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Predictive Stability Models

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Maintenance of ICH Stability Guideline Series - Rapid Stability Prediction Based on Modeling

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The view expressed in the following is the ones of the presenter and does not necessary express the view of either the CHMP, BWP, EDQM or the Paul-Ehrlich-Institut (including other sections)

Outline

- Guidance documents
    - Maintenance of ICH Stability Guideline Series

- Extrapolation of data

- (Prime) Tool box

- (Enhanced) Stability Modelling

Regulatory Guidance Documents

- ICH Q5C: Stability Testing of Biotechnological / Biological Products
- ICH Q1A (R2): Stability Testing of New Drug Substances and Drug Products
  - Frequency, conditions
- ICH Q1B: Stability Testing: Photostability Testing of New Drug Substances and Drug Products
- ICH Q1C: Stability Testing: Requirements to New Dosage Forms
- ICH Q1D: Bracketing and Matrixing Design for Stability Testing of Drug Substances and Drug Products
- ICH Q1E: Evaluation of Stability Data
- ICH Q1F: Stability Data Package for Registration Applications in Climatic Zones III and IV (WHO GL)
- Guideline on the requirements for quality documentation concerning biological investigational medicinal products in clinical trials

Maintenance of ICH Stability Guideline Series (ICH Q1A-F and ICH Q5C)

- Clarification of technical components of current guidelineData and evaluation strategies for defining the retest/shelf-life period (DS) and shelf-life (DP)
  - Baseline considerations in designing a stability protocol (e.g., storage temperatures/%RH/study time points, stability-indicating methods
  - Clarification of how in-use stability and container closure integrity studies are conducted
  - Expectations for products requiring [re]constitution or dilution
  - Clarify the difference between accelerated and stressed stability conditions
  - Acceptance criteria for stability testing versus release testing

- Address new technology and modern tools/strategies used as part of enhanced product understanding:
  - Modelling techniques, criteria for selection of batches, applicability, and caveats/limitations.
  - Expectations for statistical approaches and potential for Artificial Intelligence modelling methodologies.
  - Expectations for the justification of appropriate studies to determine shelf life for drug products and retest date for drug substances.
  - Advances in understanding accelerated stability conditions and prior knowledge which may support extrapolation.

ICH Q1 Step 2 Draft Guideline - Table of Contents

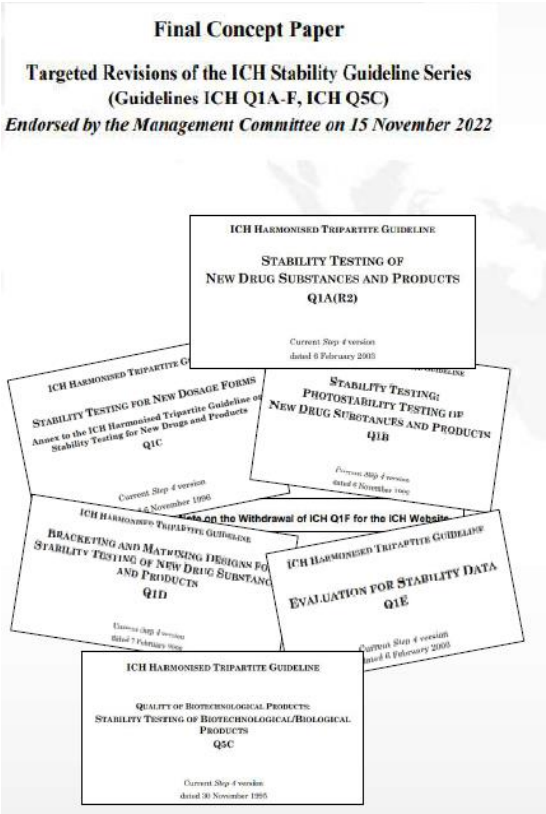
1. Introduction
2. Development Stability Studies Under Stress and Forced Conditions
3. Protocol Design for Formal Stability Studies
4. Selection of Batches
5. Container Closure System
6. Testing Frequency
7. Storage Conditions
8. Photostability
9. Stability Considerations for Processing and Holding Times for Intermediates
10. Short-Term Storage Conditions
11. In-Use Stability
12. Reference Materials, Novel Excipients and Adjuvants
13. Data Evaluation
14. Labelling
15. Stability Considerations for Commitments and Product Lifecycle Management
16. Glossary
17. References
18. Annexes
    - Annex 1: Reduced Stability Protocol Design
    - Annex 2: Stability Modelling
    - Annex 3: Stability of Advanced Therapy Medicinal Products (ATMPs)

