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Stability Modeling for Biotherapeutics and Vaccines

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Agenda

01 Stability Modeling background

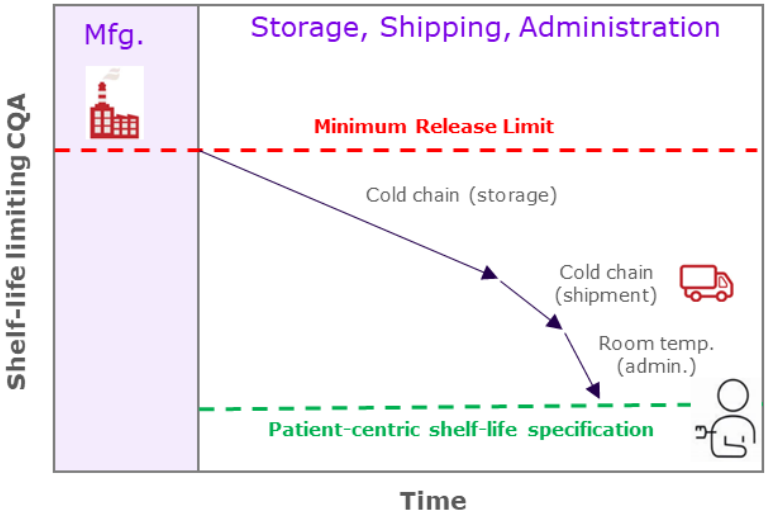
02 Advanced Kinetic Modeling - Main Applications

03 Regulatory landscape

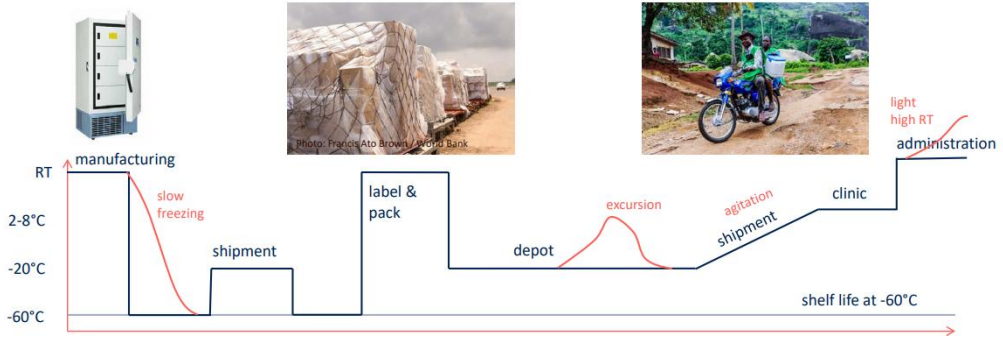
04 Conclusions and perspectives

Stable pharmaceutical products?

- Usually, main CQA slowly declines during storage



- Shelf-life is usually defined for constant storage condition (e.g. 2 – 8°C)
- Degradation rate is highly dependent on temperature (cold-chain breaks, shipment and handling, …)
- Knowing degradation rate of vaccine during storage and shipment is of huge interest



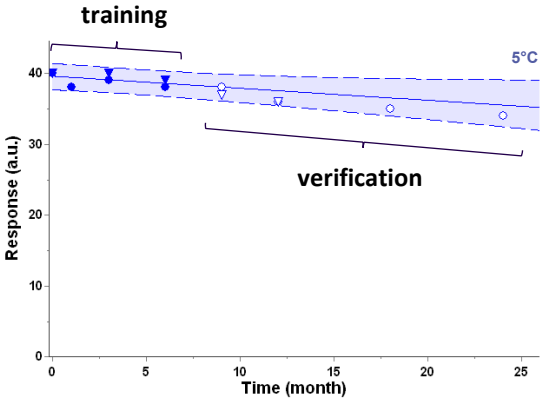
- Hesselink *et al.*, CMC Lead, CEPI, 2020 Best practices for determining and updating storage temperate and shelf life Workshop
- Campa *et al.*, Specification for vaccines, 2025, Chapter 36 in Specification of Drug Substances and Products, Third Edition
- Schnetzinger *et al.*, Stability Preparedness: The Not-So-Cold Case for Innovations in Vaccine Stability Modelling and Product Release, Vaccines, 2024

