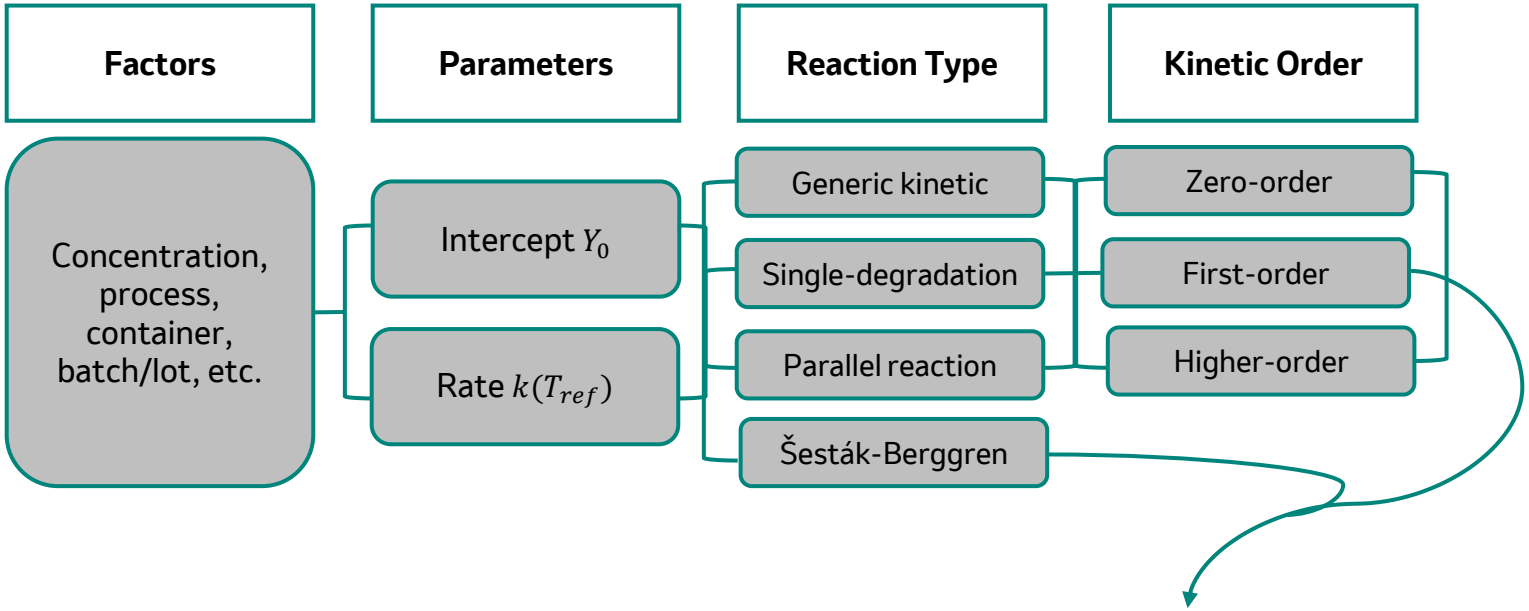
Example #2: High concentration mAb

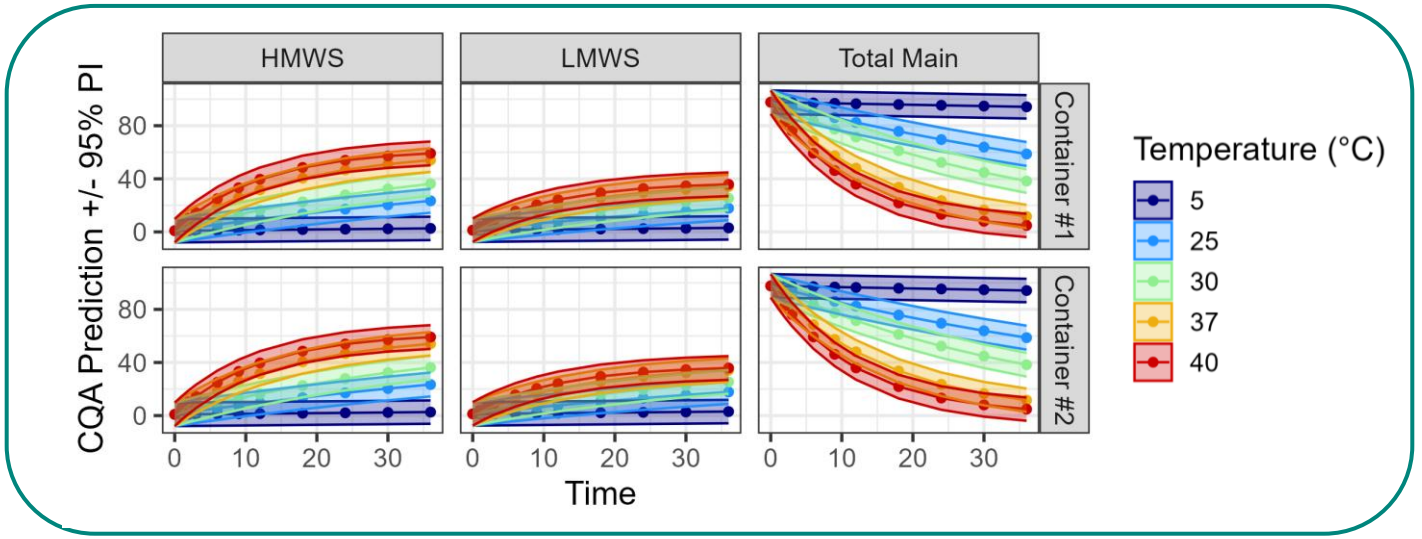


*R^2 is not a recommended metric

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COMING SOON: stablr Package





Thank you to
Sam Gleich,
Michael Johnson,
Federico Ferrari

The Scientific Foundation: Validation & Risk-Based Frameworks

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Considerations for Validation of Models

