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

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Plenary Session: What's New in the World of Stability: Navigating the New ICH Q1 Landscape

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Outline

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

ICH Q1 Revision Timeline & IQ's Impact

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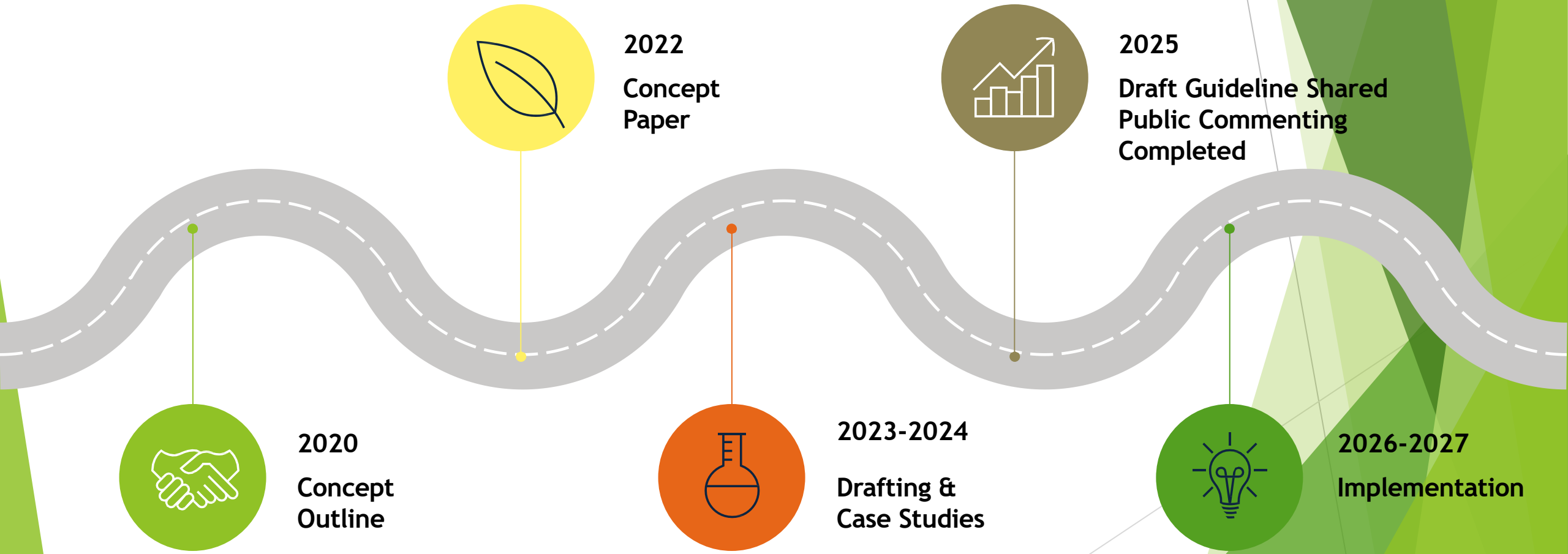
ICH Q1 Revision Annex 2 on Stability Modeling

*"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

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Why we need IQ / How our WG helps…

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

"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

The Toolbox: Mature Models for Biologics & Vaccines

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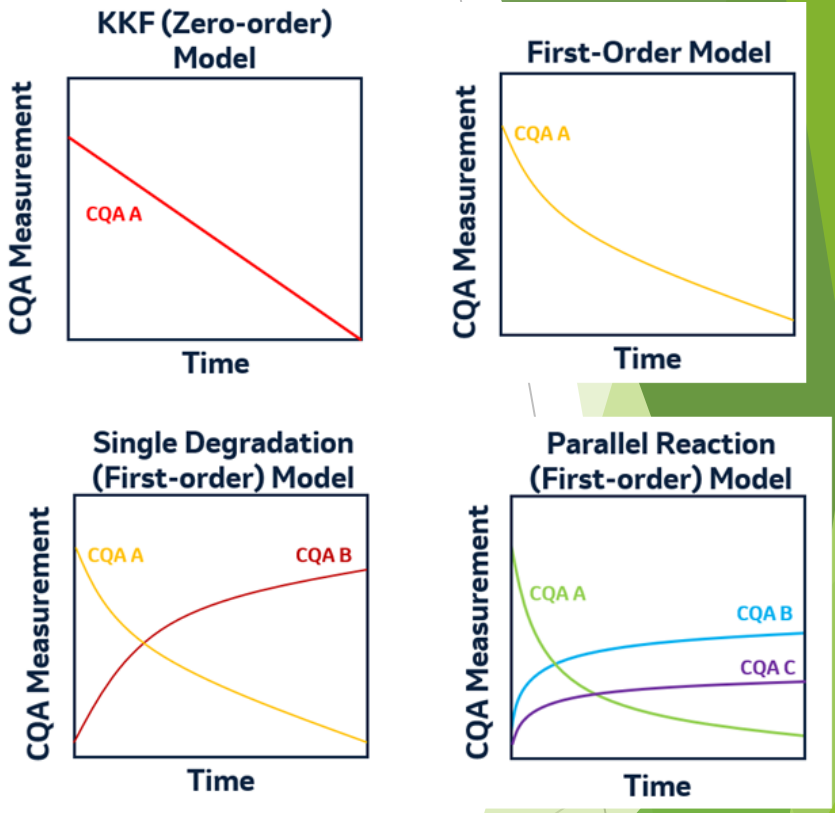
Overview of Fit-For-Purpose Models