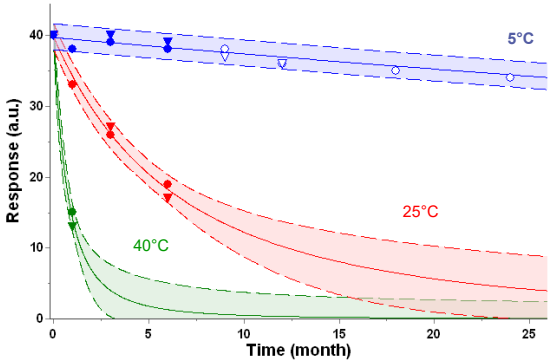
Stability Modeling using 6-months stability data

Single-temp.
(linear regression)

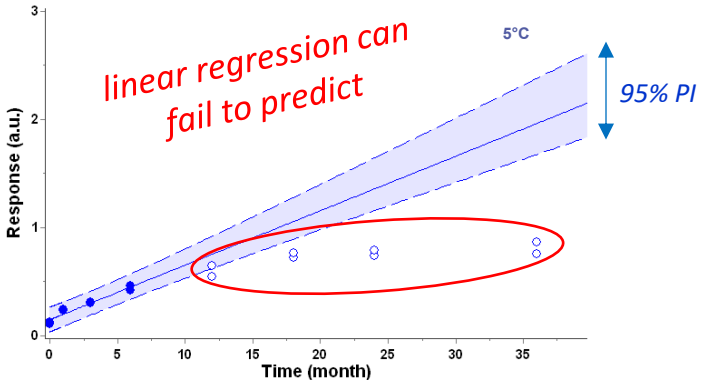
Multi-temp.
(Arrhenius-based model)

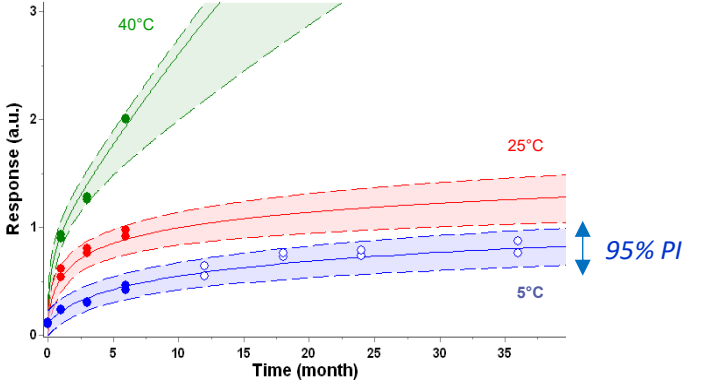
Real life use-case #1





Real life use-case #2





Stability Modeling – single- *vs* multi-temperature

- **Interest of multi-temperature applying Advanced Kinetic Modeling (AKM)**

Table 6
Summary of Model Categories for Predictive Stability.

Model Category	Most Common Subtype	Application	Sub-Type
Single-temperature (*e.g.* 5°C)	Linear and non-linear mixed regression	Well-controlled products exhibiting known or simple behaviors. Model applicable to predict stability of products at this single temperature	Frequentist or Bayesian Non-Hierarchical or Hierarchical[b] With/Without Prior Knowledge Product-Specific or Analogous Product
Multi-temperature (*e.g.* 5°C, 25°C, 40°C)	Arrhenius-based modeling with kinetic model[a]	Universal for many product types. Model applicable to predict long-term stability of products at recommended storage condition (*e.g.* 5°C) and beyond (impact of temperature excursions, cold-chain breaks, etc.)	
	Other model types	Applicable for certain protein degradation mechanisms, such as aggregation, and proteins with higher cold denaturation temperature	
Machine Learning & Artificial Intelligence **Complementary Molecular Simulations**		Emerging use cases (forward-looking for regulatory interactions)[c]	

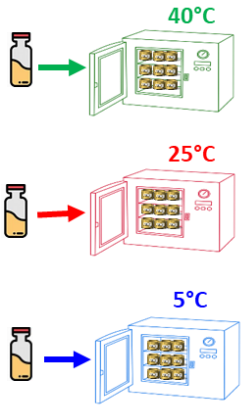
[a] Applying Arrhenius-based models together with one-step and multi-step reactions (*e.g.* via truncated Šesták-Berggren equation), also named advanced kinetic models (AKM), allowing to model data that show Arrhenius and other behaviors.

[b] The stability of various batches can be modeled as single individual batches or for instance grouped together as batches from the same production site (hierarchical modeling).

