Predictive Stability for Biologics Using Kinetic Modelling

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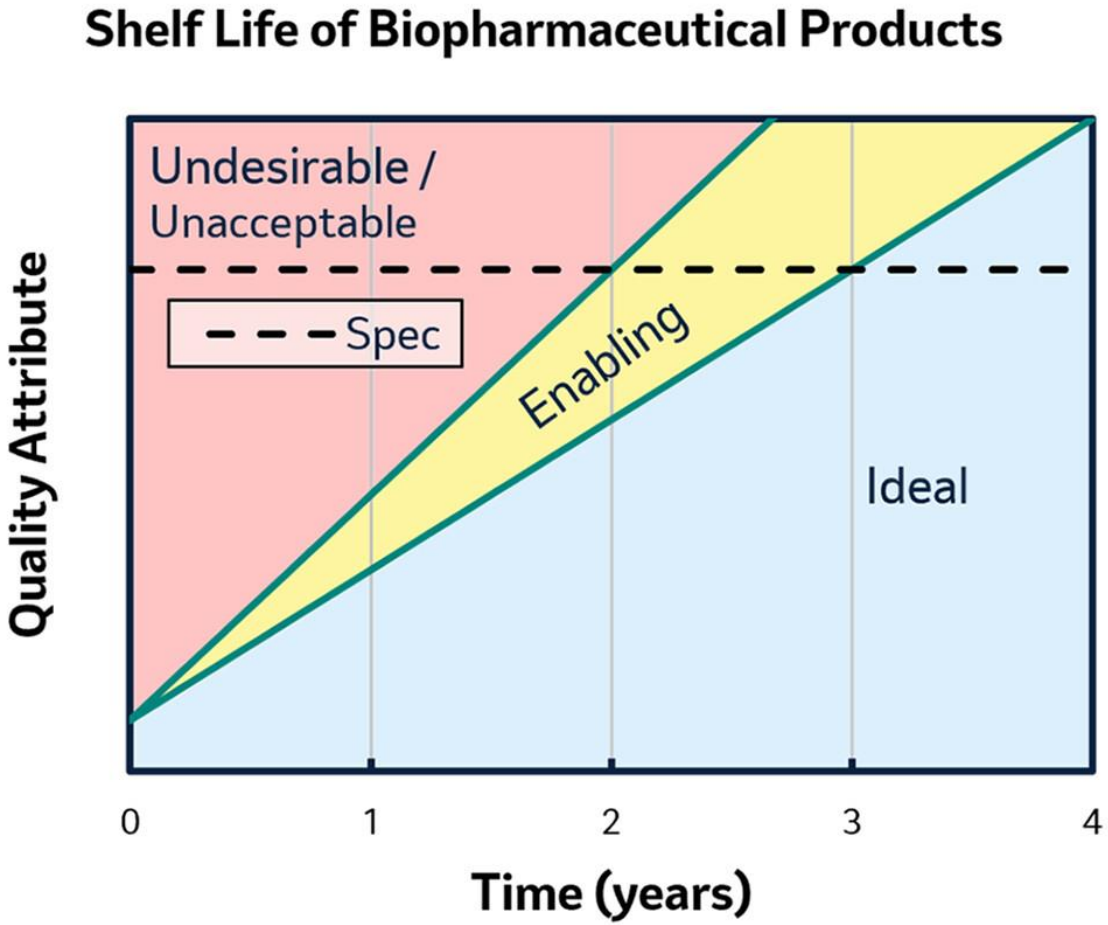
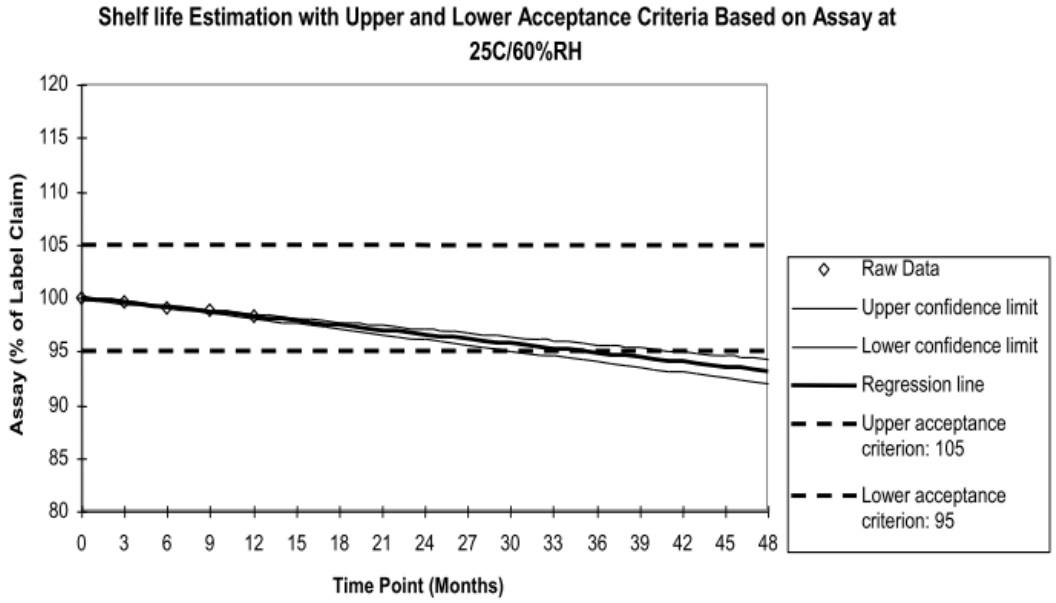
The Importance of Pharmaceutical Shelf Life

- Drug products must remain safe and effective up until patient administration
- Must establish a “shelf life” when all quality attributes stay within an acceptable specification
- Sterile pharmaceutical products generally require 2+, ideally 3+ years of shelf life, ensuring product safety, sufficient time for travel logistics, and minimization of product wastage.