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.	



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)

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.

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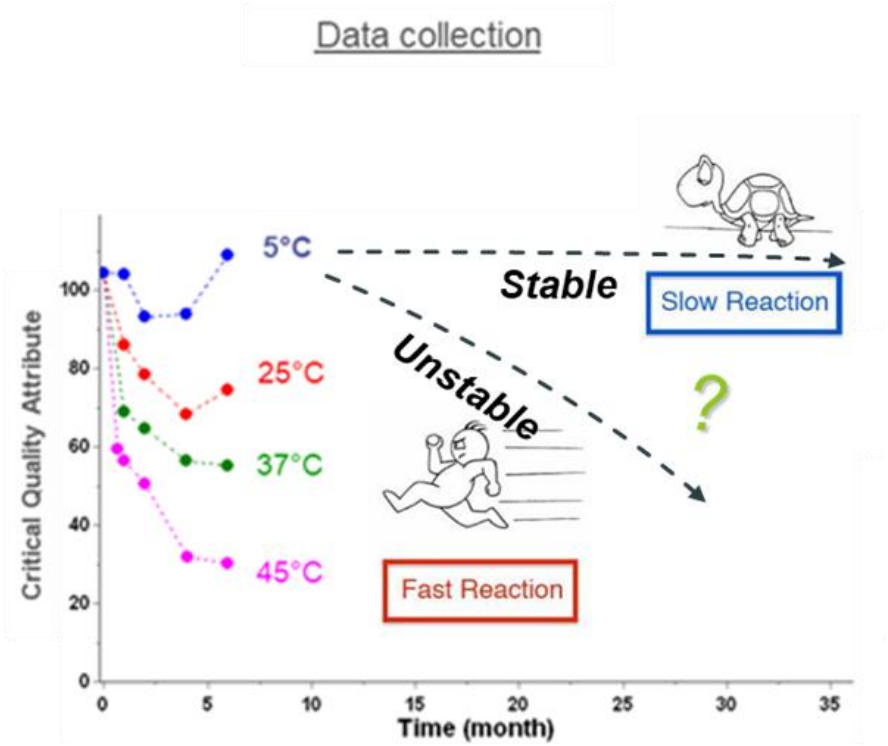
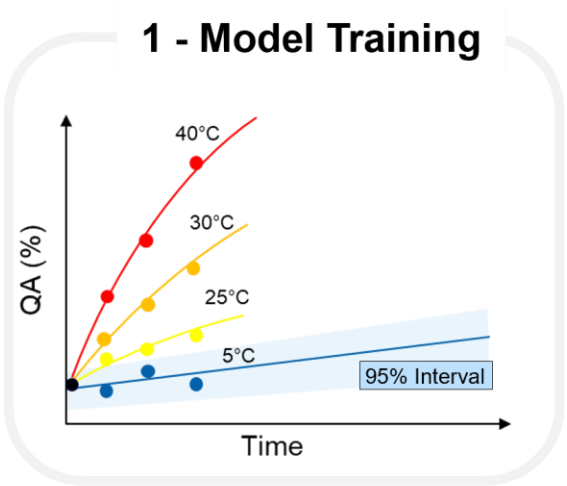
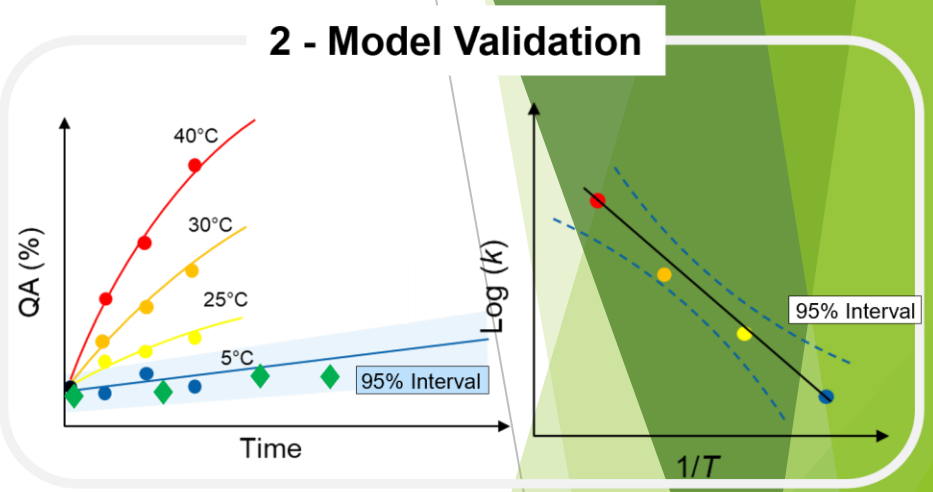
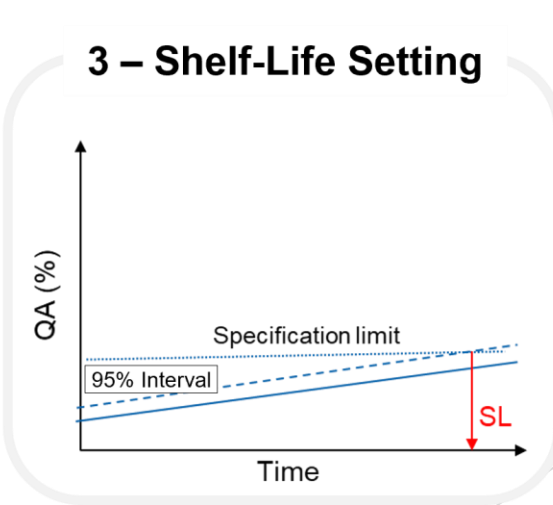
General Model Approach