Section 18, 3 Annexes:

- Annex 1 includes guidance on bracketing and matrixing currently captured in ICH Q1D. New guidance is provided on knowledge and risk-based protocol reductions.

- Annex 2 provides guidance on stability modelling. It includes guidance currently provided in ICH Q1E and new guidance on using enhanced stability modelling.

- Annex 3 provides stability guidance on ATMPs (Advanced Therapy Medicinal Products) which are new to ICH. This annex is supplemental to the core ICH Q1 Draft Guideline and is not a stand-alone guideline for ATMPs.



Revision Section 13.2.9 Extrapolation for Biologicals

- Extrapolation beyond the period covered by available long-term primary stability data may be considered for a well characterised biological drug substance stored frozen, for which the quality attributes are known, and their corresponding criticality and residual risks evaluated to ensure patient safety.

- Extrapolation of drug substance shelf life 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

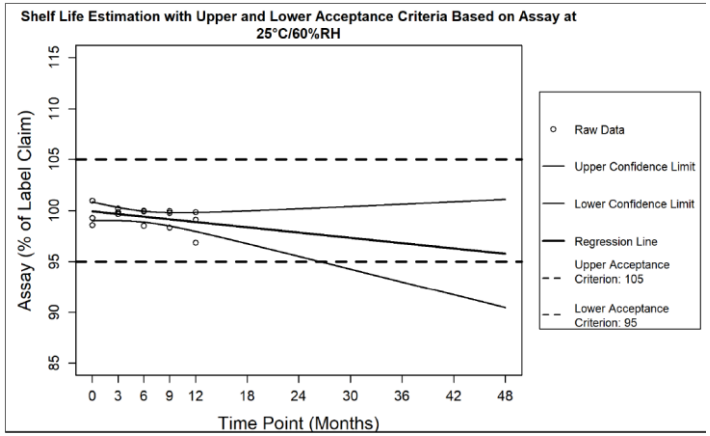
Prior knowledge based shelf life?

Assign an initial shelf-life supported by prior knowledge, provided that the criteria for manufacture, product attribute testing, formulation, container, and storage are appropriately considered.

- Assess the product for “fit to platform”
- Assess investigational product stability data (test data) against tolerance intervals established from the prior knowledge stability data set (reference data, statistical approach?)
- Refinement of approach, how to notify authorities?

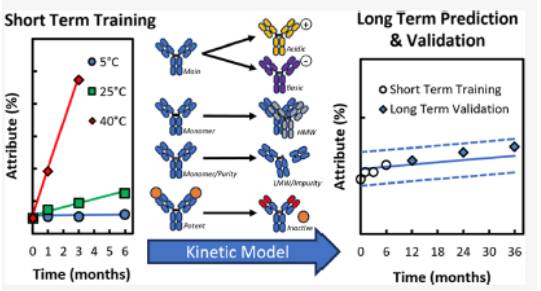
18 ANNEXES
Annex 1 Reduced Stability Protocol Design
Annex 2 Stability Modelling

A2-1 Statistical Evaluation of Stability Data from Single or Multi-factor Study Designs: Single-factor regression line for assay of a synthetic chemical drug product with upper and lower acceptance criteria of 105 percent and 95 percent of label claim for assay, respectively.