Current Challenges of Setting Biopharmaceutical Shelf Life

- Shelf-life, or long-term stability, determination is a development bottleneck:
- Current guidance requires real time data collection with no extrapolation (commercial) or minimal extrapolation with only intended storage temp (clinical), so essentially need to wait 24M from product generation to claim you have a 2-year shelf life
- Speeding up shelf-life determination would improve CMC development timelines
- Biologics also have unique challenge of many attributes to track for product quality, and complex degradation pathways



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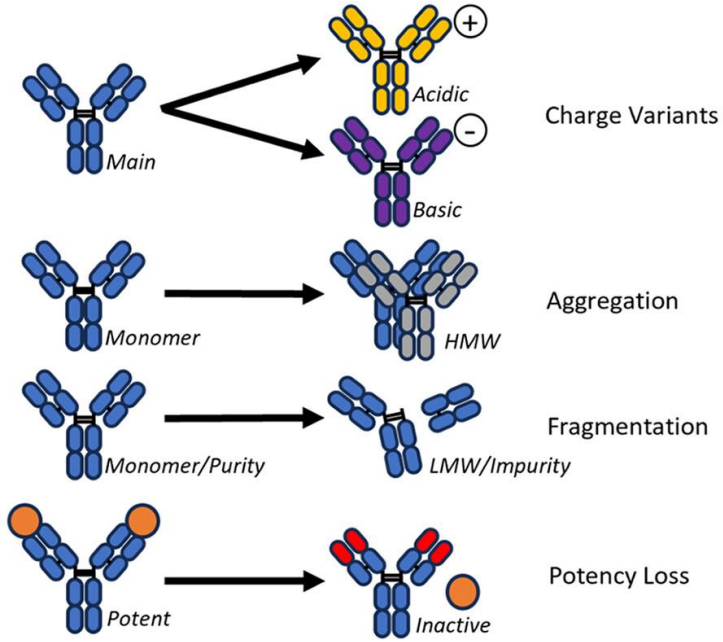
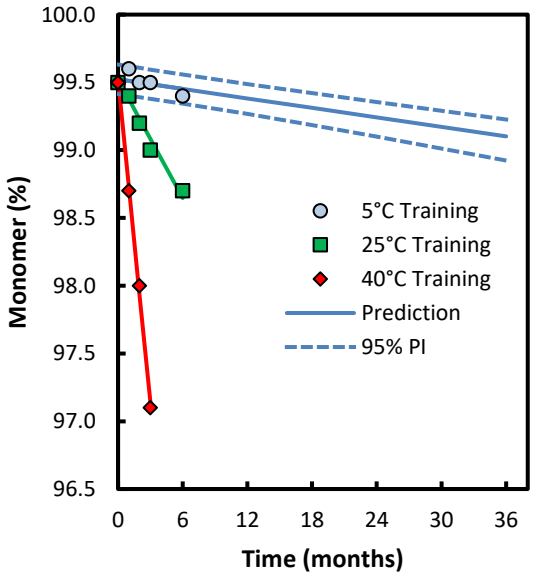


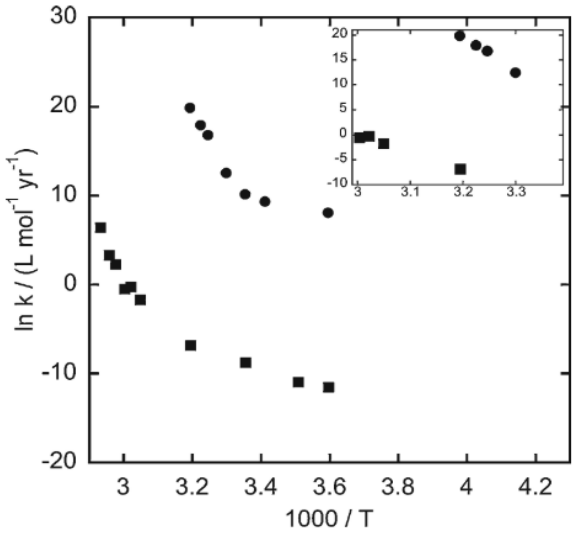
Can we predict long-term stability using short-term data combined chemical reaction kinetics?

- Pharmaceutical degradation is generally worsened as temperature increased, so collecting multiple higher temperatures can theoretically predict degradation at lower temperatures.
- Historically, in biologics this has been considered not possible due to non-Arrhenius behavior, but recent publications have demonstrated cases for monoclonal antibodies that are well described by Arrhenius behavior
- Growing evidence we can use short term data sets at higher temperatures to predict long term, low temp trends.