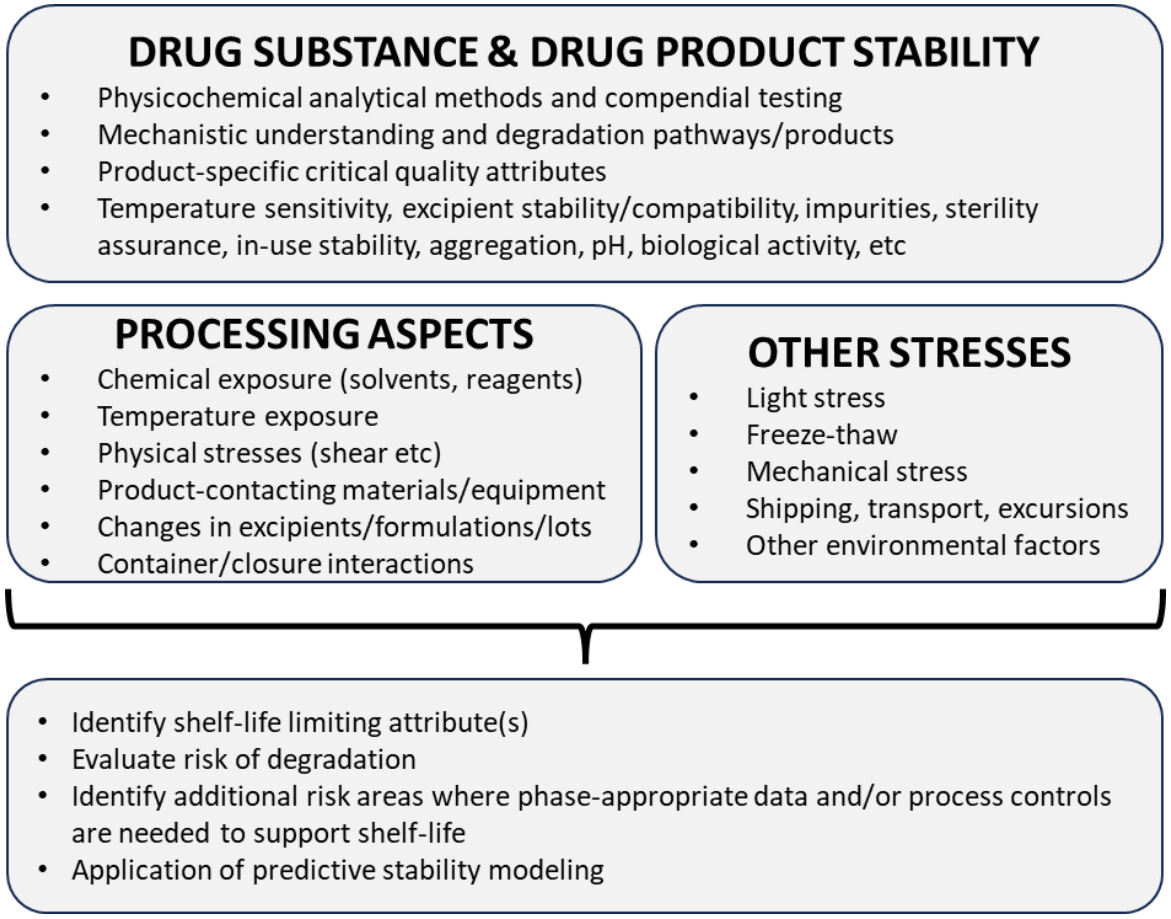
- **Robust Scientific Basis**
  - ✓ Pharmaceutical rationale (analytical/process) for why a model applies to a given product
  - ✓ Incorporate range of experience for CQAs
  - ✓ Prior knowledge: previous batches, analogous molecules/products
  - ✓ Deep understanding of degradation patterns and risks
  - ✓ Decision tree for CQAs (high risk vs low risk / modellable vs non-modellable)