A2-2 Enhanced Stability Modelling

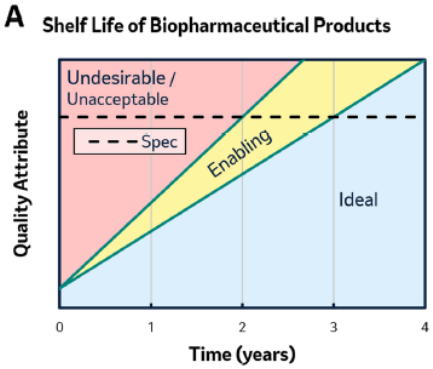
A2-2 Enhanced Stability Modelling

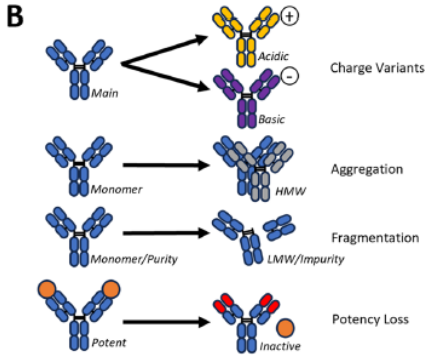


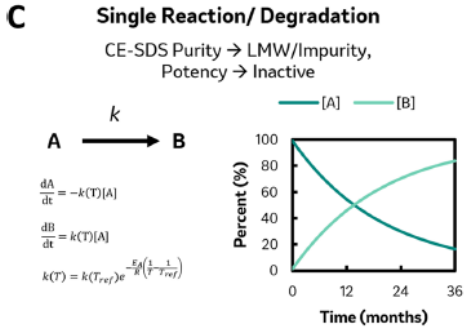
- A2-2.1 General Principles of Enhanced Stability Modelling
- A2-2.2 Model Development
  (1) utilise only the product-specific representative batch stability data (long-term and/or accelerated)
  (2) utilise prior knowledge from analogous-molecules combined with the product-specific information
- A2-2.3 Evaluation of Data for Stability Modelling
- A2-2.4 Model Validation and Verification
- A2-2.5 Risk Management and Model Lifecycle Considerations

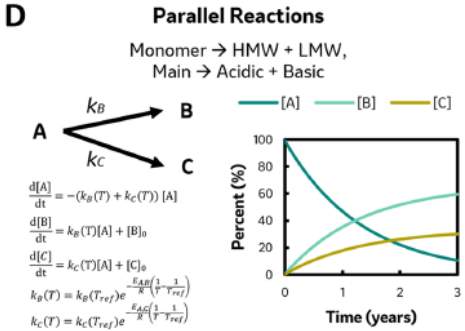
Predicting long-term stability trends from the short-term data

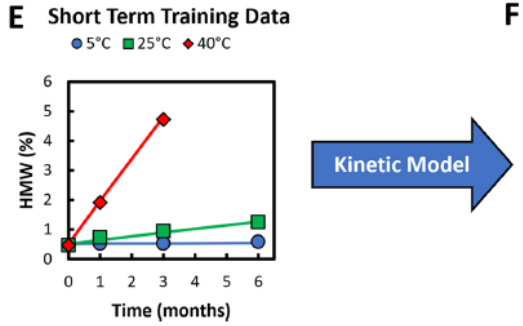
From Dillon et al. (2024) Predicting the Long-Term Stability of Biologics with Short-Term Data. Molecular Pharmaceutics 21(9), 4673-4687