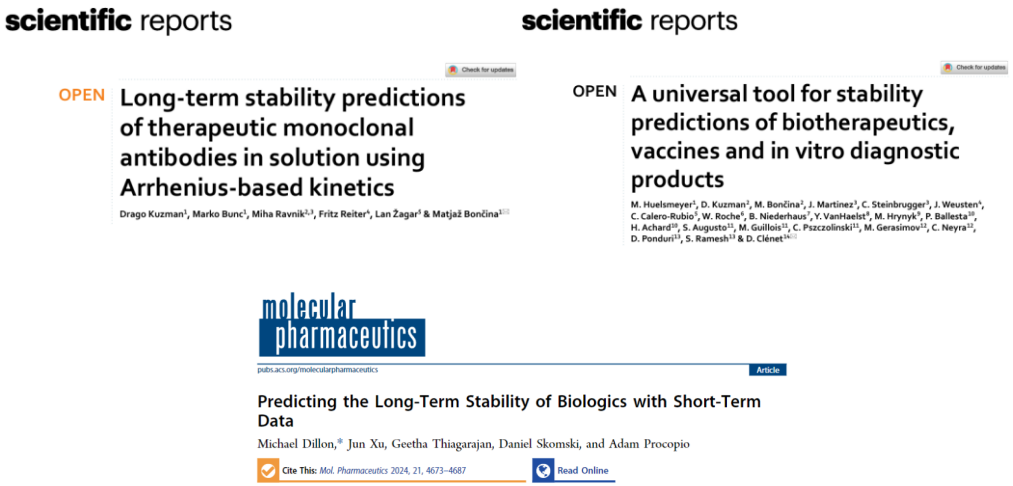
Fit of monomer degradation to 1st order with Arrhenius kinetics



Non-Arrhenius rate constants for aggregation of bG-GSF (circles) and mAb (squares) (*reproduced from Wang & Roberts. AAPS Journal. 2013.*)



Increasing number of publications shows capability of Arrhenius models to predict long-term stability



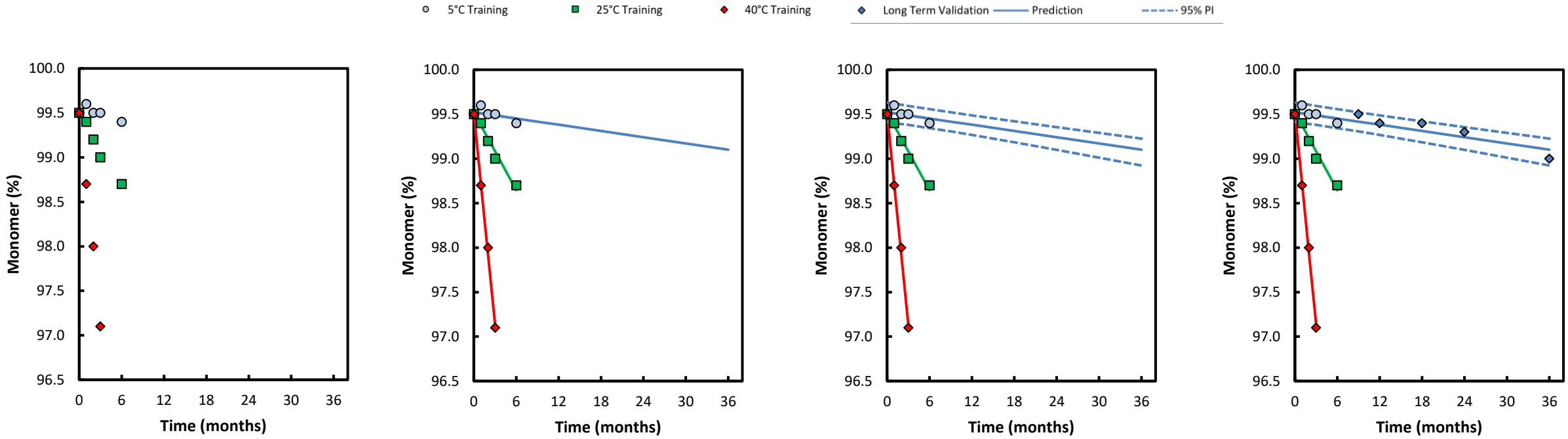
Prediction Workflow

Obtain early timepoint data

Fit to kinetic model

Generate prediction intervals by Monte Carlo Simulation

Validate Against Real Data



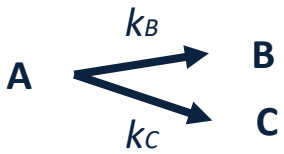
Model Algorithm

- Load Data
- Solve for Model Parameters and RMSE
- Monte Carlo Simulation for 95% Prediction Intervals
- Calculate Upper and Lower Estimates

Kinetic Model Equations

Parallel Reactions

Monomer → HMW + LMW,
Main → Acidic + Basic



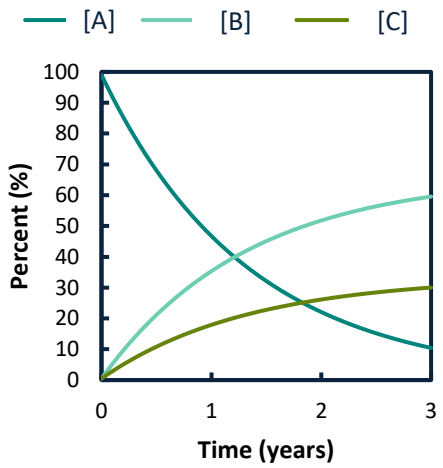
$$\frac{d[A]}{dt} = -(k_B(T) + k_C(T))\,[A]$$

$$\frac{d[B]}{dt} = k_B(T)[A] + [B]_0$$

$$\frac{d[C]}{dt} = k_C(T)[A] + [C]_0$$

$$k_B(T) = k_B(T_{ref})e^{-\frac{E_{A,B}}{R}\left(\frac{1}{T}-\frac{1}{T_{ref}}\right)}$$

$$k_C(T) = k_C(T_{ref})e^{-\frac{E_{A,C}}{R}\left(\frac{1}{T}-\frac{1}{T_{ref}}\right)}$$