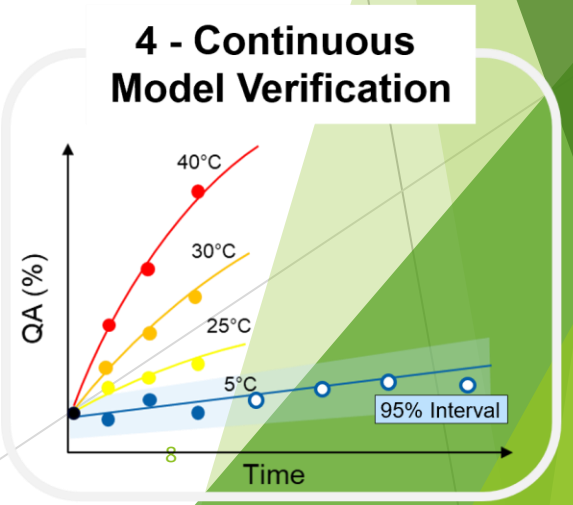
Workflow for Application of Predictive Stability Assessment for Shelf-Life Determination











Proof of Concept: Success Stories Across the Industry

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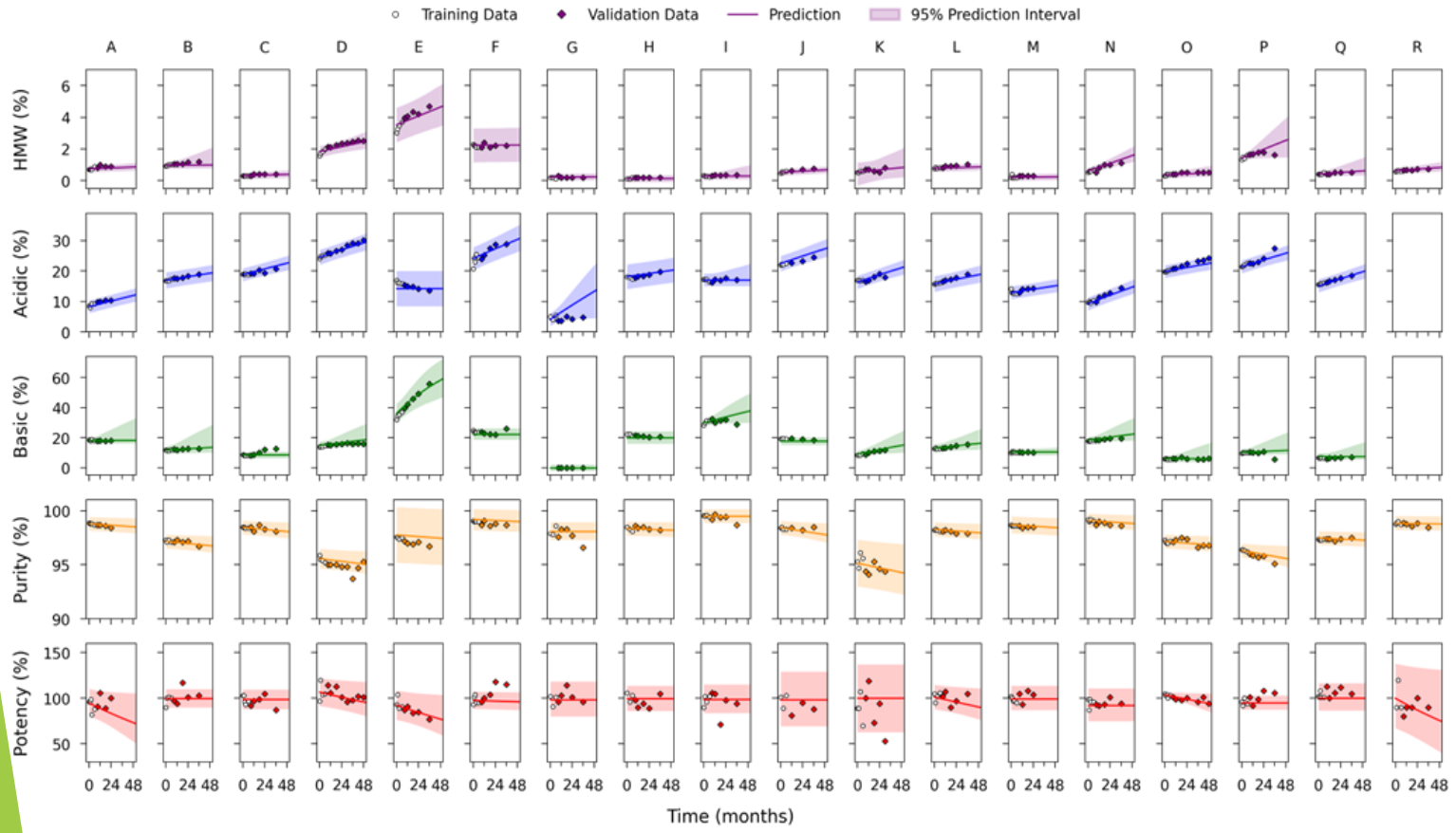
Examples from >18 Biologics Products