- **Effective Fit-for-Purpose Designs**
  - ✓ Phase-appropriateness
    - ✓ Modality-appropriate
  - ✓ Model selection/input data considerations
    - ✓ Justification and representativeness
  - ✓ Model validation
    - ✓ Statistical metrics: Goodness of fit / Predictive accuracy / Uncertainty quantification
    - ✓ For example: RMSE - *Root Mean Square Error*, MAE - *Mean Absolute Error*, prediction interval coverage
    - ✓ Software validation
    - ✓ Affirm applicability of Arrhenius relationships to a given product

Validation: model performance demonstrated on independent/hold-out data (prior batches or later timepoints)
Ongoing Verification: continued alignment of the prediction with accruing real-time stability post-decision

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Scientific Foundation & Risk Framework



Holistic picture: understanding molecule, degradation patterns, risks (higher temperatures, humidity, light, oxidation, heat, freeze/thaw), odd attributes, then apply enhanced stability modeling

Companies will continue to adhere to existing scientific risk management and due diligence procedures, which predictive kinetic stability modeling well complements

Model credibility needs to be demonstrated during validation. Maintain commitment to model verification with real-time and accolated stress testing.

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Perspective in *Journal of Pharmaceutical Sciences*: https://doi.org/10.1016/j.xphs.2025.103873

Overcoming Challenges

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Challenges & Solution

In the following slides challenges are discussed

- Modellable vs Non-modellable CQAs

  Not all attributes need to be modeled; non-model scientific risk-based justification can be pursued for certain attributes

- Complex CQAs and solutions
- Credibility justification of the model

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Broad Application to Critical Quality Attributes (CQAs)

Broad range of examples of Critical Quality Attributes (CQAs) assessed for large molecules modeled with predictive stability. Many industry examples for predictive stability kinetic modeling with risk-based approach toward establishing a phase appropriate shelf life: setting initial shelf-life, retaining shelf-life after a change in process or formulation, de-risk excursions, etc.