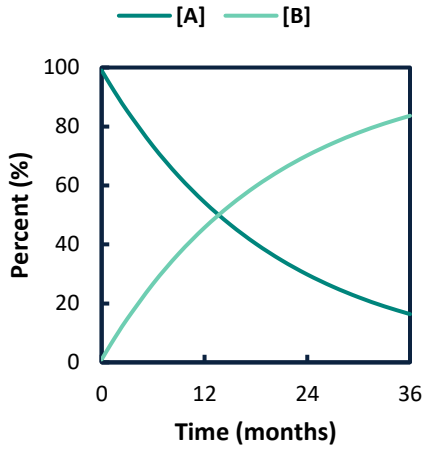
Single Reaction/ Degradation

CE-SDS → LMW, Potency, PS80

$$\frac{dA}{dt} = -k(T)[A]$$

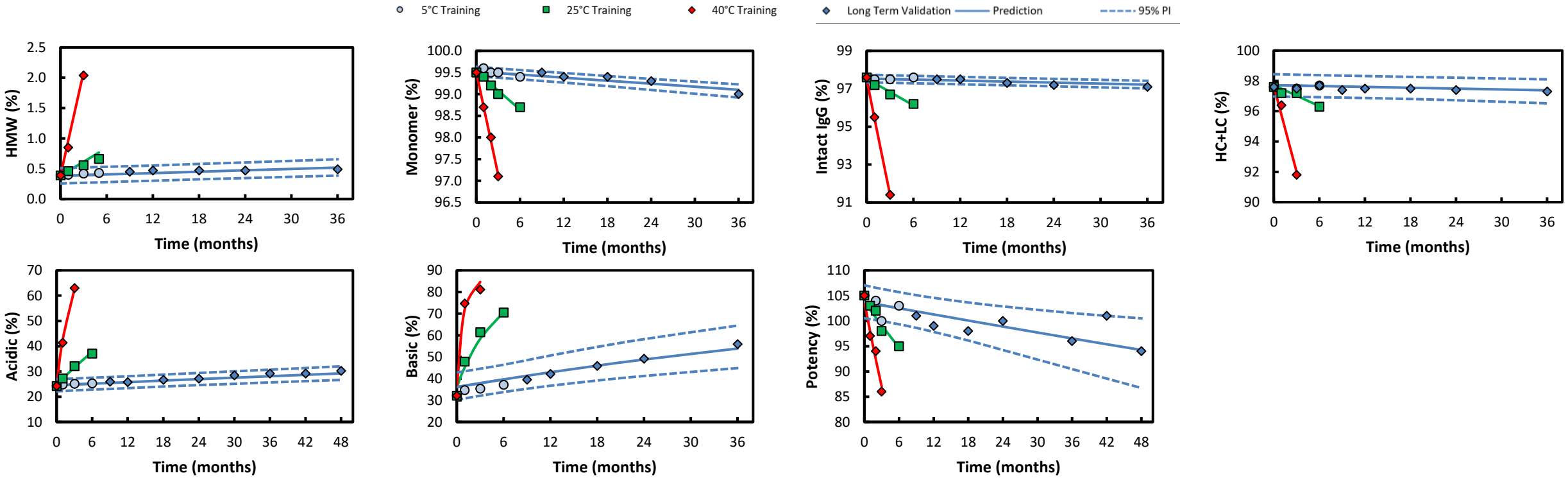
$$\frac{dB}{dt} = k(T)[A]$$

$$k(T) = k(T_{ref})e^{-\frac{E_A}{R}\left(\frac{1}{T}-\frac{1}{T_{ref}}\right)}$$



Examples of Biologics Quality Attribute Predictions

- Biologics require prediction of not just one, but multiple quality attributes to set shelf-life,
- In each case below, kinetic model was trained on only 6M of data from 5, 25, and 40C data sets. Then predicted out to 36+ months (solid and dashed lines). Then real long-term data from IND/BLA filings (diamonds) compared alongside, showing excellent agreement with predictions
- Shown for key quality attributes of HMW (aggregates), monomer, Intact IgG, HC+LC, charge variants, and potency



Model Validation on Multiple Drug Products

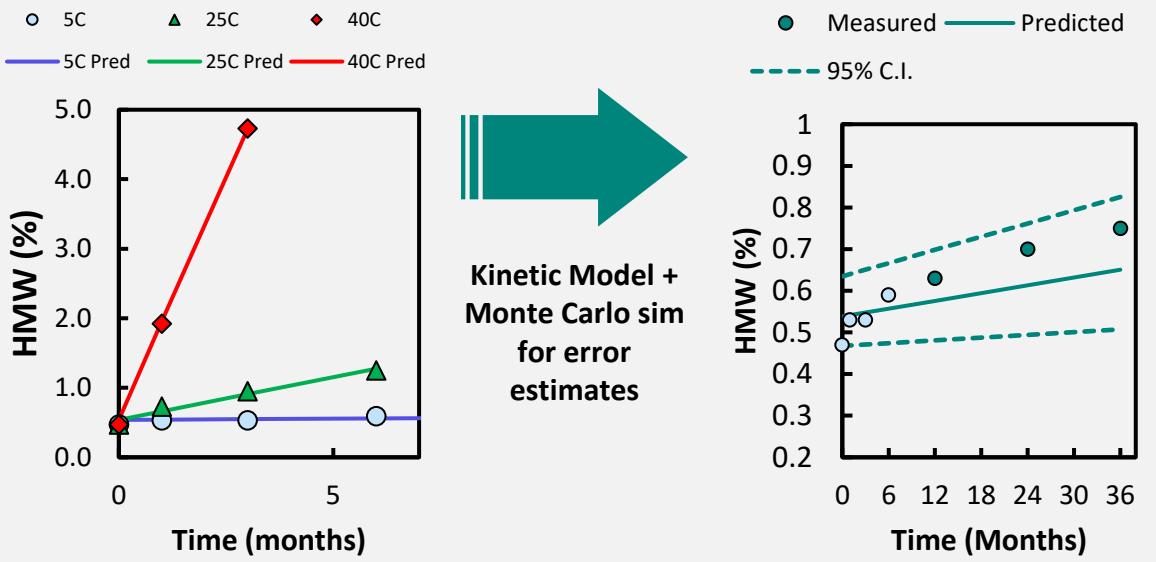
- Drug product (DP) validation set comprised of mAbs, ADCs, conforms, fusion protein
- IgG1 and IgG4
- Liquid and Lyophilized formulations
- Concentration range
  - Low: < 25 mg/mL
  - Medium: >25 and < 100 mg/mL
  - High: ≥ 100 mg/mL