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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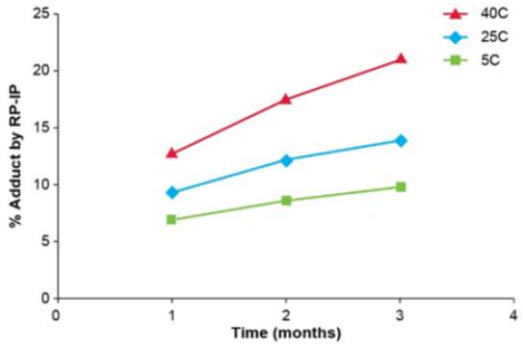
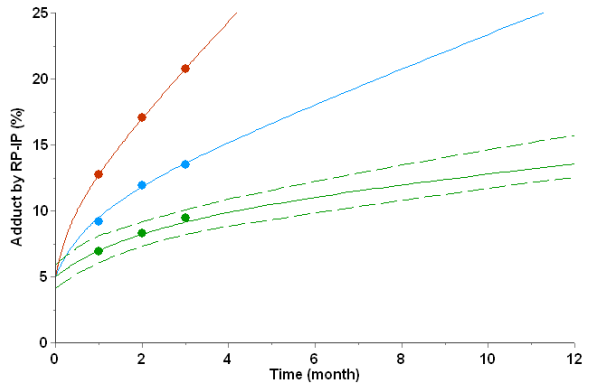
Examples from >5 Vaccine Products

