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Advanced Kinetic Modelling

A universal tool for Stability Predictions of Biotherapeutics and Vaccines

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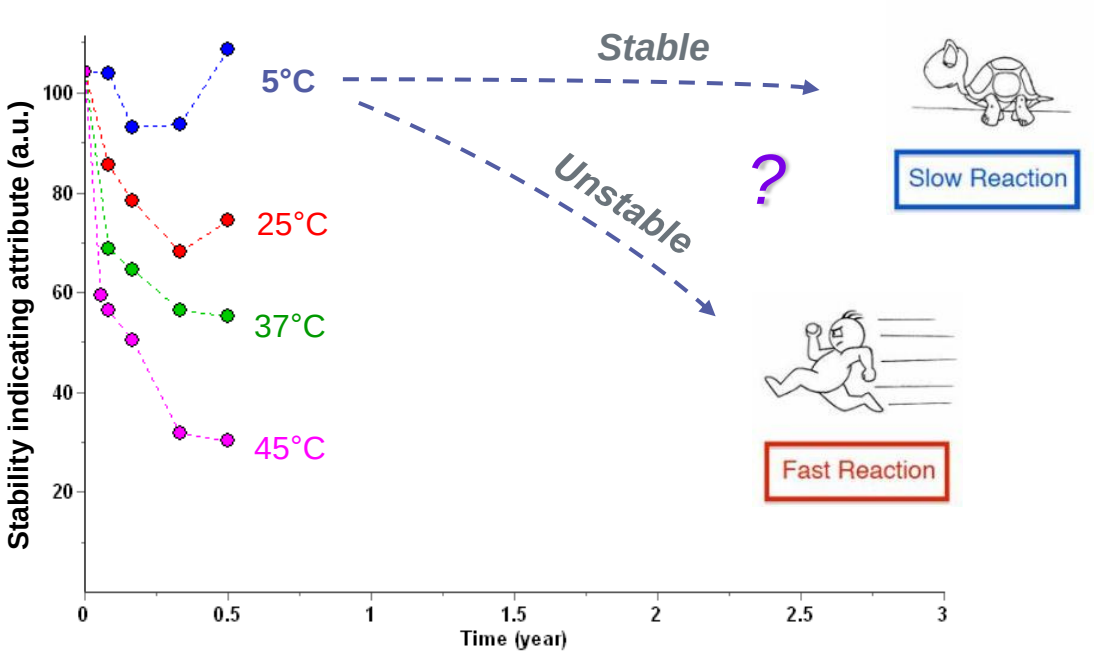
01 Advanced Kinetic Modelling (AKM)

Overview

Advanced Kinetic Modelling (AKM): Introduction



A methodology which provides accurate description & prediction of **stability behavior of quality attributes** (good modelling practices need to be adopted) to support a variety of applications

- Arrhenius-based equations that best fit stability data obtained at the recommended and accelerated storage condition (+5°C,+25°C, +37°C .) [2-3] are identified
- A large library of possible models of varying complexity are explored which approximate various possible product degradation pathways [1]
- A universal method applicable for biologicals and vaccines [4]

Kinetic model – Arrhenius based

$$\frac{d\alpha}{dt} = \underbrace{A_1 . exp\left(-\frac{E_{a1}}{RT}\right) . (1-\alpha)^{n_1} . \alpha^{m_1}}_{\text{1-step}} + \underbrace{A_2 . \exp\left(-\frac{E_{a2}}{RT}\right) . (1-\alpha)^{n_2} . \alpha^{m_2}}_{\text{2-step}}$$

A	Pre-exponential factor
E	Activation energy
n	Order of the reaction
m	Reaction order for autocatalytic type component
T	Temperature

[1] B. Roduit et al., Thermochimica Acta **2014**, 579, 31–39. [2] D. Clénet, Eur J Pharm Biopharm **2018**, 125, 76–84 . [3] C. Roque et al., PDA Chapter; **2021**, ISBN 978-1-945584-22-0.
[4] M. Huelsmayer et al., Scientific Reports, **2023**

Recommended good modeling practices

1. Appropriate study design

   Ensure sufficient data: Minimum 3 batches, 3 different temperatures & cumulatively 20-30 data points.

   Significant change visible at least at accelerated temperatures

2. Screening of models

   Fitting a library of possible models to the data of varying complexity starting with simple models

3. Model identification

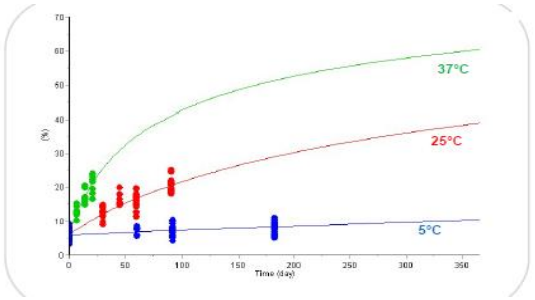
   Identify the best model based on statistical scores (AIC, BIC etc), goodness of fit parameters (RSS) and robustness (Model performance at different temperatures),

4. Predictions

   Make predictions using the model along with prediction bands (Bootstrap intervals)

Verification: The model predictions are verified using newly generated/hold-out stability data

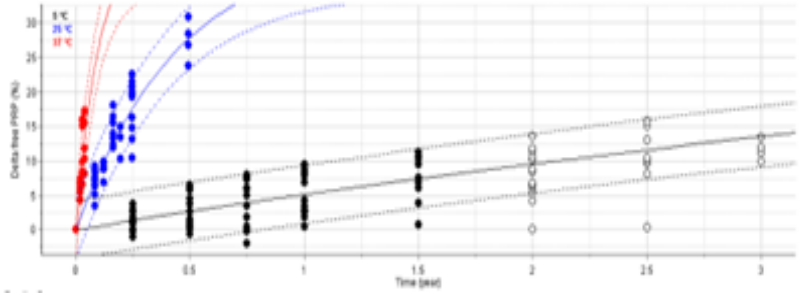
Illustration



Mode Comparison

#		w AIC (%)	w BIC (%)	Nb param	Nb points	Rss	E1 (J/mol)	ln(A1*s) (-)	n1 (-)	m1 (-)	E2 (J/mol)	ln(A2*s) (-)	n2 (-)	m2 (-)	p (-) RH	Alpha storage...	Yinit (%
57	☑	17.9	75.5	3	208	672.726	98675.766	22.415	4 *	0 *	-	-	-	-	-	1E-10 *	6.031
52	☐	11.923	3.666	4	208	668.575	99794.392	22.974	5.389	0 *	-	-	-	-	-	1E-10 *	5.943
56	☐	4.328	18.255	3	208	681.972	97999.069	22.064	3 *	0 *	-	-	-	-	-	1E-10 *	6.107
26	☐	4.107	5.21E-4	7	208	654.911	96088.742	20.819	0 *	0 *	1.459E+5	44.483	0.612	0 *	-	1E-10 *	6.101
51	☐	2.169	4.912E-2	5	208	672.726	98677.856	21.944	4 *	0 *	98673.245	21.438	4 *	0 *	-	1E-10 *	6.031