Drug Product	Molecule	mAb Subtype	State	Conc (mg/mL)
A	mAb	IgG4	Liquid	Medium
B	mAb	IgG1	Liquid	Medium
C	mAb coform	IgG1 + IgG4	Liquid	Low
D	mAb	IgG1	Liquid	High
E	mAb	IgG4 Human	Liquid	High
F	ADC	IgG1	Liquid	Low
G	ADC	IgG1	Lyophilized	Low
H	mAb	IgG4	Liquid	Low
I	mAb	IgG4	Lyophilized	Low
J	mAb	IgG4	Liquid	High
K	mAb	IgG1	Liquid	High
L	mAb	IgG4	Liquid	Low
M	mAb coform	IgG1 + IgG4	Liquid	Low
N	mAb	IgG4	Liquid	Medium
O	mAb	IgG1	Liquid	Medium
P	mAb	IgG1	Liquid	Medium
Q	mAb coform	IgG1 + IgG4	Liquid	Low
R	Fusion Protein	N/A	Lyophilized	Medium

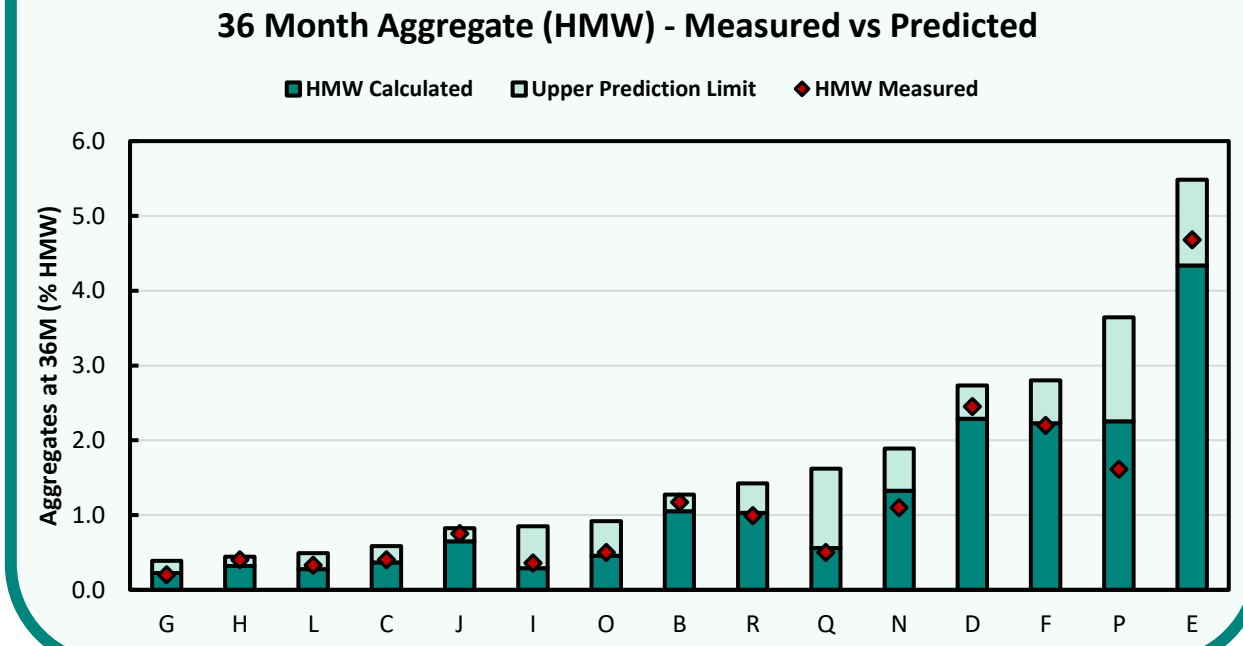
Model Validation on Multiple Drug Products – HMW Example

- For each DP, model trained on its own 6M data from 5, 25, 40C → determine kinetic parameters → predict into future
- Compared 36M predictions against real measured 36M data from filings, showing excellent agreement (right bar chart)