[c] Some molecular modeling techniques can be used to determine the main reaction sites: such as using Robinson's model to determine the deamidation sites and using WCN (water coordination number) or SASA (solvent accessible surface area) to determine the methionine oxidation sites.

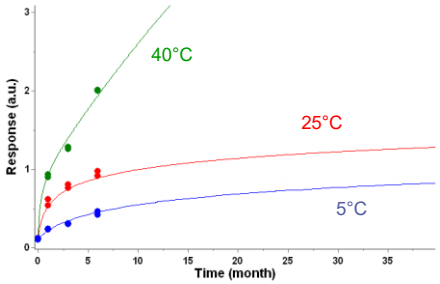
Stability Modeling for Biologicals and Vaccines

Incubation



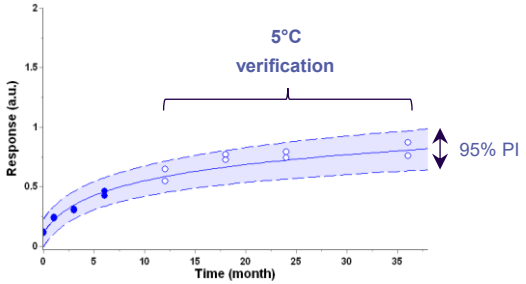
Analysis + AKM

Building of kinetic model using short-term stability data

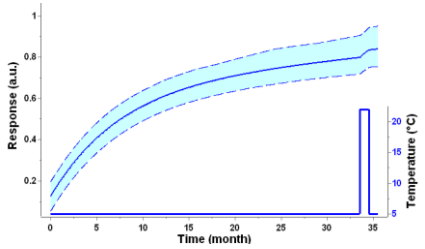


Stability predictions

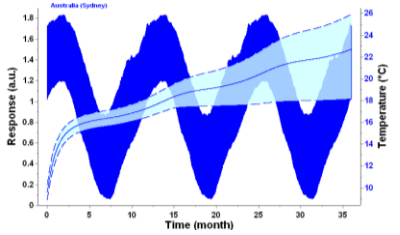
Isotherm



Time out of refrigeration

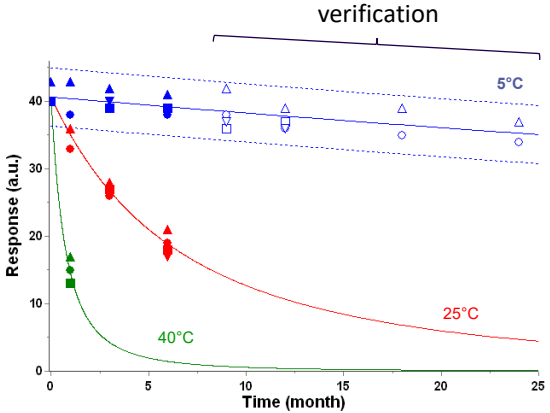


Ambient temperature



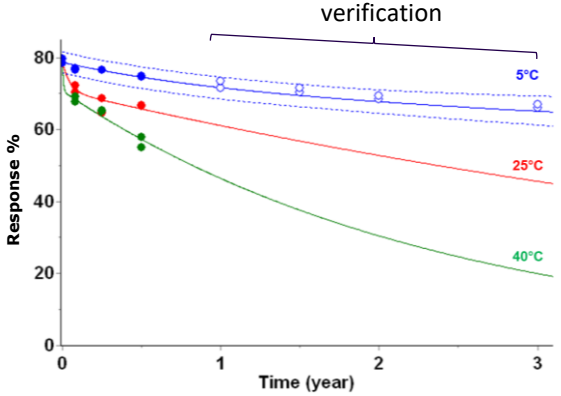
From simple to more sophisticated kinetic models

$$\frac{d\alpha}{dt} = A.\exp\left(-\frac{Ea}{RT}\right).(1-\alpha)^{1}$$



\- Degradation profile complexity +

$$\frac{d\alpha}{dt} = A_1.\exp\left(-\frac{Ea_1}{RT}\right).(1-\alpha)^{n_1} + A_2.\exp\left(-\frac{Ea_2}{RT}\right).(1-\alpha)^{n_2}$$



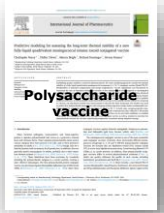
Application of AKM has been demonstrated for its robustness, reliability and accuracy of predication for multiple modalities / CQAs