$$\frac{d\alpha}{dt} = 5.40E9.\exp\left(-\frac{98.6E3}{RT}\right).(1-\alpha)^4$$



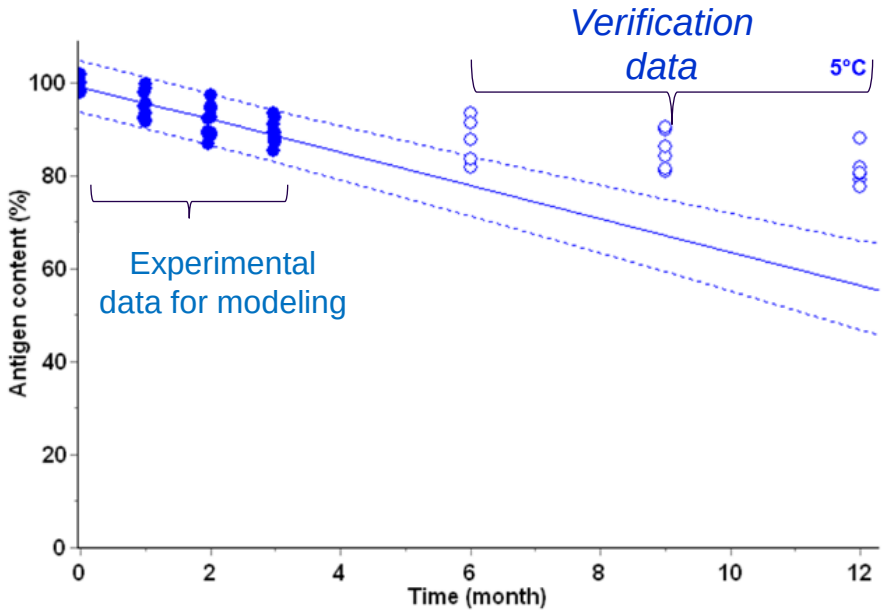
Comparison with Linear regression models

- International Conference on Harmonisation (ICH) guidelines proposes using regression (primarily linear) models bulit on real-time stability data with statistical tests for Batch “poolability” tests for the purpose of shelf-life determination

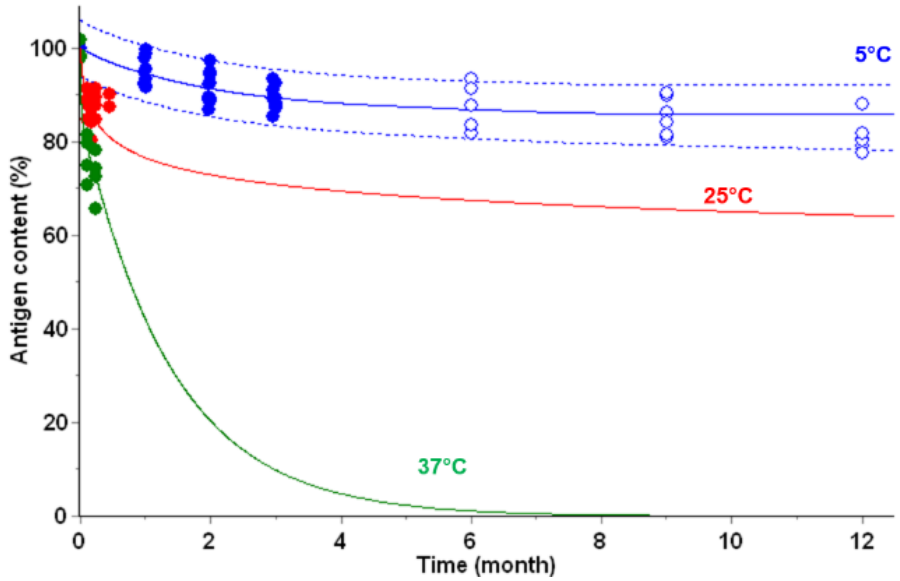
- Despite their wide usage, these models very often fail to adequately describe the complex stability behaviour of bioproducts, which frequently involve more complex and multi-step reactions.

- This has implications for key applications like shelf-life estimation which the AKM successfully address.

ICH linear regression (5°C)



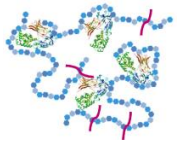
AKM (5°C, 25°C, 37°C)



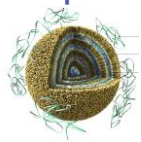
Advanced Kinetic Modelling (AKM) Advantage

- By applying advanced kinetic modeling (AKM) to multiple observations obtained over a relatively **short period of time** at **multiple temperatures.**
- Models are found to make **accurate predictions** over **long time periods** for a **range of temperatures**
- This approach has already been used to simulate the stability of several attributes of a wide range of products (biotherapeutics, classical and mRNA-based vaccines) exhibiting from simple to very complex degradation pathways