Use 6M Data (5, 25, 40C) to predict Long Term 5C Stability



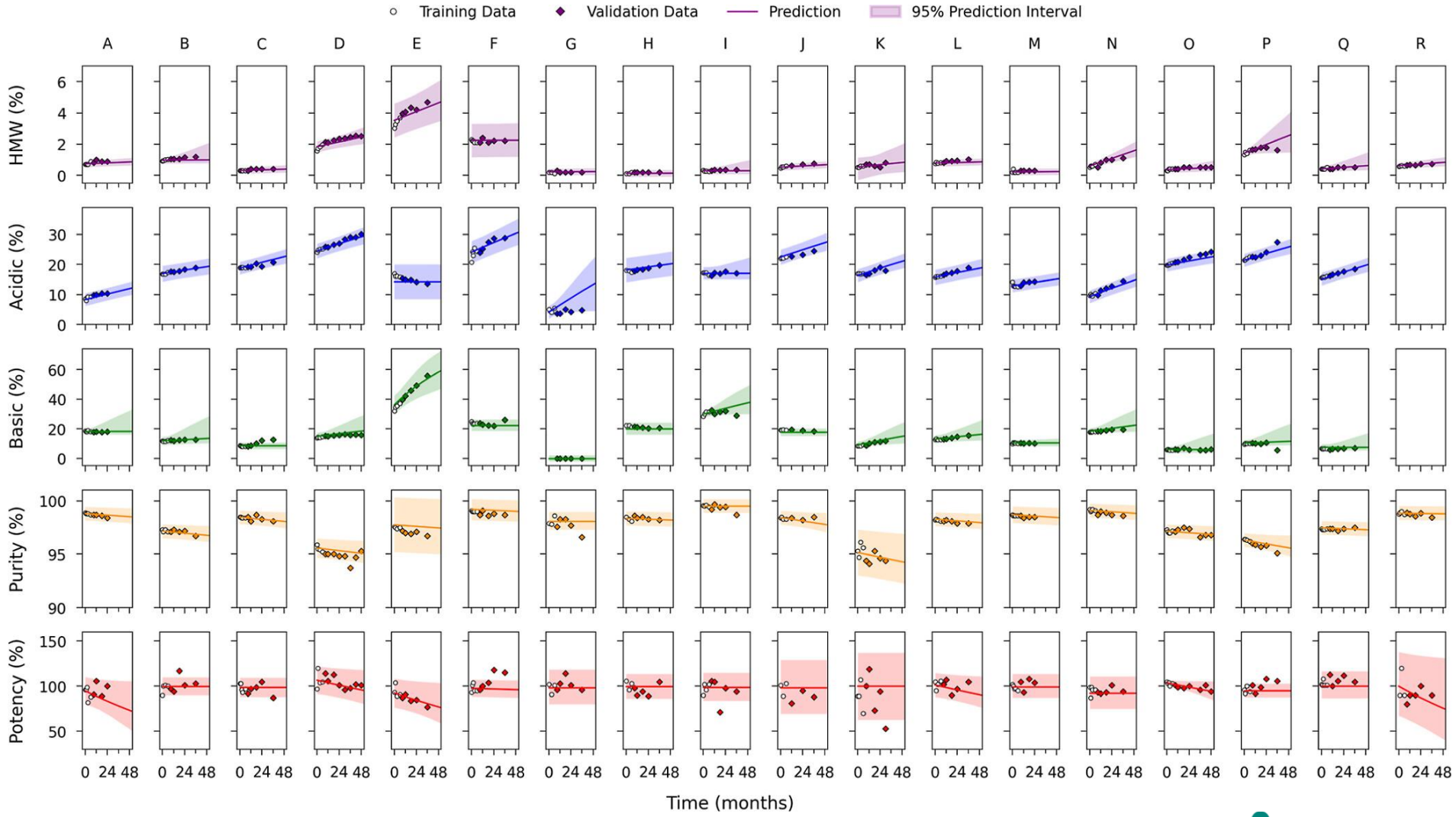
Validation on bio DPs with 36M data (mAbs, co-forms, ADCs, & fusion protein)



Model Validation on Multiple Drug Products – Multiple Attributes

Excellent agreement with real long-term data within 95% prediction intervals

Models trained up to 6M 5, 25C, and 3M 40C. For clarity, only 5C data and predictions shown here.



Kinetic Models Shows Improved Prediction to Linear Regression at Early Timepoints

Linear regression on 5C (intended storage) condition is current industry standard to set shelf life. We wanted to compare if our model could yield earlier, more accurate predictions