Broad application across various types of vaccines

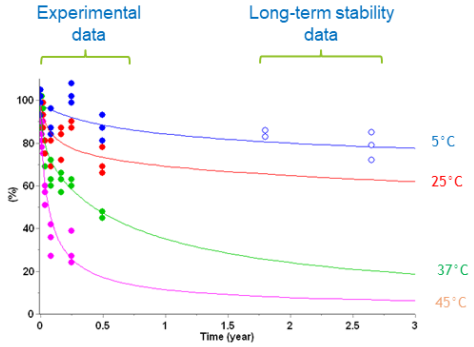
mRNA Vaccine





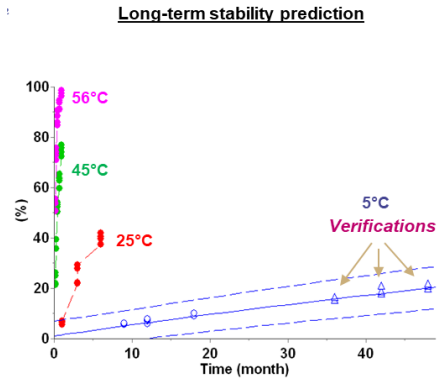
M. Packer et al., 2021

Inactivated Virus-Based Vaccine



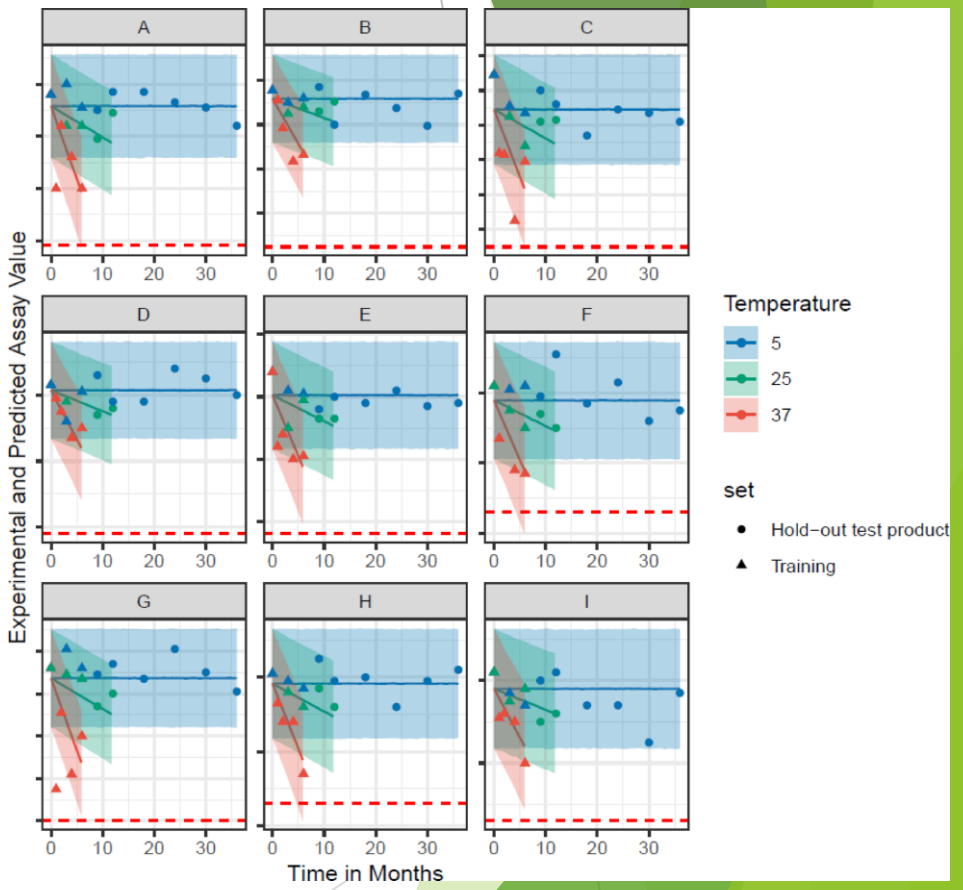
C. Campa et al., 2021

Polysaccharide-based vaccine



C. Neyra et al., 2025

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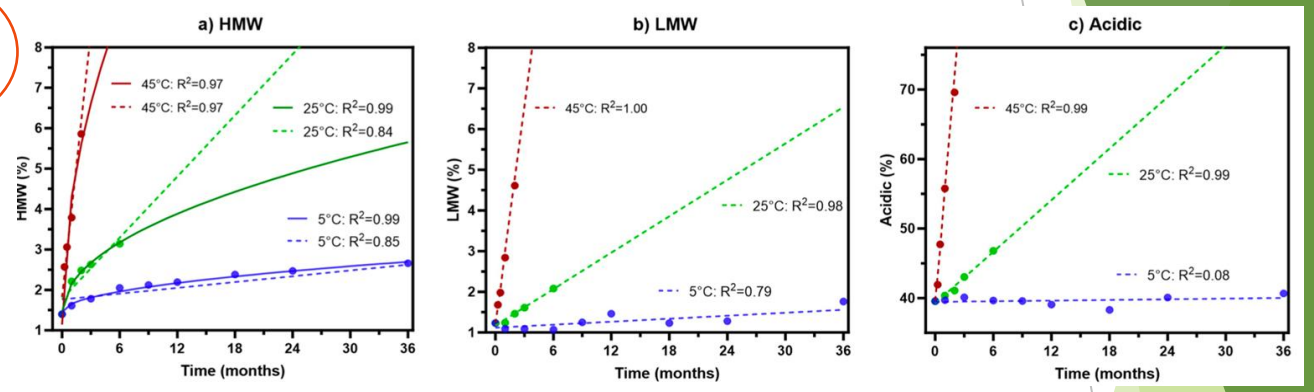
Case Study: Achieving Positive Patient Outcomes with Predictive Stability during COVID