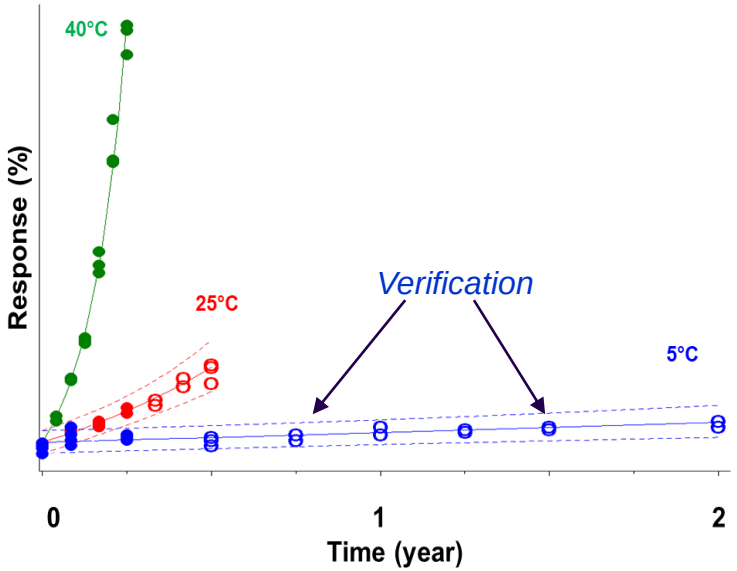
mAb
Impurity

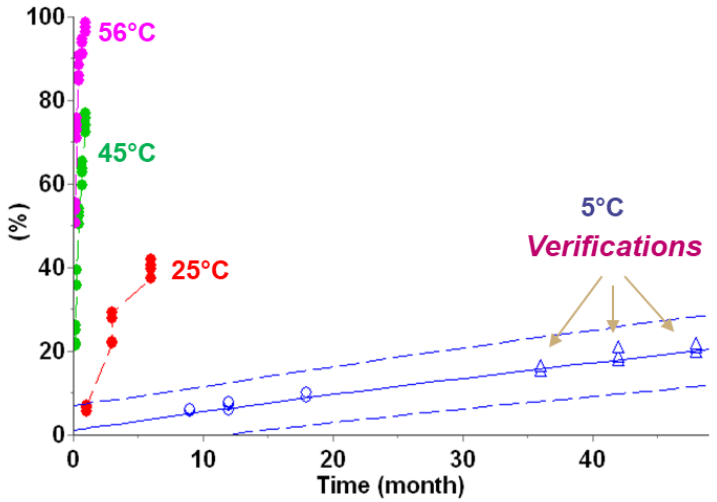


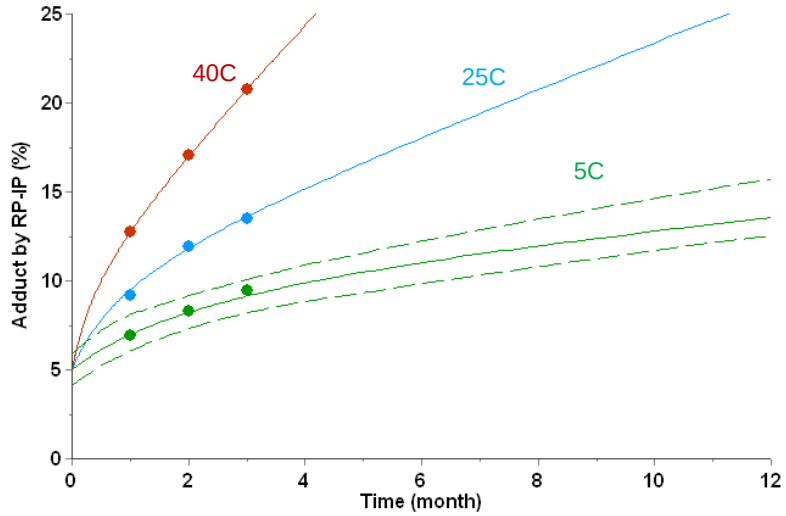
Conventional vaccine
Depolymerization



LNP-formulated mRNA vaccine
Adduct formation







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Regulatory landscape

- With **EMA** for a commercialized multi-valent vaccine
  - 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
  - For the first time, acceptance criteria was claimed based on kinetic model

- With Health Authorities in Thailand for an inactivated virus-based vaccine
  - 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

- With Health Authorities in USA for a live attenuated virus-based vaccine
  - 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

- With Health Authorities in Brazil for a commercialized live attenuated virus-based vaccine
  - Stability Modeling Supporting Stability 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

- Cross- company proven experience (e.g., Vaccines Europe task force) on reliability of stability modeling when following some key modeling best practices. AKM discussed in several external Stability Working Groups for COVAX/SWAT, EFPIA and BIO.

- A Vaccine Europe stability taskforce comprised of modeling, stability, and CMC experts from across industry promoted the use of such modeling to determine the proposed vaccine shelf life in the absence of real time stability data on the commercial batches.

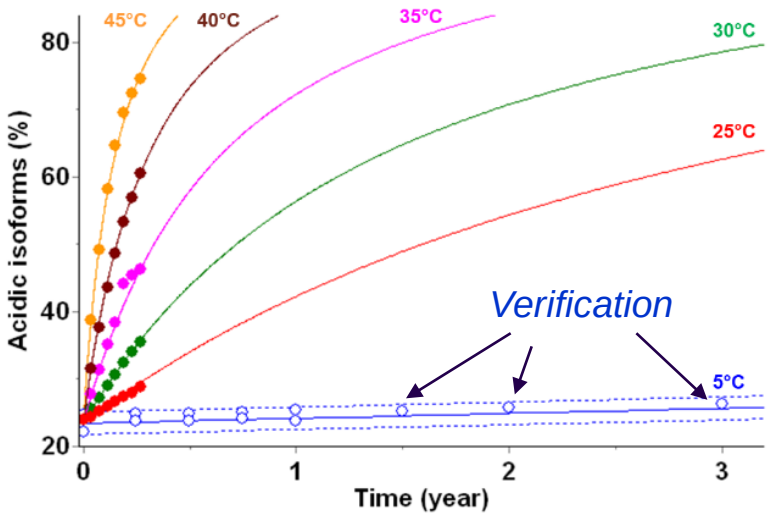
02 Advanced Kinetic Modelling (AKM)

Stability prediction of critical quality attributes of biotherapeutics and vaccines in liquid and freeze-dried pharmaceutical forms

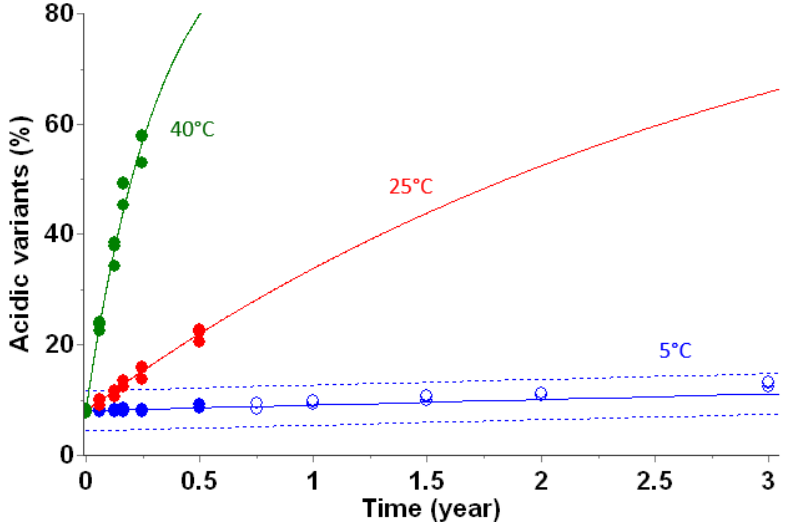
Predicting stability of CQA of biotherapeutics and vaccines in liquid and freeze-dried formulations

- Chemical or physical stability of bioproducts were accurately described applying AKM
- Long-term stability (up to 3 years) were accurately predicted by the models