Modality	Critical Quality Attributes (CQAs)	References
Biologics	high molecular weight species and aggregates (HMW% including dimers etc) and fragments, impurities, charge variants (acidic/basic species), chemical modifications (N-terminus pyroglutamate% and other free fatty acids), other stability indicators (glass transition temperature), potency, etc.	(Huelsmeyer, Kuzman et al. 2023)·(Lennard, Zimmermann et al. 2024)·(Dillon, Xu et al. 2024)·(Kuzman, Bunc et al. 2021)·(Bunc, Hadzi et al. 2022)·(Doshi, Martin and Tomlinson 2020)
Vaccines	potency, antigen recovery, antigen purity, antigenicity determined by ELISA, vaccine depolymerization, adduct formation in LNP formulated mRNA vaccine, acetone quantity, etc.	(Huelsmeyer, Kuzman et al. 2023)·(Didier Clenet 2021)·(Campa, Pronce et al. 2021)·(Anthony Scaccia 2025)·(Schnetzinger, Clénet et al. 2024)·(Neyra, Clenet et al. 2021)·(Moriconi, Onnis et al. 2020)·(Clénet, Hourquet et al. 2019)·(Clénet 2018)·(Clénet, Imbert et al. 2014)·(Roduit, Hartmann et al. 2014)·(Ferrari, Skomski et al. 2025)
ADCs (Antibody Drug Conjugates)	HMW%, charge variants, purity, potency, etc	(Dillon, Xu et al. 2024)
Peptides	HMW%, main/purity of therapeutic peptides, etc	(Evers, Clenet and Pfeiffer-Marek 2022)·(Dai, Davis et al. 2023)·(Oliva, Fariña and Llabrés 2012)
Small Molecules		

Comprehensive CQA Assessment

- Assess all stability-indicating CQAs and their scientific risks (as would be done without the model)
- Assess whether each CQA is modellable or is non-modellable
- Non-modellable CQAs can be well-controlled using prior/platform science knowledge and risk assessments

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Definition of Challenging CQA

- **CQA's that don't exhibit any stability change**
  - pH, protein content
- **Complex biomechanisms**
  - potency/bioactivity (mechanism of action dependent, high assay variability)
- **Stochastic behavior** beyond standard kinetics[1]
  - particulation, container-closure integrity
- **Stressor-induced** mechanisms beyond temperature (agitation, light, etc)
  - aggregation, oxidation, surfactant degradation

[1]such as from impurities from process residuals, container extractables & leachables etc.

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Example 1: Knowledge-Driven Rationale for No Significant Change in Protein Content Data

Prior Knowledge-Driven Justification for Non-Modeled CQAs

The industry has studied protein concentration and pH of many products and batches of stability data across different modalities.

Different formulations and a wide range of protein concentrations demonstrated no significant change in protein content and pH over a wide range of target protein concentrations including real-time + accelerated stability.

While there can be changes in protein content and pH due to leachables, container integrity, etc, suitable mitigation is possible with robust manufacturing controls and extensive data and knowledge of the container closure system.

Therefore, with suitable controls protein concentration & pH could be a non-modelled stability attribute