Roduit et al. Thermochimica Acta (2014)

Clenet et al. J. Pharm. Sci. (2014)

Clenet EJPB (2018)

Campa et al. Vaccines (2021)

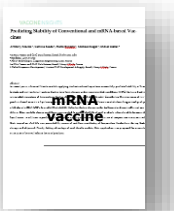


Neyra et al. Vaccines (2021)

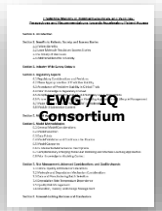
Evers et al. Pharmaceutics (2022)

Huelsmeyer et al. Sci Rep. (2023)

Lennard et al. J.Pharm.Sc. (2024)



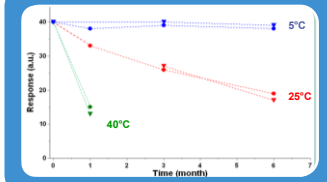
Scassia et al. Insights Vaccine (2025)



Kromski et al. J. Pharm. Sci. (2025)

AKM – Good Modeling Practices

1



Accelerated Stability Study

- Incubate samples at 3 (or more) different temperatures (e.g. 5°C, 25°C, 40°C) for 3 or 6 months
- For a complete screening of kinetic models, perform periodic analyses to get at least 20 or 30 experimental data points, including few replicates

2

Kinetic models

$$\frac{d\alpha}{dt} = A_1 . exp\left(-\frac{E_{a1}}{RT}\right) . (1-\alpha)^{n_1} . \alpha^{m_1}$$

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

Fit experimental data by screening kinetic models

- Run fitting procedures including various models, from simple 1st-order to more complex reactions (Prout-Tompkins, Avramy-Erofeev, Sourour-Kamal, Finke-Watsky, …)

	Kinetic equations	Min. required datapoint
One-step model	$\frac{d\alpha}{dt} = A . \exp\left(-\frac{E_a}{RT}\right) . (1-\alpha)^n . \alpha^m$	At least **10 to 20 stability datapoints** required for model containing 2 to 4 kinetic param.
Two-step model	$\frac{d\alpha}{dt} = A_1 . \exp\left(-\frac{E_{a1}}{RT}\right) . (1-\alpha)^{n_1} + A_2 . \exp\left(-\frac{E_{a2}}{RT}\right) . (1-\alpha)^{n_2} . \alpha^{m_2}$	At least **20 to 40 stability datapoints** required for model containing 4 to 8 kinetic param.

AKM – Good Modeling Practices

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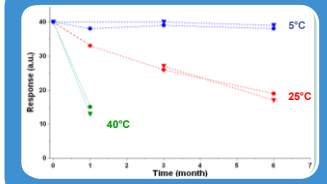

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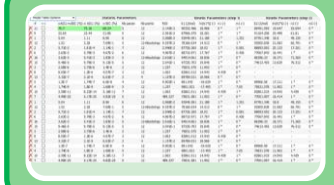
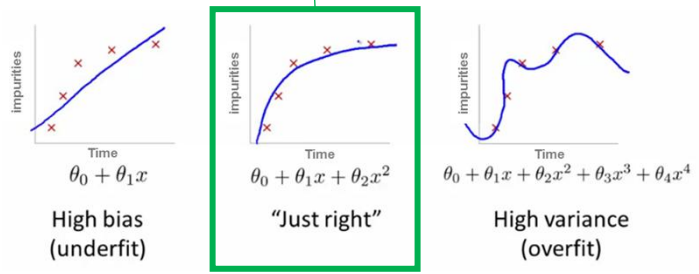


Identify the more appropriate / just right kinetic model(s)

- Model(s) well describing the reaction progress is identified according to various statistical parameters (quality of fit by RSS, RMSE, model comparison by AICc, BIC, …)



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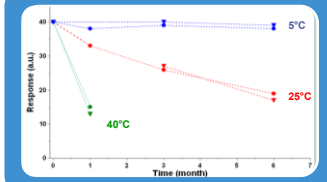

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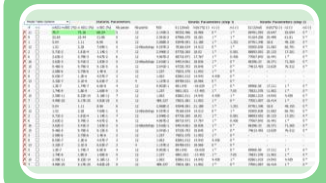

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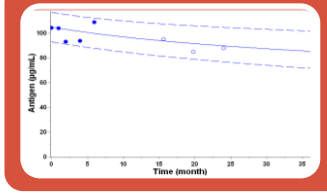

Determine accuracy of predictions (prediction interval)

- Determination of the confidence and prediction intervals (e.g. at 95% or 99% level) by bootstrapping, monte carlo sampling, delta method, or Bayesian statistics.

