Use of Predictive Stability for Shelf-Life Setting or Extension

WCBP 2025 Mini Case

Linda Lemieux[1], Li Cui[2] and Edel Mullen[3]

[1] Merck & Co., Inc., Rahway, NJ, USA
[2] Daiichi Sankyo, Inc., Basking Ridge, NJ, USA
[3]Amgen, Inc., Cambridge, MA ·

Introduction

Use of Predictive Stability for Shelf-Life Setting or Extension

- Earlier/Accelerated regulatory submissions since stability data often rate limiting (especially for biologics and vaccines)
- Extended shelf life in new product applications to ensure product supply
- Science and risk-based stability assessment (shelf-life setting and comparability for post approval changes)

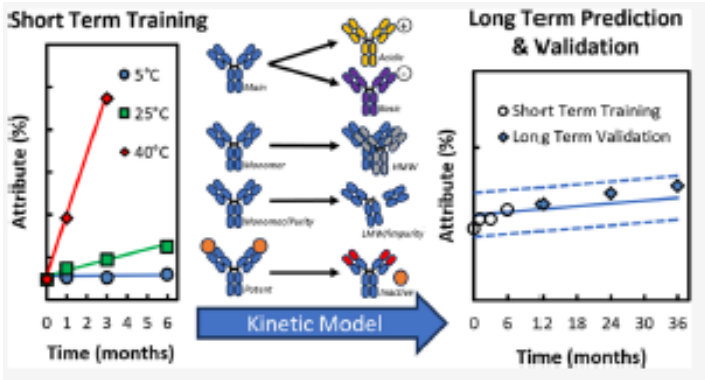
Predictive Stability- Modeling Tools

Various Arrhenius based models have been successfully used for Predictive Stability

- Moisture-modified Arrhenius Equation
- Accelerated Stability Assessment Procedure (ASAP)
- Advanced Kinetic Modeling

More advanced models were developed for biologics, which often have complex degradation profiles

- Bayesian
- Frequentist
- AI/ML



Dillon, M et al. Predicting the Long-Term Stability of Biologics with Short-Term Data. *Molecular Pharmaceutics*. 2024.

Predictive Stability- Modeling Tools

- What type of products have you applied predictive stability?
- What kind of statistical methods and modeling tools do you use for predictive stability?
- What are the advantages and limitations of each?
- Do you use different methods depending on which quality attributes are identified as molecular liabilities?
- How do you justify attributes that are not able to be modeled?

Challenges and Potential Solutions: Unique Characteristics of Biologics

Biologics often have complex degradation mechanisms that can be difficult to model accurately. For instance, they may exhibit non-linear degradation patterns, such as an initial rapid decline followed by a slower, long-term decrease.

Enhanced Modeling (e.g. Bayesian) can be utilized to account for complexity and variability in the prediction with enough prior knowledge.

AI can be used to develop sophisticated machine learning models that can learn from complex degradation data. For example, neural networks can be trained on historical stability data to predict future stability under various conditions

Changes in manufacturing processes or sites can affect the stability of biologics. Ensuring comparability and consistency in stability predictions across different manufacturing conditions is a significant challenge.

Predictive stability modeling is a comprehensive tool that can provide additional assurance that the changes are comparable and do not impact the shelf life of the product instead of relying solely on N=3 data. AI can create digital twins of the manufacturing process, allowing for virtual testing of changes in manufacturing conditions. This helps in predicting the impact of these changes on product stability without extensive physical testing.

Biologics are often sensitive to temperature variations, making it difficult to predict their stability under different storage conditions. Accelerated stability testing at higher temperatures may not always accurately reflect real-time stability

Predictive Stability Modeling can be used to assess and optimize accelerated stability testing protocols by identifying the most predictive conditions and time points. This can help in better correlating accelerated test results with real-time stability

Predictive Stability - Unique Characteristics of Biologics

- Are you using predictive stability to establish degradation profiles or evaluate process changes for biologics?
- How is it being used to anticipate impacts of process changes?
- Have you used predictive stability models for post approval changes?
- What conditions (temperature, pH, light, oxidation stress etc.) do you include in accelerated stability studies?
- How do you distinguish analytical variability from the complex degradation profiles in predictive stability models?