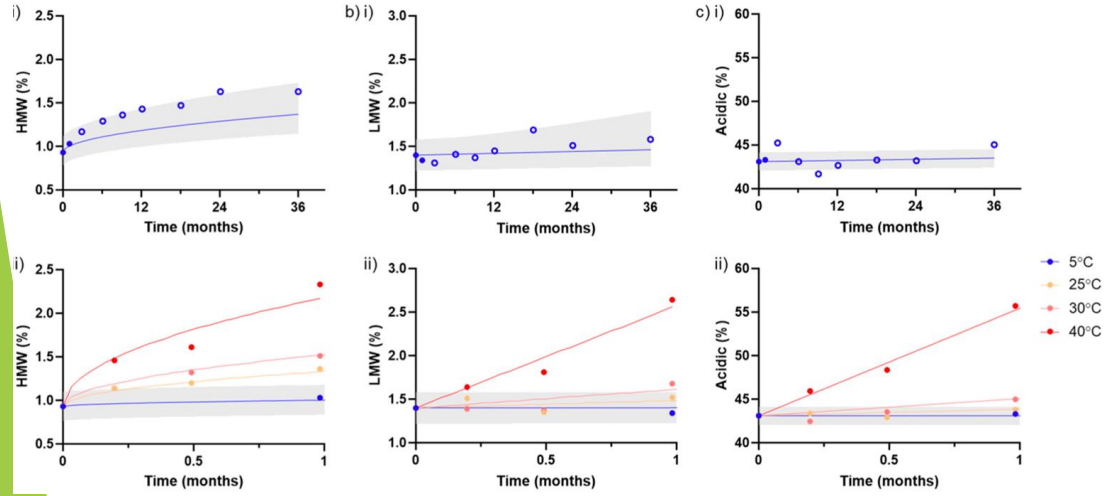
$$HMW(t,T) = HMW_0 + A_{HMW} * \exp\left(-\frac{E_{act}}{RT}\right) * t^{1/2}$$

$$LMW(t,T) = LMW_0 + A_{LMW} * \exp\left(-\frac{E_{act}}{RT}\right) * t$$

$$Acidic(t,T) = Acidic_0 + A_{Acidic} * \exp\left(-\frac{E_{act}}{RT}\right) * t$$

$k(T)$





- 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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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	EMA[82]	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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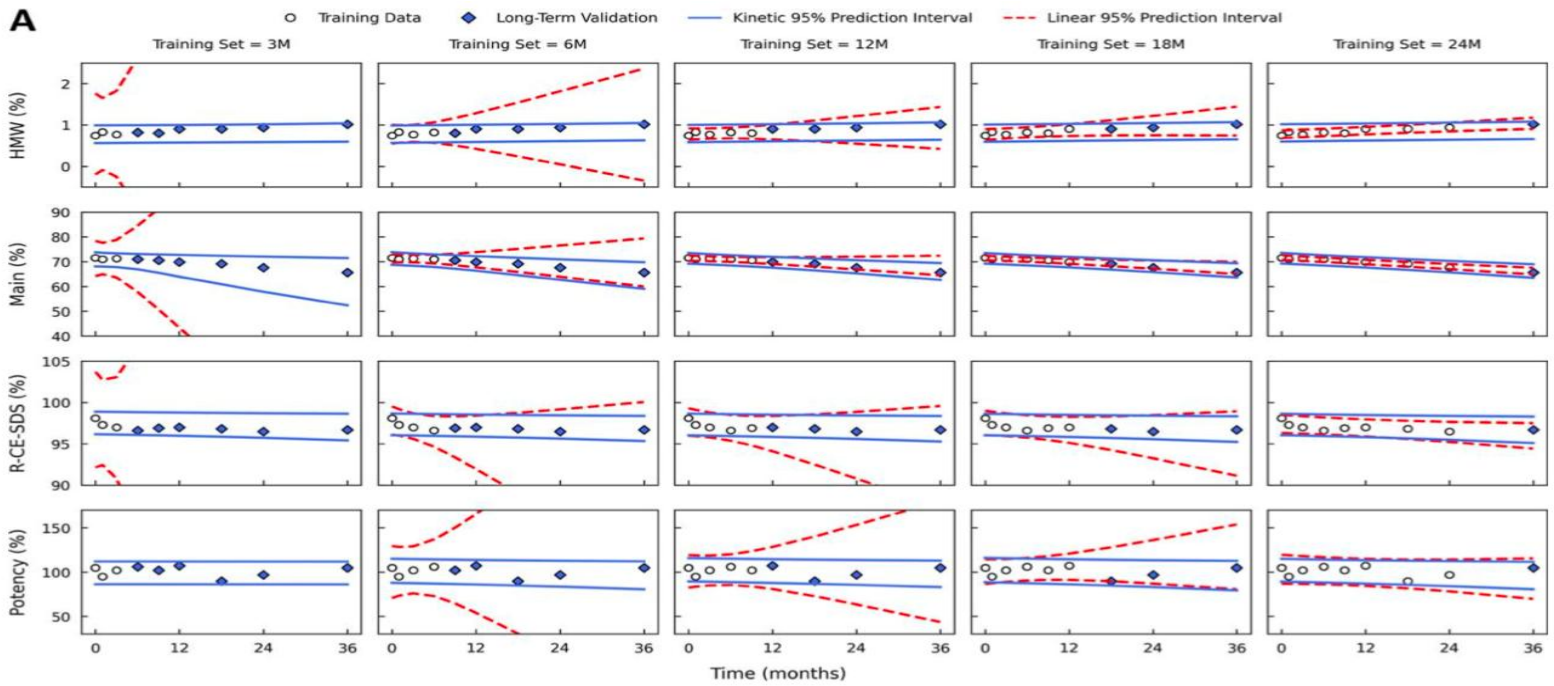
Model Selection
Example of Arrhenius Model vs. Linear Regression



