Using Prior Knowledge for Setting the Shelf Life of Biologics Products

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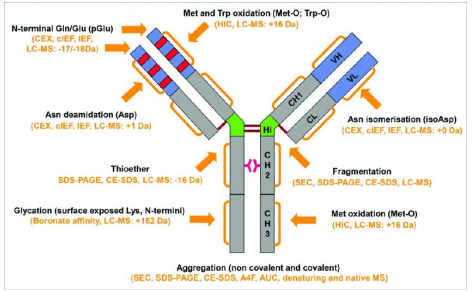
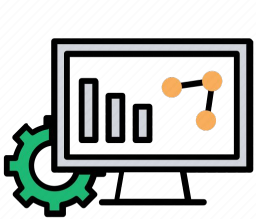
Insights from the evaluation of an IgG1 mAb product portfolio by an Arrhenius-based model

Typical utilization of stability data for Biologics

- Stability data and a stability program is important - ensures the product is stable (safe and efficacious) until retest period or shelf life
- Stability data are generated in accordance with ICH Q1's/Q5C - launch and post-marketing
- Limited use of prior knowledge, enhanced product-scientific understanding and risk-based approaches - real-time data define the expiry date with some exceptions
  - Post-marketing comparability for drug substance
  - Limited acceptance from health authorities world wide
- Potential of enhanced product-scientific understanding not really utilized - especially for well established commercial products for post-marketing activities



Evaluation of an IgG1 mAb product portfolio



- Main motivation is to explore whether Arrhenius-based kinetics can be used for accurately predicting the stability of mAb's
- Robust real-time stability prediction by using stability data from accelerated conditions and stress-conditions
- Demonstrate how predictive stability can be used to estimate the shelf-life of biologics
- Five (5) commercial mAbs products
- Focus on size and charge quality attributes prone to changes

Data quality

- Enough data with the right data granularity
- Three (3) temperatures above real-time temperature with ≥ four (4) data points per temperature to ensure
  - **Degradation reaction follows a linear trend (for use of a linear model)**
  - **Arrhenius manner, i.e. the relationship between inverse of temperature is proportional to the log of reaction rate**
- Quality attributes with small absolute change with two (2) decimal places - size
- Quality attributes with bigger absolute change with one (1) decimal place - charge
- At least four (4) data points per individual batch

Modeling

- Arrhenius equation $k_T = Ae^{-Ea/RT}$

  kT is the degradation rate, A is the Frequency factor, Ea is the Activation energy for the reaction, R is the universal gas constant and T is the absolute temperature in Kelvin

- Why Arrhenius?
  - **Allows usage of stability data collected at accelerated and stress conditions to predict how a DP will behave at storage conditions**
  - **Simple model where limitations could be learned by utilizing product-scientific knowledge/prior knowledge**

Svante Arrhenius in 1889

Results - Arrhenius fit for prediction (R^2)

In order to ensure Arrhenius behaviour R^2 score is used.

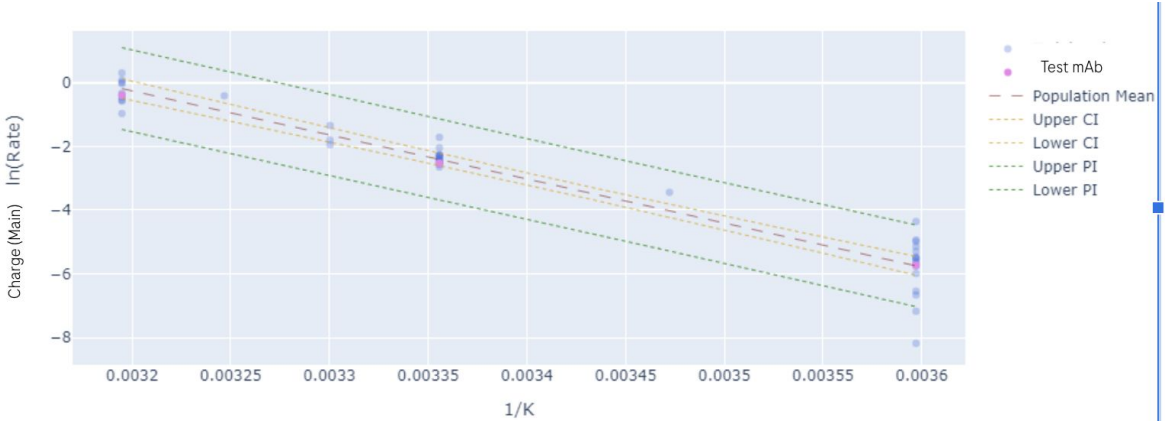
mAb	Size (Main)	Size (HMW)	Charge (Main)	Charge (Acidic)	Charge - specific peak A	Charge - specific peak B
1	0.72	0.86	0.99	0.99	n/a	n/a
2	0.86	0.93	1	1	n/a	n/a
3	0.99	0.99	0.99	0.99	n/a	n/a
4	0.99	0.99	0.99	0.99	n/a	n/a
5	0.99	0.99	0.99	0.99	0.99	0.99

- Consistently high R^2 for all charge quality attributes
- Two (2) out of five (5) mAbs with low R^2 scores for size quality attributes indicating limitations