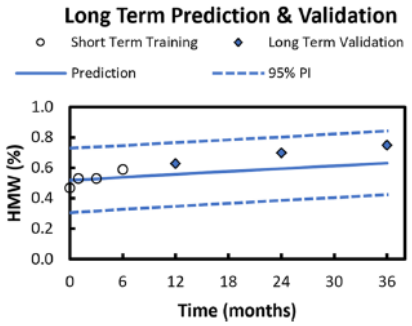








Kinetic Model

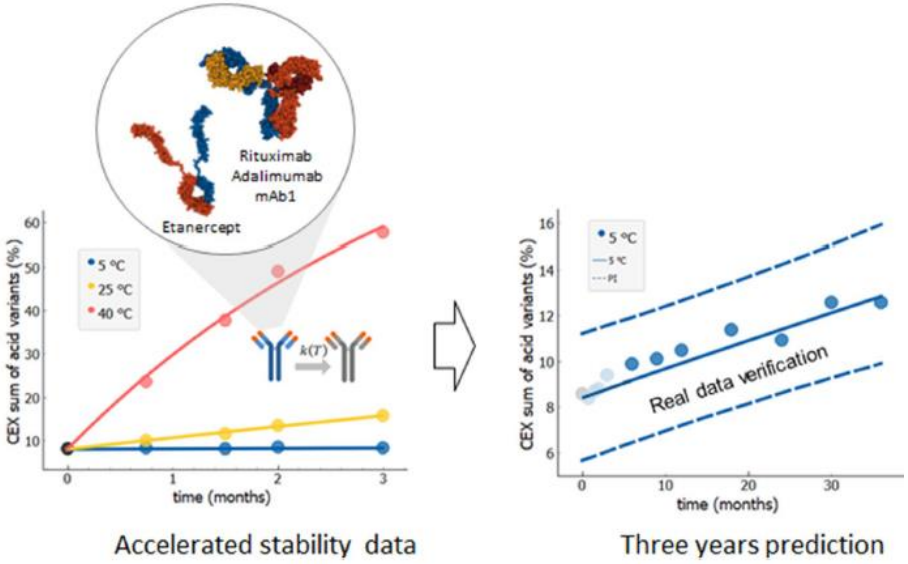


Simplified Biotherapeutic Degradation Models

$$\frac{d\alpha}{dt} = v \times A_1 \times exp\left(-\frac{E_{a1}}{RT}\right) \times (1-\alpha_1)^{n1} \times {\alpha_1}^{m1} \times C^{p1} + (1-v) \times A_2 \times exp\left(-\frac{E_{a2}}{RT}\right) \times (1-\alpha_2)^{n2} \times {\alpha_2}^{m2} \times C^{p2}$$

$$\frac{d\alpha}{dt} = A \times exp\left(-\frac{E_a}{RT}\right) \times (1-\alpha)$$

Stability profiles of Charge profiles, aggregation, fragmentation, potency at standard storage conditions.