Kinetic first-order model using multiple-temperature 5, 25, and 40 °C data (blue lines) shows more precise prediction compared to linear regression on just 5 °C (red) when limited timepoints available

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

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, software validation
    - ✓ Goodness of fit, accuracy
    - ✓ Affirm applicability of Arrhenius relationships to a given product

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Scientific Foundation & Risk Framework

DRUG SUBSTANCE & DRUG PRODUCT STABILITY

- Physicochemical analytical methods and compendial testing
- Mechanistic understanding and degradation pathways/products
- Product-specific critical quality attributes
- Temperature sensitivity, excipient stability/compatibility, impurities, sterility assurance, in-use stability, aggregation, pH, biological activity, etc

PROCESSING ASPECTS

- Chemical exposure (solvents, reagents)
- Temperature exposure
- Physical stresses (shear etc)
- Product-contacting materials/equipment
- Changes in excipients/formulations/lots
- Container/closure interactions

OTHER STRESSES

- Light stress
- Freeze-thaw
- Mechanical stress
- Shipping, transport, excursions
- Other environmental factors

- Identify shelf-life limiting attribute(s)
- Evaluate risk of degradation
- Identify additional risk areas where phase-appropriate data and/or process controls are needed to support shelf-life
- Application of predictive stability modeling

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.

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

Overcoming the Challenges

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Challenges & Solution

In the following the challenges are discussed which are

- Non-modellable CQAs
- 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
- 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 (MoA dependent, high assay variability)
- Stochastic behavior beyond standard kinetics
  - particulation, container-closure integrity
    - (e.g. due to impurities from process residuals, excipients, container extractables & leachables etc.)
- Stressor induced mechanisms beyond temperature (e.g. agitation, light, etc)
  - aggregation, oxidation, surfactant degradation

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

- 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.

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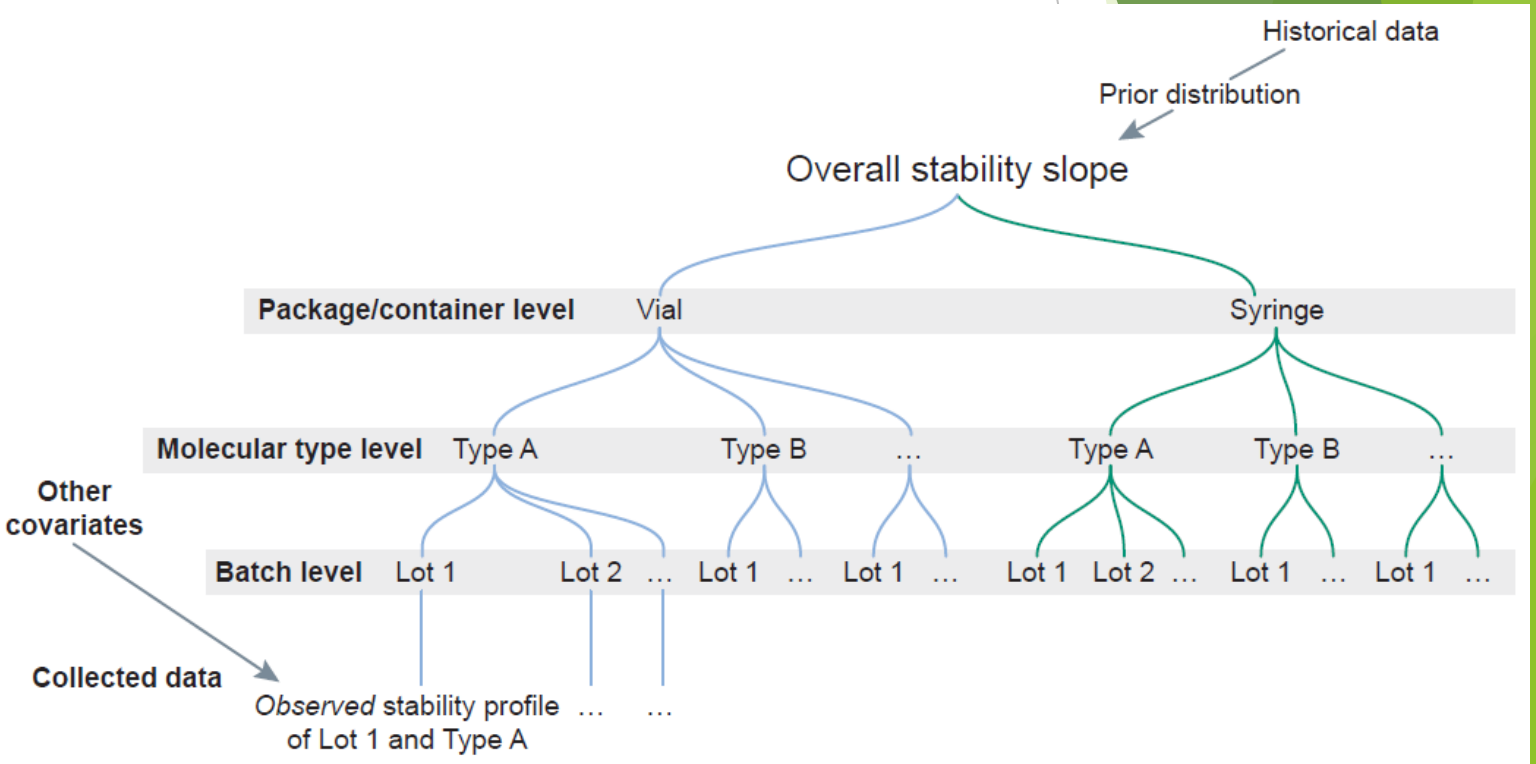
Data and Knowledge-Driven Rationale
Prior Knowledge for Different Images & Potency