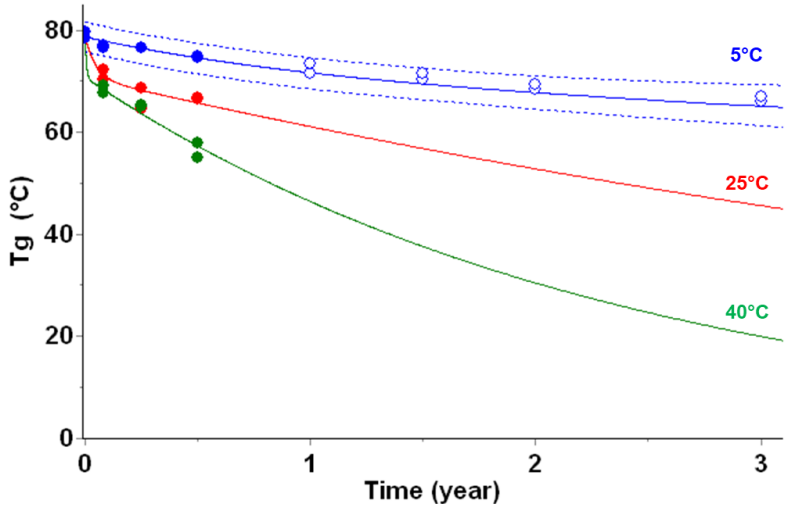
abbvie - liquid mAb
Acidic isoforms



NOVARTIS – liquid mAb
Acidic variant



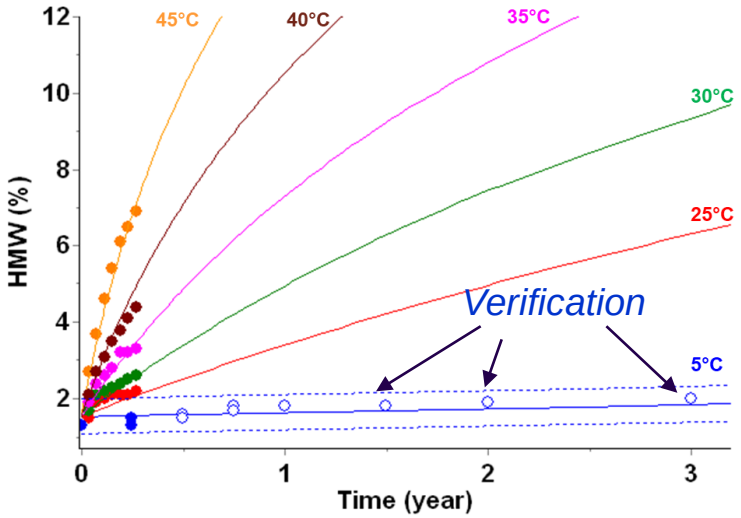
sanofi - freeze-dried mAb
Glass transition temp.



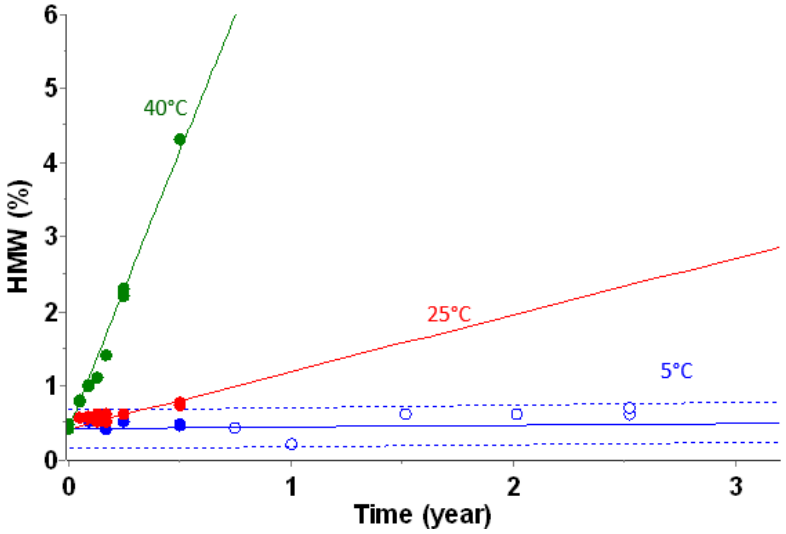
Stability prediction of aggregation in biotherapeutics

- 3-years stability at 5°C accurately predicted for high molecular weight species using 3 to 6 months experimental data from 5°C to 45°C

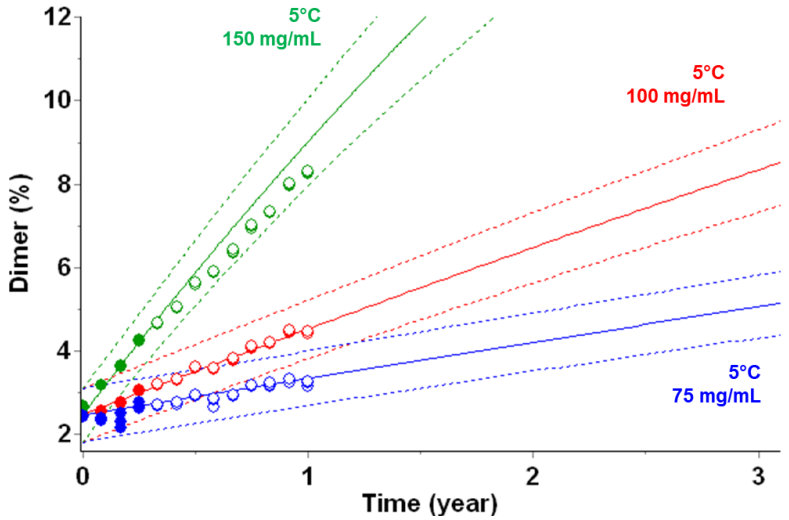
abbvie - liquid mAb
HMW



NOVARTIS – liquid mAb
HMW



sanofi – Single variable domain
Dimers



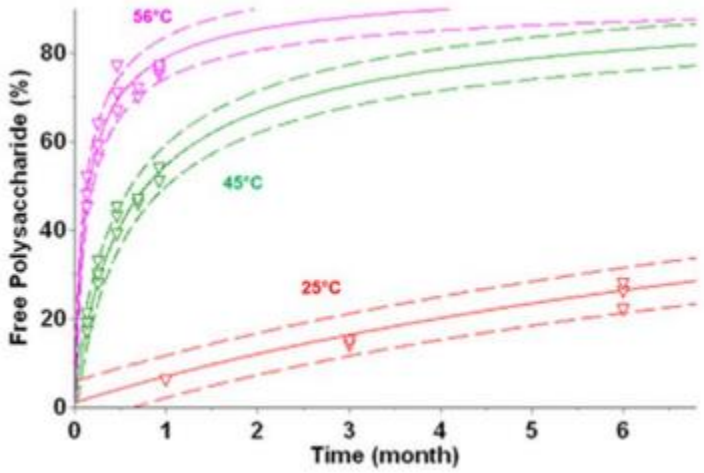
03 Advanced Kinetic Modelling (AKM)