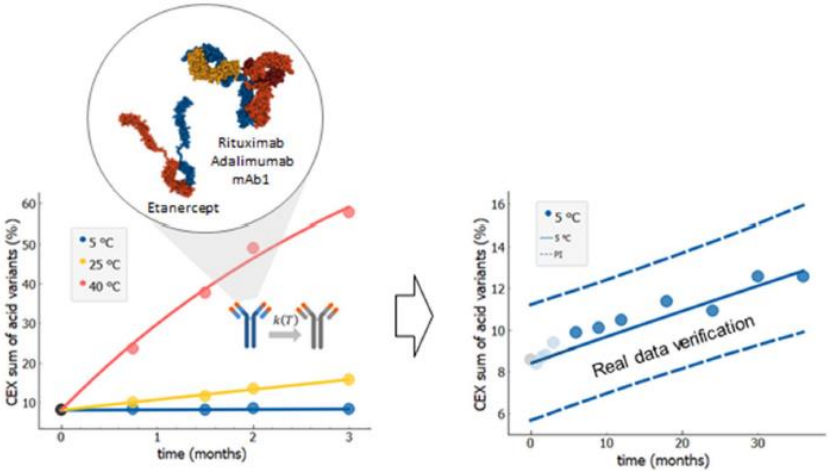
Accelerated stability data

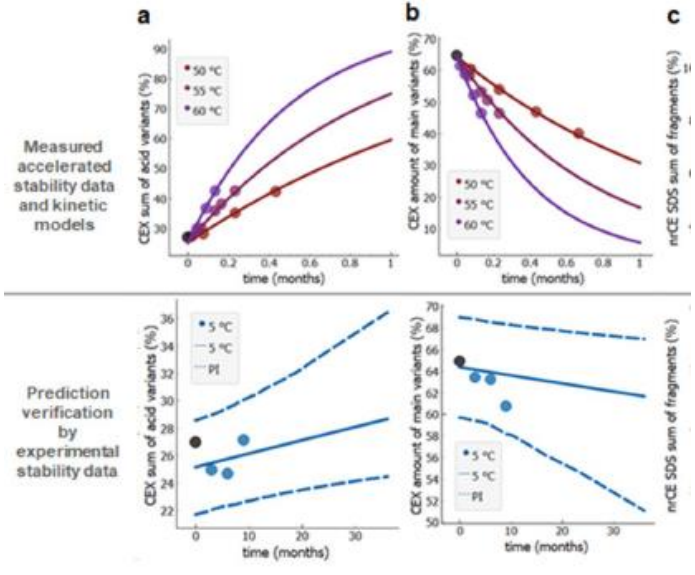
Three years prediction

Sci Rep. 2021 Oct 15;11(1):20534. doi: 10.1038/s41598-021-99875-9.

Rapid stability prediction based on Modeling

- Leveraging Prior Knowledge to Support Early Phase Clinical Trial Applications but also later phases
- (Best) Practices for Design and Performance of In Use Stability and Compatibility Studies
- Stability Predictions Using Modelling (Arrhenius-Based Kinetics)

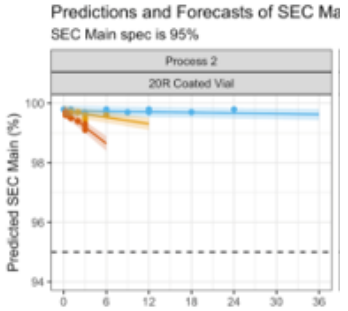




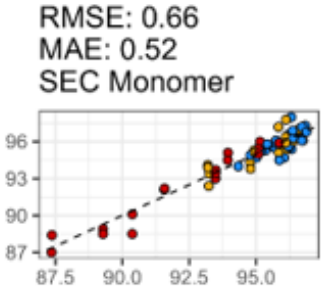
Kuzman, D., Bunc, M., Ravnik, M. et al. Long-term stability predictions of therapeutic monoclonal antibodies in solution using Arrhenius-based kinetics. Sci Rep 11, 20534 (2021). https://doi.org/10.1038/s41598-021-99875-9

Bayesian Hierarchical Models & Comparability Results

- Bayesian hierarchical models that allows additional covariates to be incorporated into the model framework.
- Sufficient data set must be available for initial model
- Model Training and Evaluation
  - measured values are compared to the model predictions
- Root mean squared error (RMSE) and mean absolute error (MAE) are calculated
  - The RMSE and MAE are metrics that describe model accuracy.
  - Lower RMSE and MAE values indicate less error in the model predictions and therefore higher model accuracy.



CQA¤	RMSE¤	MAE¤
SEC-HPLC·monomer¤	0.064¤	0.052¤
SEC-HPLC·high·molecular·weight·¤	0.061¤	0.046¤



Model Solution and Calculation of Prediction Intervals (?)

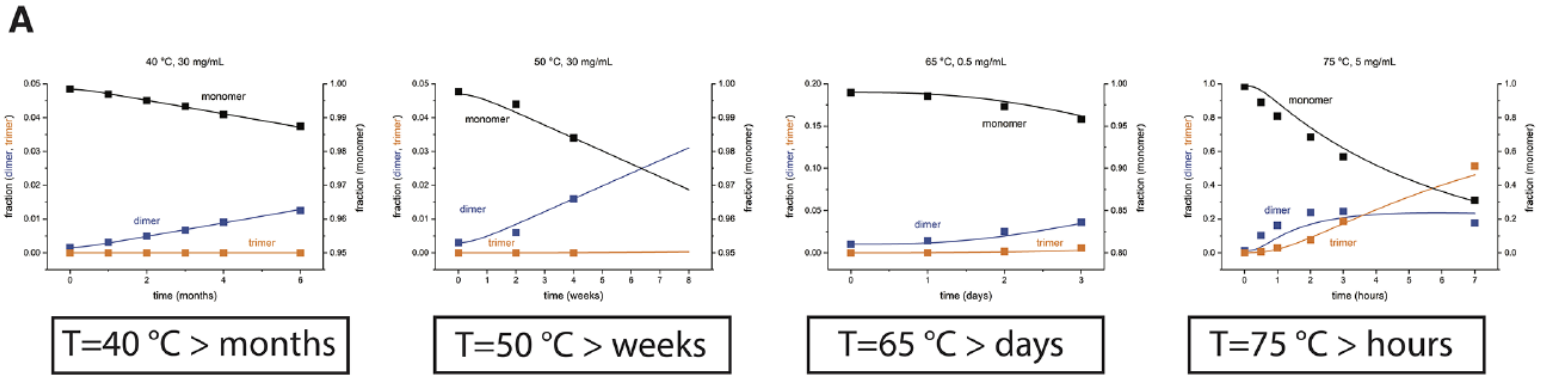
“To enable more robust predictions with higher confidence, prediction intervals are calculated for the kinetic model by Monte Carlo simulations, where random noise is added to the initial data set to account for potential measurement and model fitting variability. In this method, an initial fit to training data is performed, resulting in a “mean” fit or prediction and a model root-mean-square error (RMSE), computed by