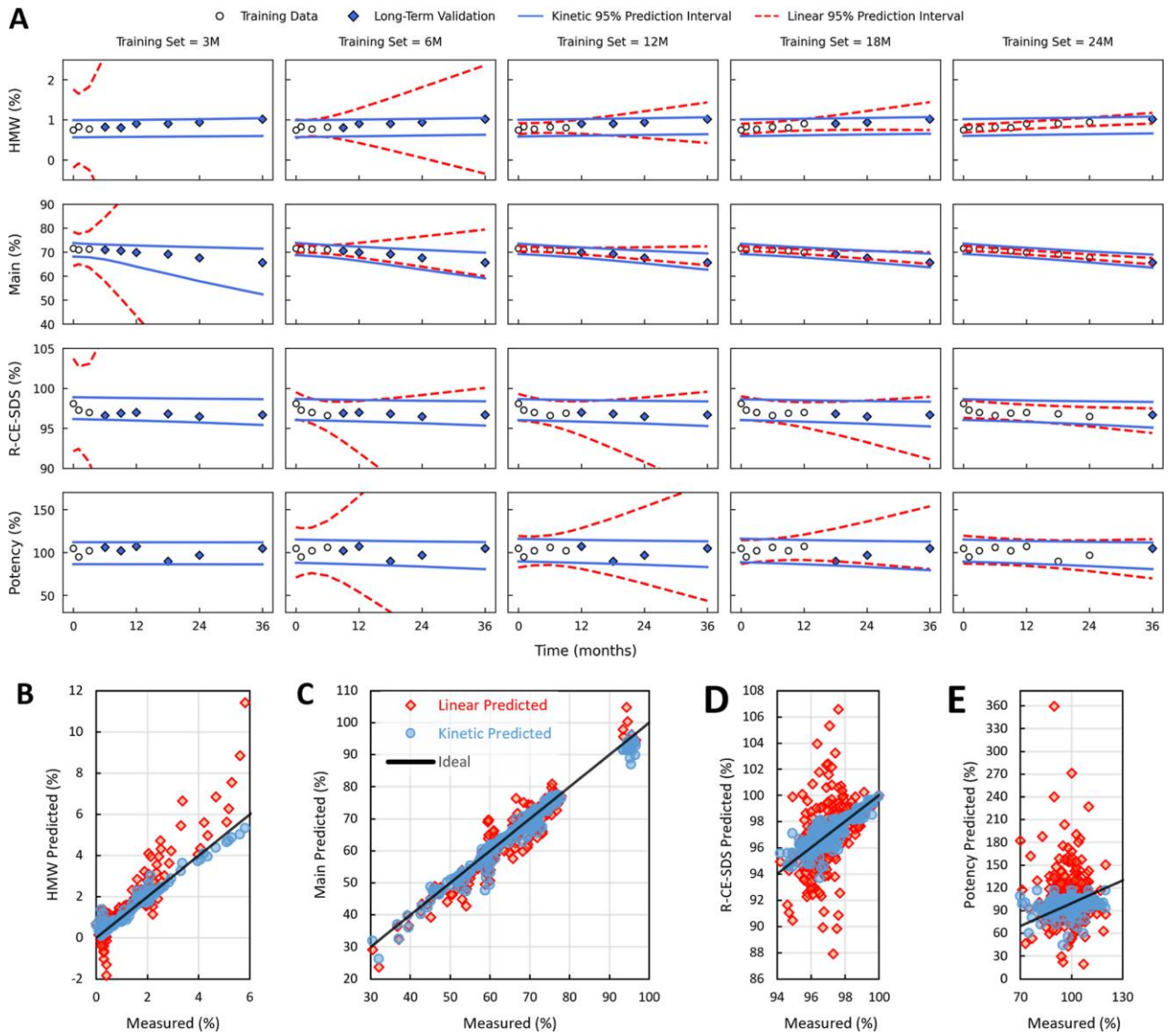
A) Kinetic model using 5, 25, and 40C data (blue lines) shows more precise prediction compared to linear regression on just 5C (red) when limited timepoints available

B) Comparison of HMW predicted vs measured for linear model (red diamond) and kinetic model (blue circle). Kinetic model closer to ideal scenario of 1 to 1 agreement (black line), indicating more accurate model.

C) Same as above for Charge variants – main

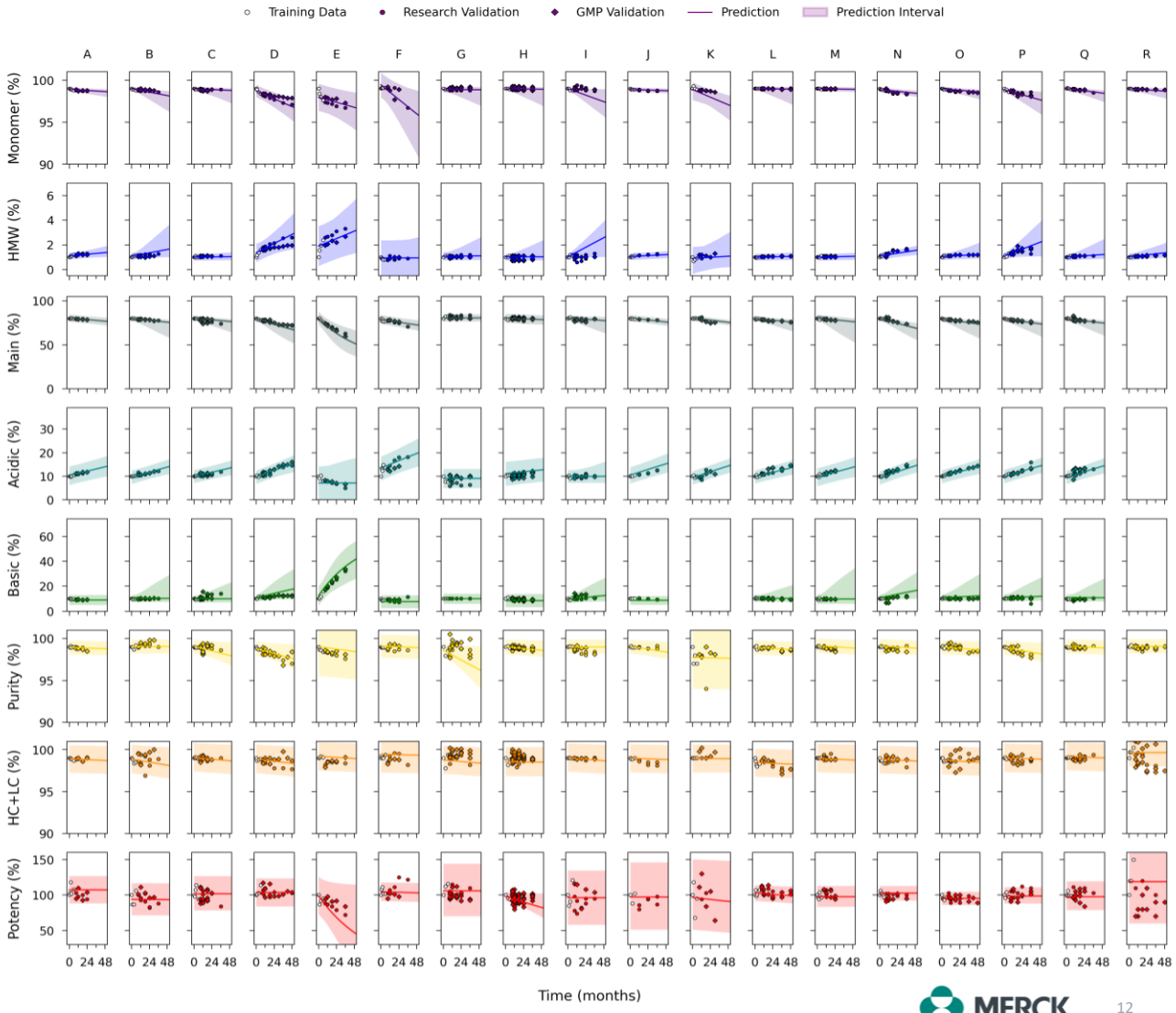
D) Same as above for R-CE-SDS purity

E) Same as above for Potency (ELISA)