Results - Shelf life prediction

1. Use all mAb data per quality attribute to calculate the Arrhenius model fit and create the prediction and confidence intervals beside for the one (1) test mAb to be verified
2. Validate that rates of test mAb fit within the prediction interval and if so, use the worst 5℃ reaction rate from the prediction to calculate the degradation profile for the product to predict the shelf life.
3. Compare this predicted shelf life against the commercial shelf life based on real-time data.

mAb	Shelf-life	Shelf-Life (PI)	Difference
1	24m	33m	38%
2	24m	25m	4%
3	36m	36m	0
4	30m	36m	20%
5	24m	37m	54%



Summary

- Stability profile of a mAb must be extensively studied and clearly defined, historical data prerequisites are given (incl. accurate analytical methods)
- Arrhenius behavior of an individual mAb can be ensured by high R^2 scores
- Size quality attributes (e.g. HMWs) are known to have complex degradation pathways which limits the usage for the model for a few mAbs
- Long-term stability prediction of individual mAbs based on multi-mAbs stability data from accelerated and stress conditions and fitting the data with Arrhenius-based model is possible
- Model refinement in progress

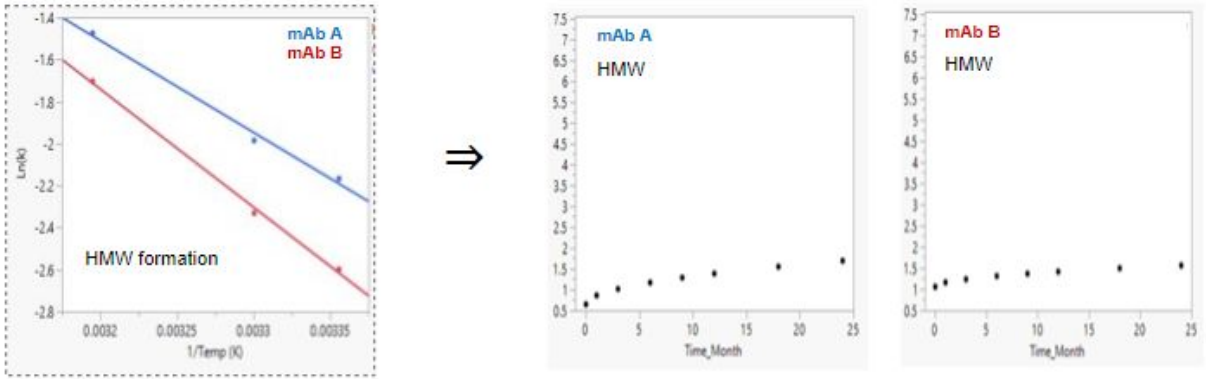
Experience with shelf-life modeling for a COVID-19 Monoclonal Antibody "Cocktail"

Motivation

- COVID-19 emergency highlighted the need for new/different stability and shelf-life approaches for biotherapeutics (e.g., monoclonal antibodies) beyond ICH Q1 series and Q5C
- Pre-pandemic situation:
  - (Prior) Knowledge- and risk-based approaches are commonly used to establish the control system of biotherapeutics
  - Stability and shelf-life for biologics expected to be based on long-term data at storage temperature (real-time data)
  - Statistical tools and well characterized stability behavior for MAbs established
- Pandemic situation: (very) limited R&D & representative stability data for specific project, real-time data just about to be started

Approach

- Predicted shelf-life of 2 MAbs through modeling based on accelerated/stress stability data, extended characterization, and Arrhenius-Theory
- Stability data compared to similar MAbs (IgG1) and formulations
- MAb A/B-High Molecular Weight (% HMW) aggregate formation modeling, 2-8C, 24 months (verification by real-time, long-term data ongoing)



Commercial shelf life of Covid-19 antibody “cocktail”

24m requested based on modeling + data package

Health Authority	DP shelf life	Data package	Comments
A	24m	3m PPQ initially 9m clinical (1) accepted	
B	24m	3m PPQ initially 6m PPQ during review	Accepted because of covid-19 response only
C	12m	3m PPQ initially 9m clinical (1) accepted	Ensures supply chain
D,E	12m	3m PPQ initially 6m PPQ during review 9/12m clinical (1) accepted	Ensures supply chain
F,G	24m	3m PPQ initially 6m PPQ during review 12m clinical (1) accepted	Accepted because of covid-19 response only

Summary

- Predictive stability models partially accepted for Covid-19 antibody “cocktail”
- Additional real-time data provided during review. Clinical stability data partially accepted too
- Pandemic experience highlighted significant potential to accelerate CMC stability using predictive modeling for biologics (e.g., mAbs), noting that models used could differ based on knowledge

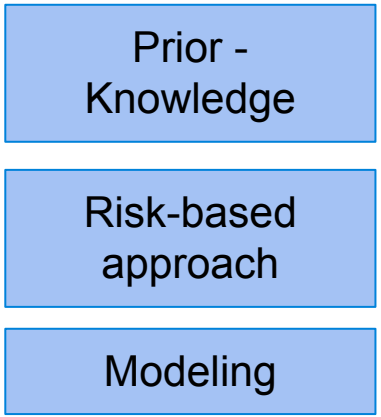
Conclusion

Conclusion

- Model approaches already existed pre-pandemic were highly useful but never used to this magnitude
- Some acceleration unique to pandemic urgency but could be further utilized to accelerate supply to patients
- Pre-Market
  - Formulation changes
  - Configuration/presentation changes
  - Accelerated launch; setting initial shelf-life

Post-Market

  - Shelf-life of post change material
  - Stability lifecycle management



Doing now what patients need next