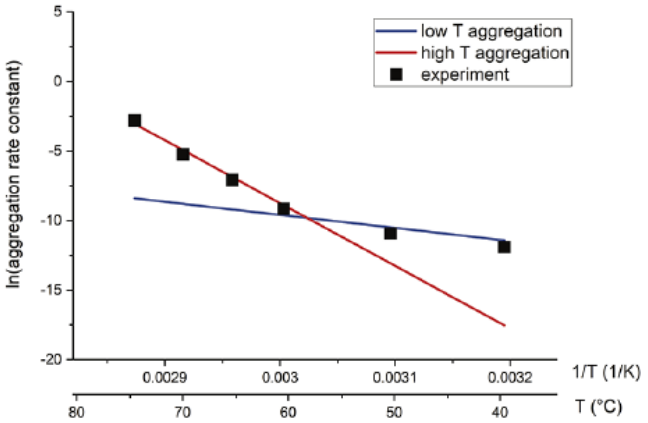
$$\mathrm{RMSE} = \sqrt{\frac{\mathrm{SS}_{\mathrm{res}}}{n - p}}$$

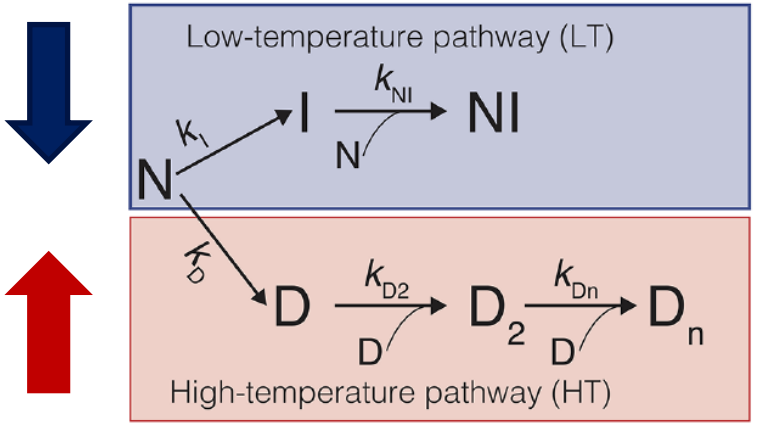
where the denominator is the degrees of freedom, n (number of observations) − p (number of parameters).”

Dillon et al. (2024) Predicting the Long-Term Stability of Biologics with Short-Term Data. Molecular Pharmaceutics 21(9), 4673-4687