Comparison of stability profiles

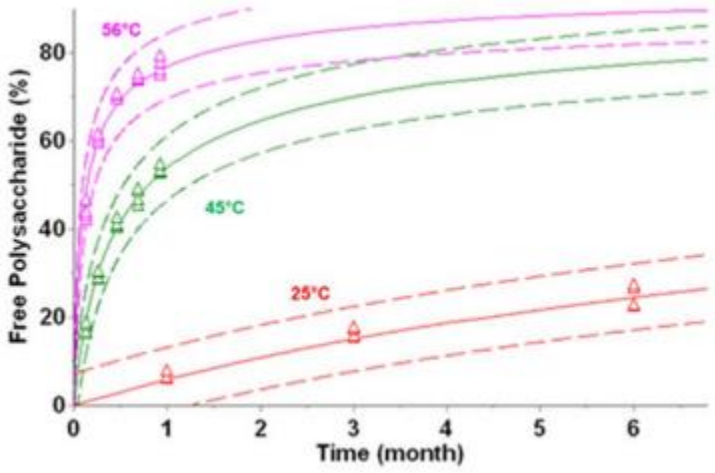
Comparison of stability profiles

- Comparison of Batch stability profiles are used to support product development (e.g. between clinical batches, technical batches, pilot batches etc.) and various post approval changes
- The comparability of Free Polysaccharide stability profiles was demonstrated for a conjugate vaccine between two different production scales through modelling of accelerated stability data (6M at 25 °C,45 °C and 56 °C)
- Further, the models also provided accurate long term predictions

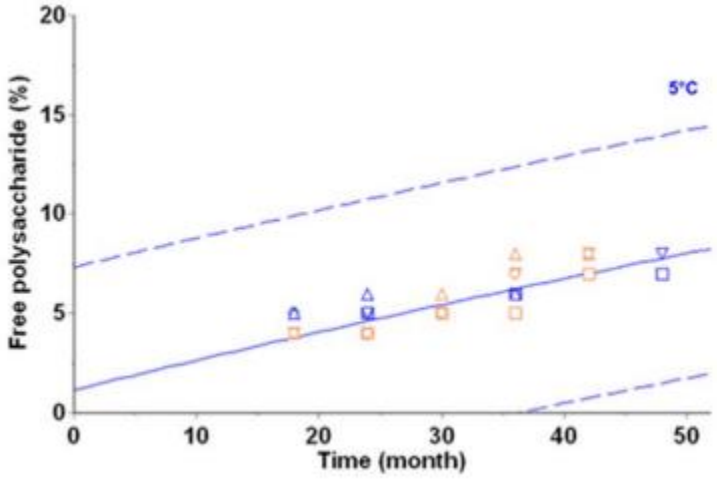
Small scale model overlaid with Large scale data



Large scale model overlaid with Small scale data



Long term predictions



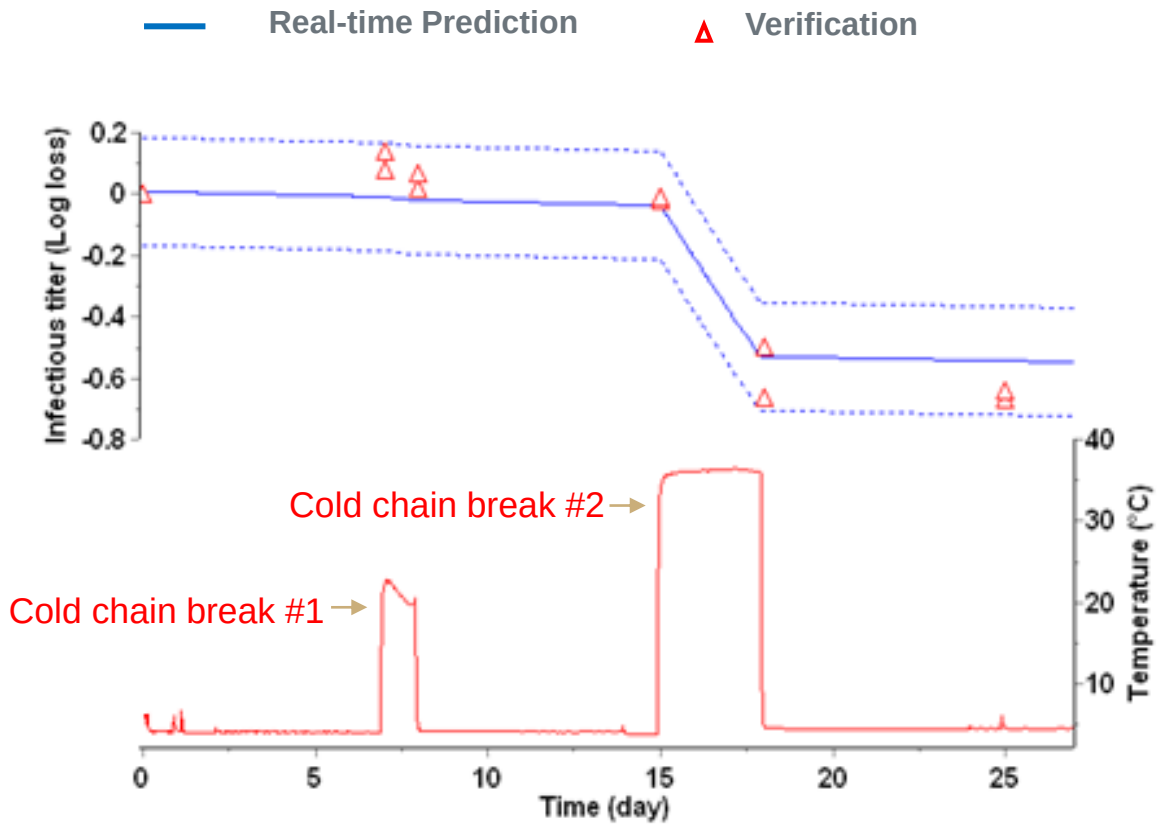
04 Advanced Kinetic Modelling (AKM)

Predictions for cold chain disruptions

Real-time Stability Monitoring of Vaccines

- Electronic time-temperature devices integrating kinetic models of vaccine would be able to inform, in real time, the level of vaccine degradation*
- Beyond conventional data loggers, such “smart trackers” enable a continuous monitoring of
  - Geolocation of products
  - Temperature and level of degradation of products
  - Humidity, Light, Choc