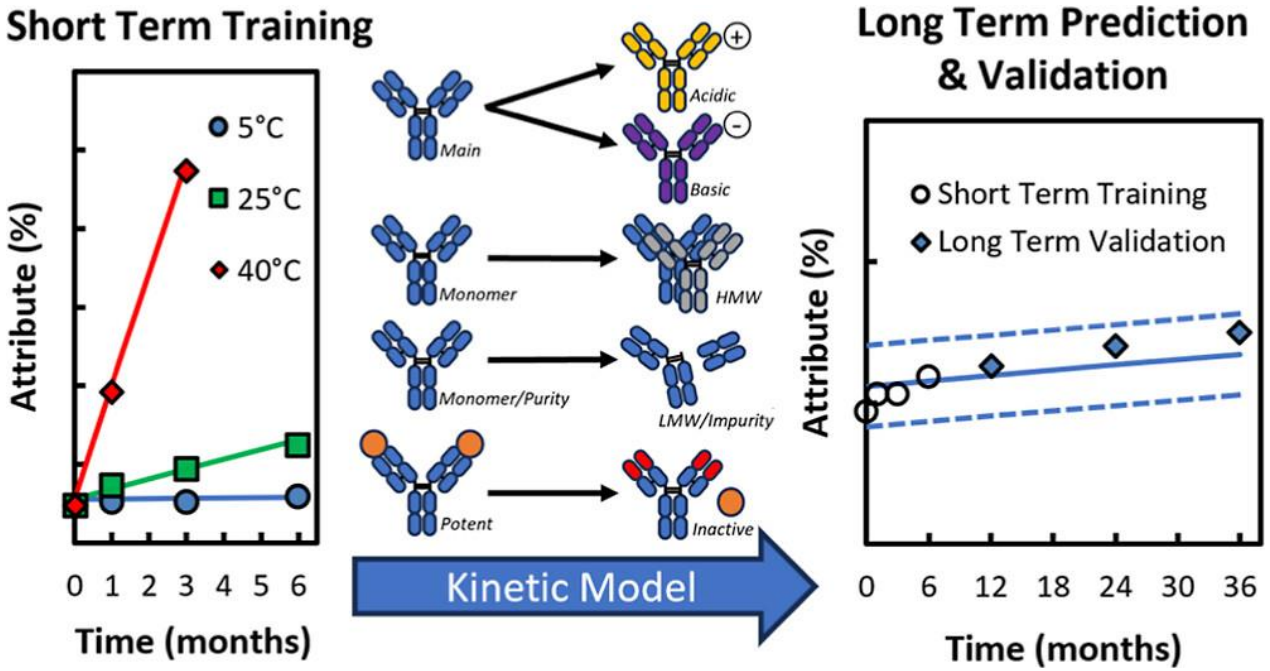
Modeling Can Predict Overall Product Success, Not Just a Single Batch

- In figure to right, model trained on single non-GMP probe stability batch and generated prediction intervals
- All future data, including future GMP batches for the product plotted within cell (normalized to same initial value).
- Future data remains within worst case prediction intervals, suggesting prediction estimates from early non-GMP probe stability batch can predict future batch success, i.e. overall product success
- Caveats: must be same formulation, process, and analytical methods when extending these extrapolations

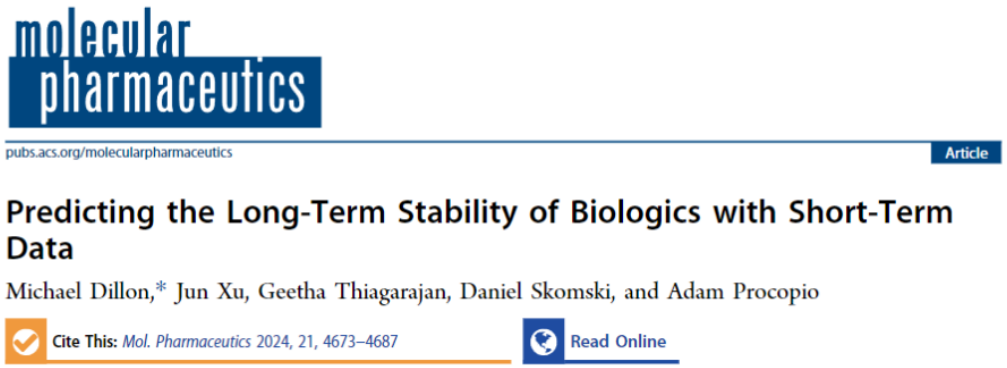


Summary

- A kinetic model was developed to predict long-term stability using short term data from accelerated temperatures
- Model rigorously validated on 18 biologics drug products of varying properties and with multiple quality attributes
- Model showed excellent agreement with long term training data and improved prediction compared to standard linear regression



For more details, please see our recent publication in *Molecular Pharmaceutics!*



Thank you!!

Thank you very much your attention and attending this talk!

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And a huge thank you to my co-authors on this work: Daniel Skomski, Jun Xu, Geetha Thiagarajan, and Adam Procopio

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