Temperature is Promoting Different Aggregation Pathways

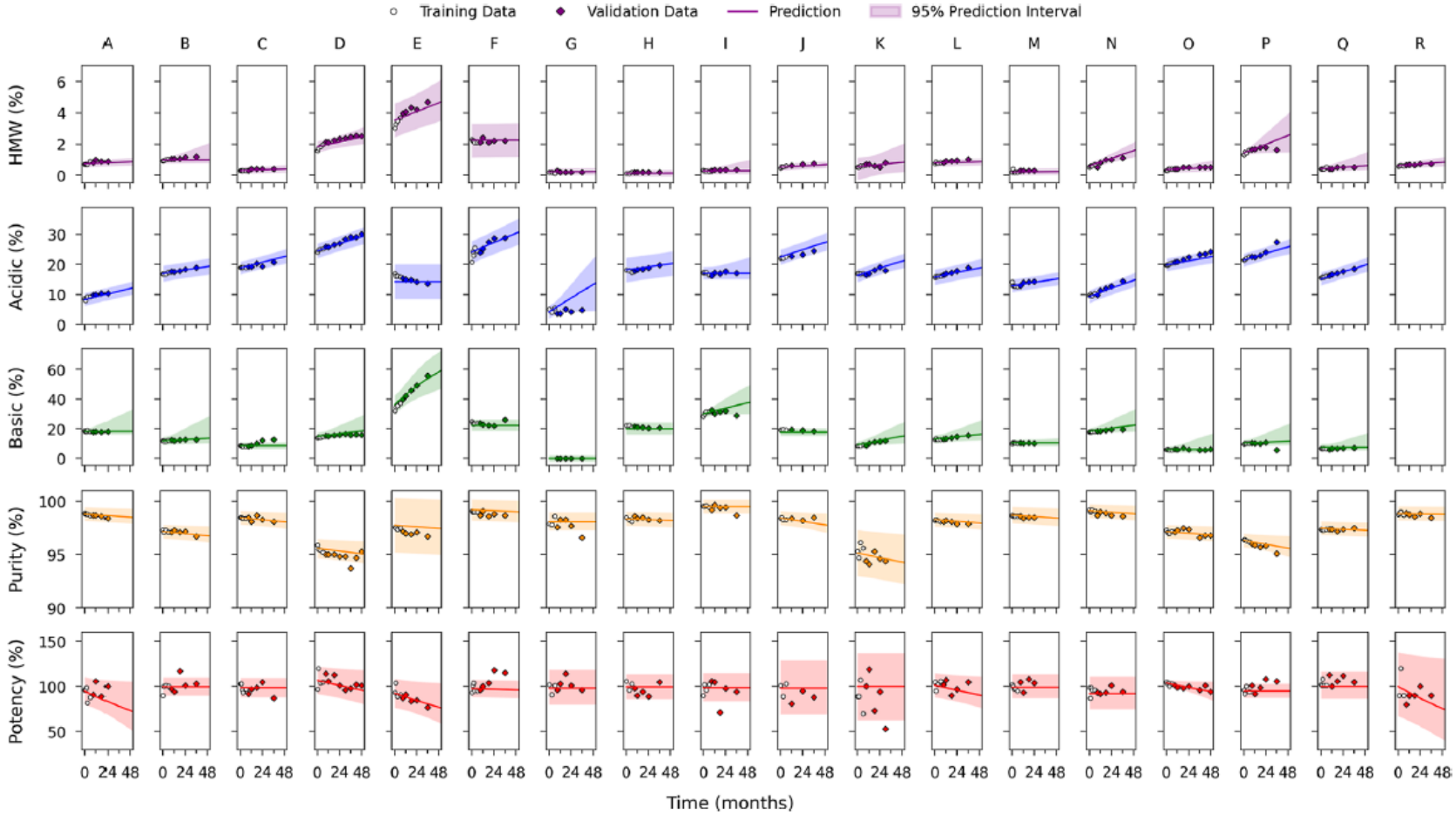






Journal of Medicinal Chemistry 2022 65 (3), 2623-2632DOI: 10.1021/acs.jmedchem.1c02010

Model Validation and Verification



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Summary

- Stability studies needed to establish suitable storage conditions, storage time/shelf life,
- No single stability indicating parameter but stability indicating profile
- Careful (pre-)planning is highly recommended
- Stability studies needed during entire product life cycle
- ICH Q5C main guidance, some principles ICH Q1s apply (Revision of GLs 2027?)
- Primary data based on long-term, real-time, real-conditions
- Extrapolation
- Long-term stability predictions/modelling are considered supportive (for the time being)

Thank you!

Questions?