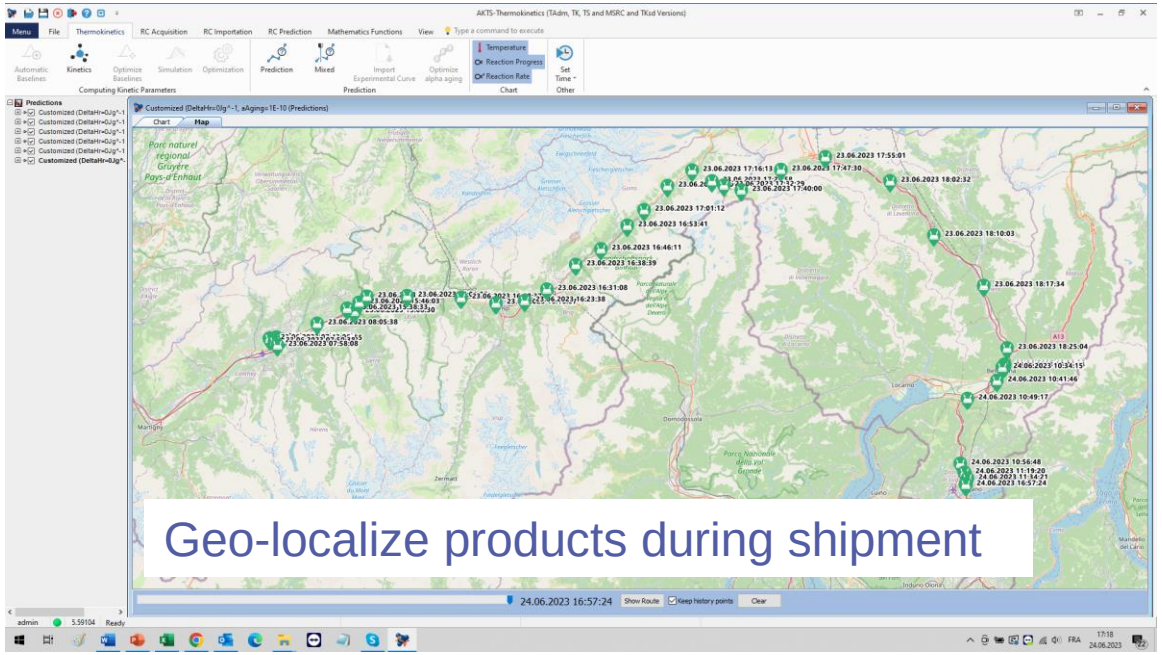
Shelf-life card integrating kinetic models

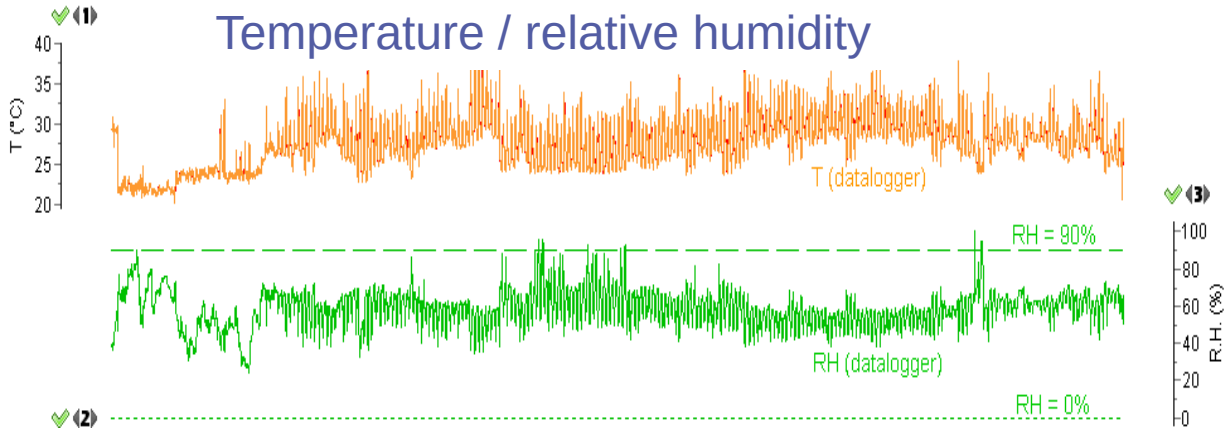


** M. Huelsmayer et al., Scientific Reports, **2023**, C. Campa et al., Vaccines **2021**, B. Roduit et al., Molecules **2019**, D. Clénet, Eur J Pharm Biopharm **2018***

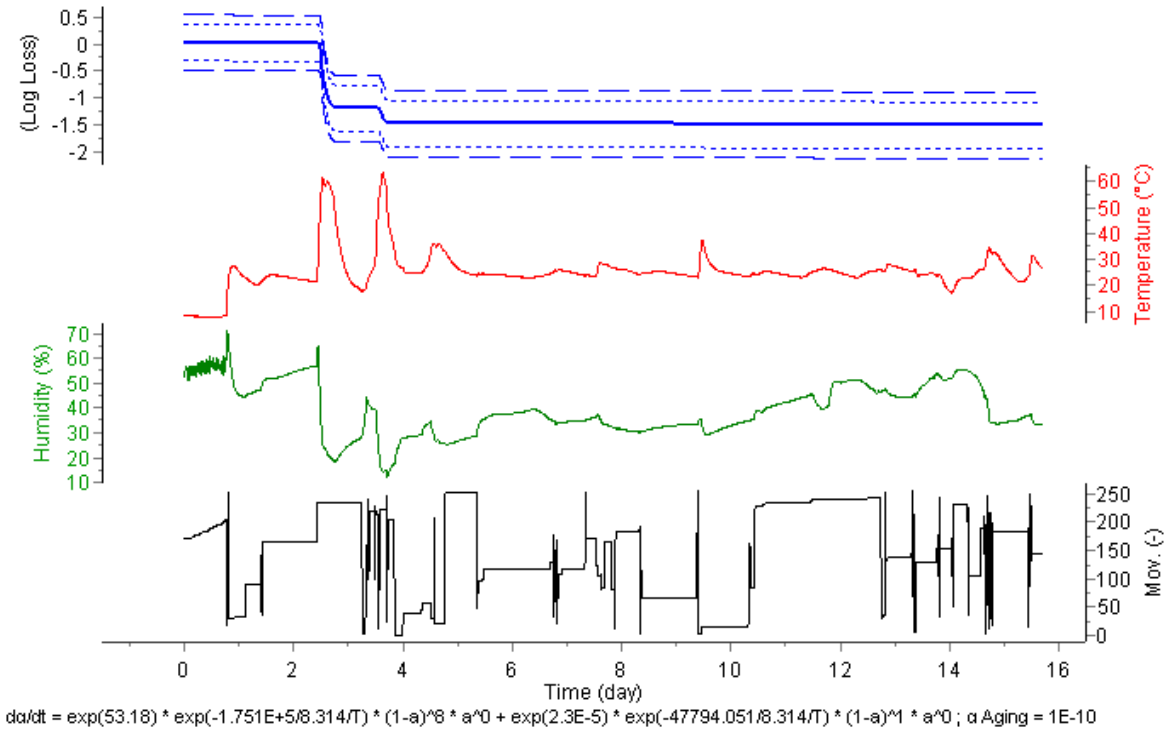
Real-time Stability Monitoring ..contd

- Geo-localize products during shipment, monitoring if they are still good or not (level of degradation)
- Monitoring product quality for all time/temperature/humidty conditions (including excursions)