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.)*



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

- **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
- **Addressing Complex Quality Attributes**
  - Leverage: prior knowledge; alternative surrogate/binary methods; increased experimental testing
  - Maintain close connectivity to control strategies for process residuals and impurities
- **Integrated Control Strategies**
  - Risk-based scientific assessments as part of a holistic drug research and development strategy
- **Continuous 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

Key Takeaways & Conclusion

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Key Takeaways: Maturation and Current Regulatory Readiness of Predictive Stability

- **Enabling Regulatory Change**
  - The revised ICH Q1 and its new Annex 2 on Stability Modeling formally enable 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, and fusion proteins.
- **Demonstrated Success**
  - Industry case studies show full regulatory acceptance (FDA, EMA, and others) 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 linear regression, especially when limited real-time data is available.
- **Holistic Validation is Mandatory**
  - Success depends on a deep mechanistic understanding of degradation, justified statistical metrics (e.g., goodness of fit), and a commitment to ongoing real-time verification
- **Addressing Challenges:** Challenges remain in meeting Health Authority (HA) expectations, specifically around:
  - More detailed **model validation**.
  - Defining the necessary **data package for submission**.
  - Finding solutions for **challenging Critical Quality Attributes (CQAs)** that do not follow kinetic behavior or exhibit high variability (e.g., Visible Particulates).

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Conclusion: The Promise of Predictive Stability

Predictive stability holds **immense promise** for accelerating patient access to new medicines by overcoming stability-related bottlenecks. This is achieved while simultaneously enhancing scientific understanding and product robustness.

- Accelerated Access
  - Overcomes stability bottlenecks to potentially speed up patient access by 6 months.
- Scientific Insight
  - Fosters deeper mechanistic understanding of degradation pathways and product robustness
- Holistic Risk Management
  - Complements existing scientific risk-based assessments and quality control strategies
- Global Alignment
  - Continues health authority dialogue to harmonize standards and minimize regional application differences
- Shared Learning
  - Advances best practices for "challenging" CQAs that do not follow standard kinetic behavior.

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Acknowledgements (IQ)

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
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
Novo Nordisk	Scott W. Roberts
Novo Nordisk	Sandra Auguste-Bowler
Pfizer	Kirsten MacArthur
Pfizer	Christine Petralia
Regeneron	Jiewei Wu
Regeneron	Michael Meleties
Roche/Genentech	Andrea Ji
Roche/Genentech	Christopher Lentes
Roche/Genentech	Aaron Hieb
Sanofi	Didier Clenet
Sanofi	Leanne Chinn
Servier	Clara Coll Satue
Servier	Alexandre Nicolas

- Thank you Boris Zimmermann (Roche Genentech) for support

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Predictive Stability Applications

Shelf-life Setting

When will DS/DP CQAs approach specification thresholds?

Comparability

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

How do temperature excursions impact long-term stability?

Informing Specifications/ Internal Limits

What is a reasonable preliminary spec given the data?

De-risking Product Launch

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