- Have you adopted the use of AI and machine learning and for what applications? Have you submitted /intent to submit AI modeled data for applications ?

Challenges and Potential Solutions: Use of Prior Knowledge

- Predictive stability relies heavily on historical data and prior knowledge.
  - Product Data (long term, real-time data on the molecule of interest)
    - Development/clinical data
    - PPQ/Primary Stability
    - Commercial data (yearly commitment)
  - Like-molecule Data
    - Molecules from platform technology
    - Molecules with similar degradation pathway

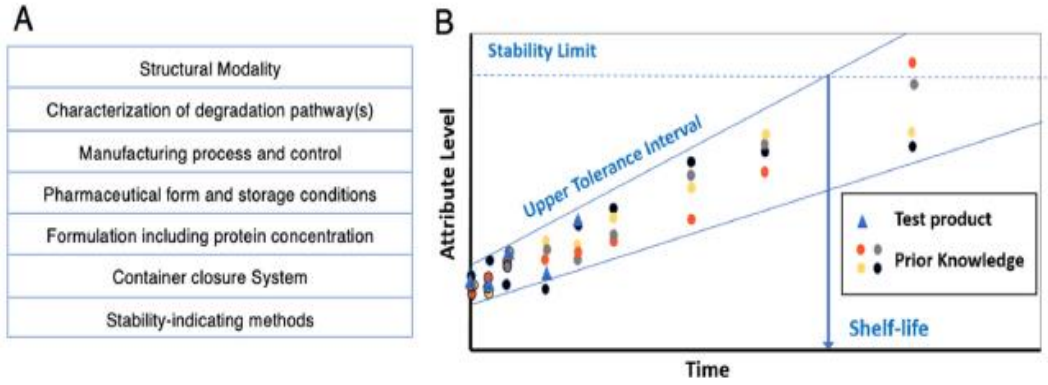


Fig. 3. Set of criteria for applying of prior knowledge data into a stability reference data set (**A**) and illustration of a prior knowledge-derived stability profile for a shelf-life limiting critical quality attribute (**B**).

Lennard, A et al. Stability Modeling Methodologies to Enable Earlier Patient Access. *Journal of Pharmaceutical Sciences*. 0000, 1-7 (2024)

Predictive Stability – Prior Knowledge

- What have you used as product specific data and like-molecule?
  - Non GMP data?
  - What defines "like-molecule"?
- How do you assess if there is sufficient prior knowledge in the model (e.g. statistical significance)?
- What are the criteria used for applying prior knowledge for predictive stability?

Challenges and Potential Solutions: Regulatory Acceptance

While regulatory agencies are becoming more open to innovative methodologies, there is still a need for extensive validation and justification of predictive models to gain regulatory acceptance

Opportunities for predictive stability with ICH Q1A-E and Q5C revision currently in progress

- Ability to leverage science and risk-based approaches
- Annex 2 Stability Modeling
  - Statistical evaluation using single and multi-factor study designs
  - Enhanced stability modeling
  - General principles for model development, evaluation of data, and model validation and verification
- Examples in constituency review draft
  - Fixed and mixed effects models
  - ASAP and AKM models
  - Bayesian model
- Training on use and applications for modeling with examples

Using explainable AI techniques, such as digital twins, has gained regulatory traction by allowing regulators to understand and trust the models used for control strategy predictions.

Challenges and Potential Solutions: Regulatory Acceptance

- What aspects do you consider when validating the predictive modeling tool?
- Where in the dossier/CTD do you leverage predictive stability for shelf-life?
- Have you used predictive stability in initial INDs, BLAs and/or PASs?
- What have agency interactions looked like ?
- What feedback has been received from regulatory agencies?
- Have you had any successful submission that have leveraged predictive stability modeling to support shelf-life extensions or a change in recommended storage conditions?