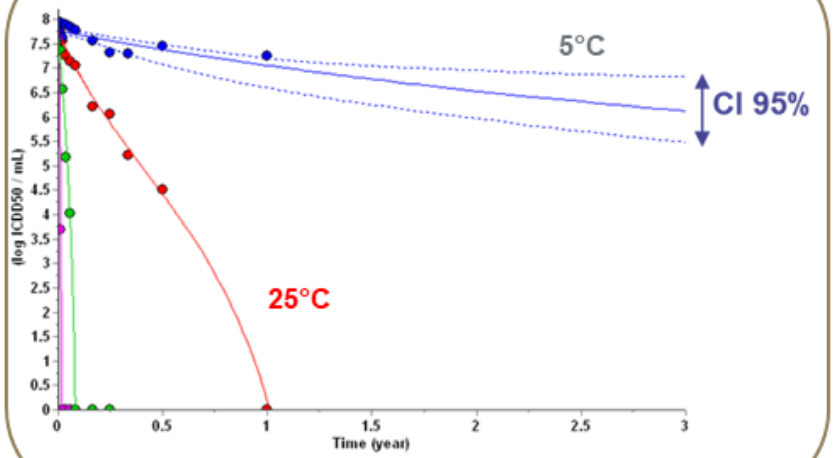
Geo-localize products during shipment and monitor level of degradation



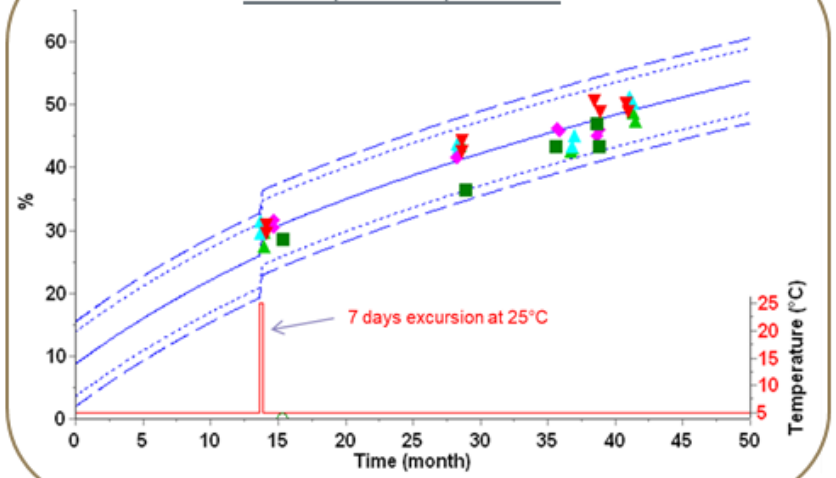
dα/dt = exp(53.18) * exp(-1.751E+5/8.314/T) * (1-a)^8 * a^0 + exp(2.3E-5) * exp(-47794.051/8.314/T) * (1-a)^1 * a^0 ; α Aging = 1E-10

AKM: Summary of Applications

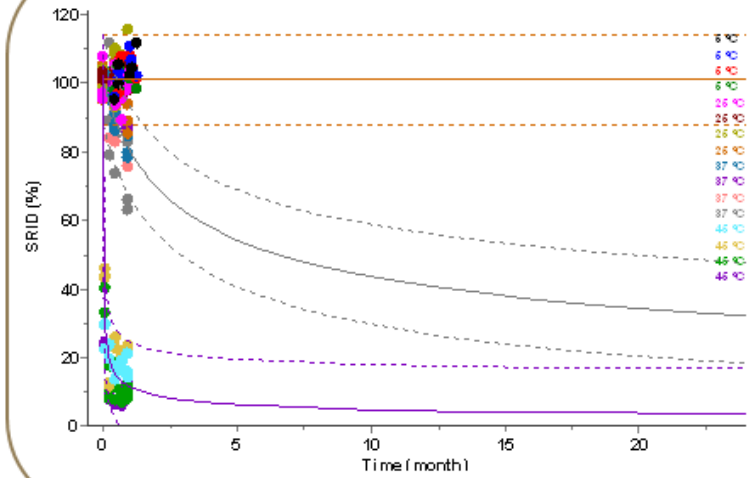
Shelf-life estimation



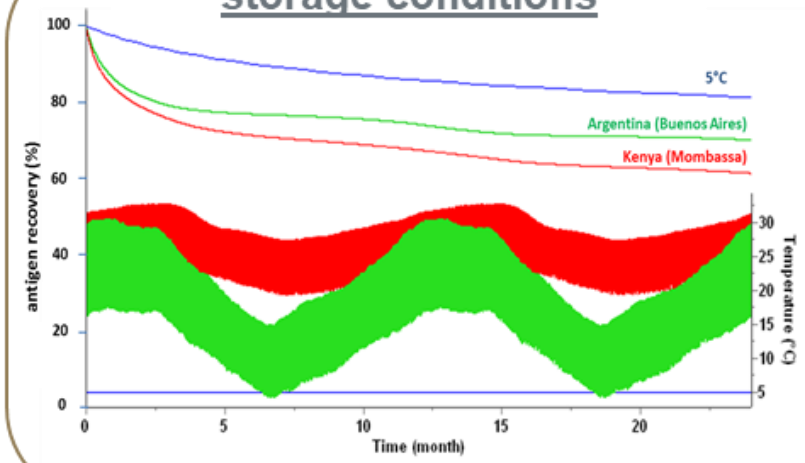
Excursions of temperature
TOR, CTC, VVM



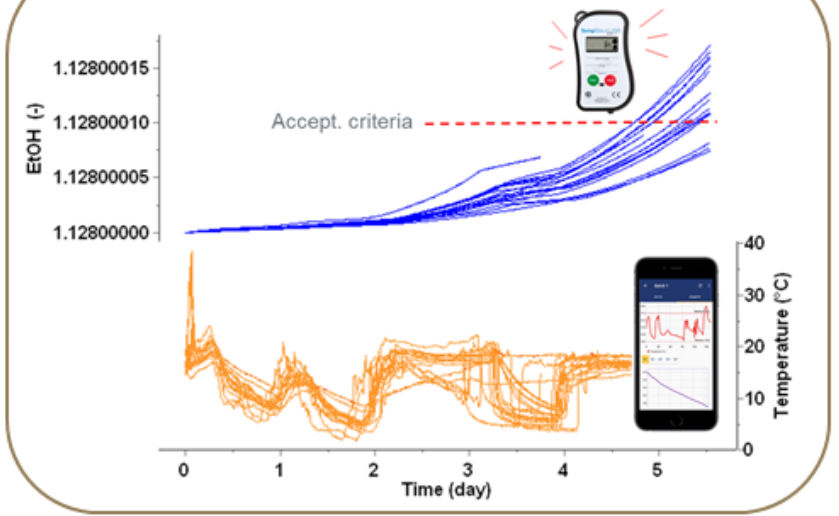
Batch-to-batch comparison



Recommend appropriated storage conditions



Real-time shelf-life monitoring



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- M. Huelsmeyer (Abbvie), D. Kuzman and M. Bončina (Novartis), J. Martinez, C. Steinbrugger (bioMérieux), J. Weusten (MSD), A. Evers (Merck), C. Campa (GSK), A. Lennard (Amgen)