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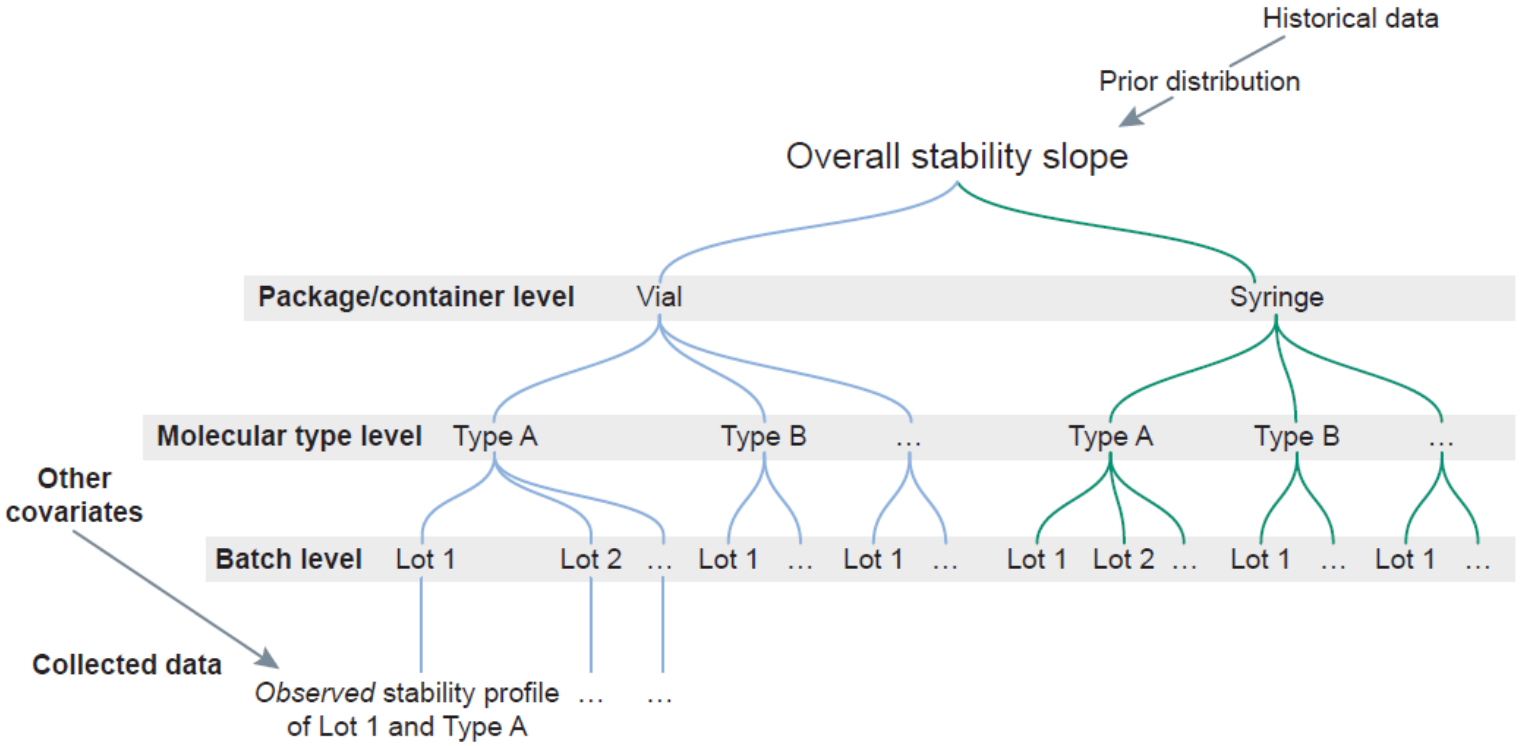
Example 2: Historical Prior Knowledge-Driven Rationale for Different Images & Potency Measurements

Integration of Prior Knowledge via Bayesian Hierarchical Models

Challenge: high assay variability in potency measurements

Solution: benefits of Bayesian Statistics:

- Seamlessly integrate data sets from **Platform Technology** *(processes, methods, etc.)*
- Share information across ***Different Process & Product Configurations*** for improved predictions *(container-closure systems, etc.)*
  - Learn from and mathematically incorporate ***Prior Knowledge*** *(data from previous drugs, products, batches, etc.)*



Federico Ferrari *et al*, Bayesian hierarchical model predicts biopharmaceutical stability indicators and shelf life with application to multivalent human papillomavirus vaccine, *Nature Scientific Reports* 2025, http://dx.doi.org/10.1038/s41598-025-99458-y

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Addressing Potential Hesitations Upfront: Justify the Model