- C. Calero-Rubio, W. Roche, B. Niederhaus, Y. VanHaelst, M. Hrynyk, P. Ballesta, H. Achard, S. Augusto, M. Guillois, C. Pszczolinski, M. Gerasimov, C. Neyra, D. Ponduri, S. Pfeiffer-Marek, E. Vetter, C. Neyra, F. Ausar, N. Rahman, O. Faure, D. Caudron, S. Petit, C. Airiau, … and all the Sanofi stability modeling user-group members

Huelsmeyer, M., Kuzman, D., Bončina, M. *et al.* A universal tool for stability predictions of biotherapeutics, vaccines and in vitro diagnostic products. *Sci Rep* **13**, 10077 (2023). https://doi.org/10.1038/s41598-023-35870-6

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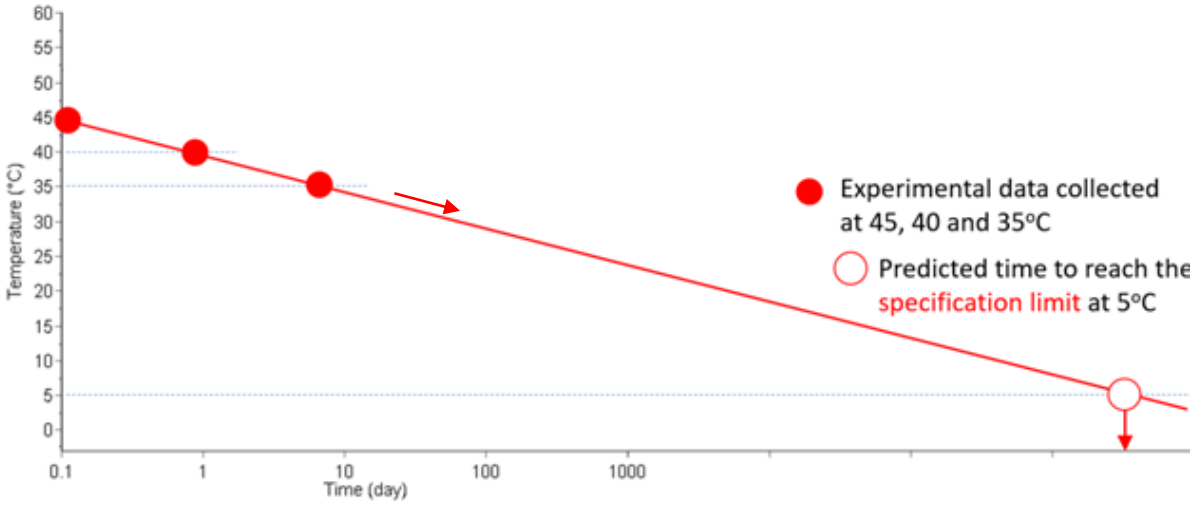
Advanced Kinetic Modelling
A universal tool for Stability Predictions of Biotherapeutics and Vaccines

Back-up slides

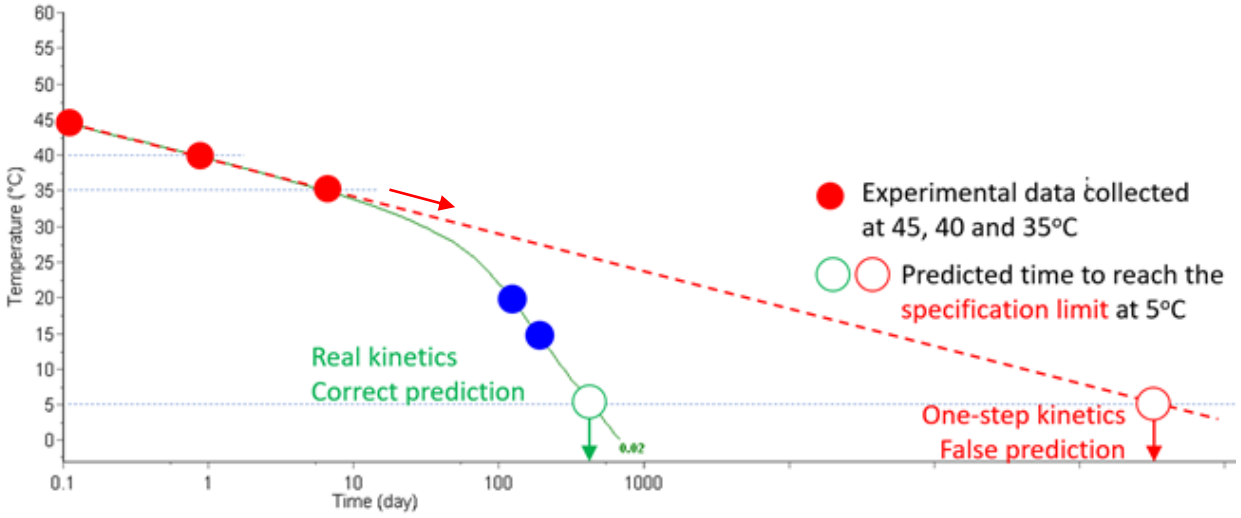
Stability predictions using isoconversional method

- For single step reactions, the Arrhenius equation and isoconversional method can be applied to extrapolate time to reach a specification limit based on short-term data obtained at elevated temperature*
- This approach assumes a specific mechanistic model will fit the data → **Applicable for single-step reactions**
- Simple Arrhenius equation can be used to predict stability of synthetics. However, simplified application of the Arrhenius relationship may be imprecise as this does not properly describe the often complex and multi-step degradation process of biological materials**

Single-step kinetics to reach a specification limit



⚠ Approach not applicable for multi-step kinetics



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** K. C. Waterman et al., Pharm. Res., **2007***

*** Oliva et al., **1999**; Kayser et al., **2011**; Hansen et al., **2016**; Clénet et al., **2014**; Clénet, **2018**; Roduit et al., **2019***

AKM as a valuable solution for updated guidelines

- The rigid application of ICH Q5C indications, like the core stability data package exemplification and requirements for real time data, is not compatible with the accelerated vaccine development and industrial plan needed for urgent global supply of COVID vaccines.*

- This is especially true in pandemic situation where stability data will be limited at filling from the commercial scale batches. Yet expiry date for commercial batches will have to be defined as packaging/labeling operations are to be anticipated to maintain the pace with vaccine market availability timelines.*

- In these circumstances, it is more logical that benefit vs scientific risk-based thinking is applied. In cases of reduced data sets, making use of prior knowledge and accelerated stability studies to base their claims on shelf life, exploiting modeling approaches, will be critical for Applicants.*

- In addition, a Drug Product will experience many planned and unplanned conditions before reaching the vaccinee: temperature, freezing, agitation, light, contact materials, administration. **

- Therefore, in the context of global supply, it is important to understand the degradation routes of the product and its sensitivity to various stresses and develop strong post-approval stability program.**

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*from Best practices for determining and updating storage temperature and shelf-life COVAX Workshop (Industry (VE) *& CEPI presentations**)*
https://media.tghn.org/medialibrary/2020/12/20201209_COVAX_Storage_temperature_and_shelf_life_workshop_presentation.pdf