Challenges	Solutions
Model Suitability and Scientific Justification	Justified model selection; appropriate data selection and representativeness; robust mechanistic degradation understanding
Risk Mitigation and Predictive Accuracy	Conservative predictions (95% statistical intervals) and independent test/validation data sets; statistical metrics for goodness of fit / predictive accuracy
Addressing Complex Quality Attributes	Leverage: prior knowledge; advanced kinetic models; alternative surrogate/binary methods; increased experimental testing
Connectivity Integrated Control Strategies	Risk-based scientific assessments in holistic drug research & development strategy; maintain close connectivity to control strategies in process residuals/impurities

Ongoing Verification and Protocol Adherence

Industry to continue ongoing model verification: after extended model-supported shelf-life has been set →continue to perform batch stability testing to end of shelf-life

Aligned with ICH Q1 Annex 2 expectations for enhanced stability modeling

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Key Takeaways & Conclusion

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Key Takeaways:
Maturation and Current Regulatory Readiness of Predictive Stability

Enabling Regulatory Change

The ICH Q1 revision draft and its new Annex 2 on Stability Modeling are consistent with enablement of predictive stability for shelf-life determination and regulatory submissions.

Mature & Robust Modeling

Enhanced models, specifically Advanced Kinetic Modeling (AKM) and Arrhenius-based approaches, are proven across diverse modalities including mAbs, ADCs, vaccines, bi/tri-specifics, and fusion proteins.

Demonstrated Success

Industry case studies shown significant regulatory acceptance for setting initial shelf-life, managing temperature excursions, and supporting site/process changes.

Superiority Over Linear Regression

Kinetic models using multi-temperature data provide significantly more precise predictions than traditional single-temperature linear regression, especially when limited real-time data is available.

Holistic Validation & Verification is Mandatory

Success depends on a deep mechanistic understanding of degradation, justified statistical metrics (e.g., model accuracy), and a commitment to ongoing real-time verification

Addressing Challenges in Health Authority Expectations

More **detailed model validation** requirements.
Defining the necessary **data package for submissions *(IQ consortium will propose industry consensus practices / for input with HAs).***
Finding solutions **for challenging Critical Quality Attributes** (CQAs) that do not follow standard kinetic behavior or exhibit high variability (e.g., visible particulates). (***IQ consortium will ideate decision trees***).

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Conclusion: The Promise of Predictive Stability

1	**Accelerated Access**	Overcomes stability bottlenecks to potentially speed up patient access by 6 months
2	**Scientific Insight**	Fosters deeper mechanistic understanding of degradation pathways and product robustness
3	**Holistic Risk Management**	Complements existing scientific risk-based assessments and quality control strategies
4	**Global Alignment / Shared Learning**	Continues health authority dialogue to harmonize standards and minimize regional application differences

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Acknowledgements (IQ Predictive Stability WG Membership)

Company (alphabetical)	Name
AbbVie	Shaoxin Feng
Amgen	Ben Ahlstrom
Amgen	Edgardo Segarra
Astra Zeneca	Chris Thompson
Astra Zeneca	Cavan Kalonia
Astra Zeneca	Matthew Scholfield
Boehringer Ingelheim	Yannick Kronimus
Boehringer Ingelheim	Armin Boehrer
Boehringer Ingelheim	Marco Kunzelmann
BMS	Michael Ackerman
Eli Lilly	Joe Berry
Eli Lilly	Elisabeth Krug
Eli Lilly	Adam Palmer Rauk
GSK	Bernard Francq
GSK	Kavitha Jakka
Johnson & Johnson	Thijs Cui
Johnson & Johnson	Declan Lowney
Merck & Co., Inc., Rahway, NJ, USA	Daniel Skomski (*co-chair*)
MSD (The Netherlands)	Jos Weusten

Company (alphabetical)	Name
Merck KGaA (Germany)	Marco Saedtler
Merck KGaA (Germany)	Christian Laue
Moderna	Gang Wang
Novartis	Marie-Eve Bury
Novartis	Drago Kuzman
Novartis	Matjaz Boncina
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Thank You!

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