[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**

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02 **Advanced Kinetic Modeling - Main Applications**

03 Regulatory landscape

04 Conclusions and perspectives

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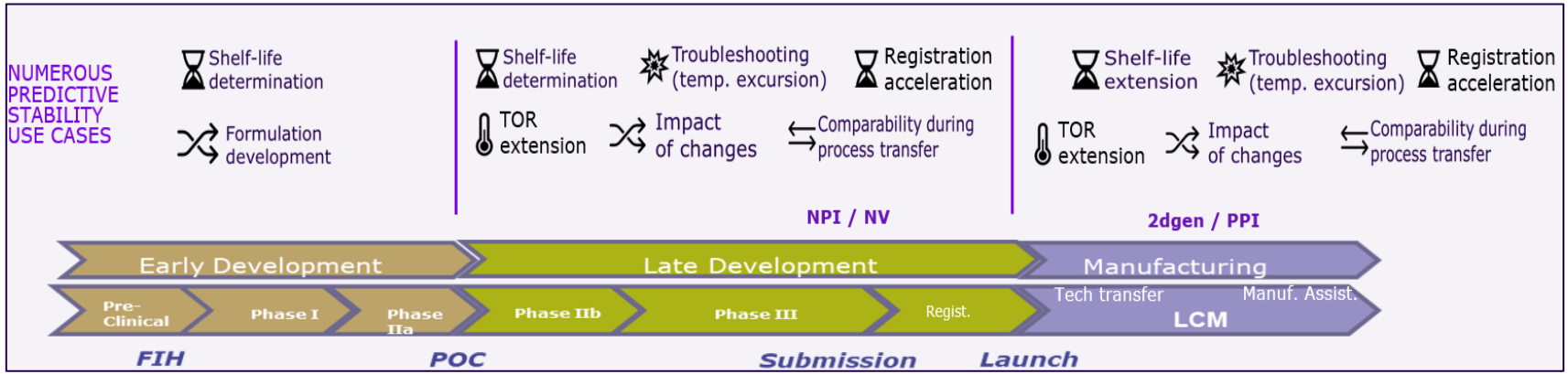
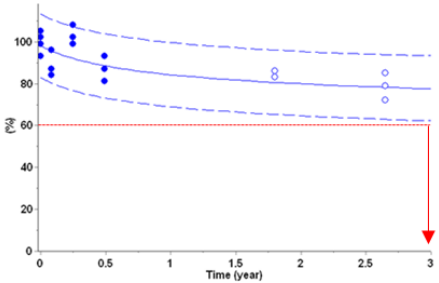
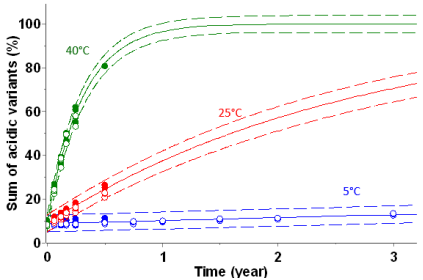
Predictive stability using AKM – Main applications



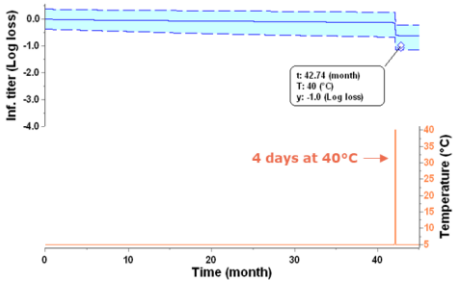
Shelf-life determination



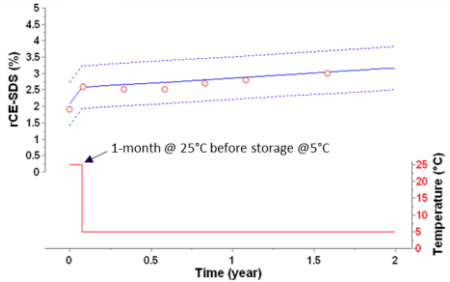
Comparability during process transfer



Impact of « cold-chain » break



Time out refrigeration (TOR)



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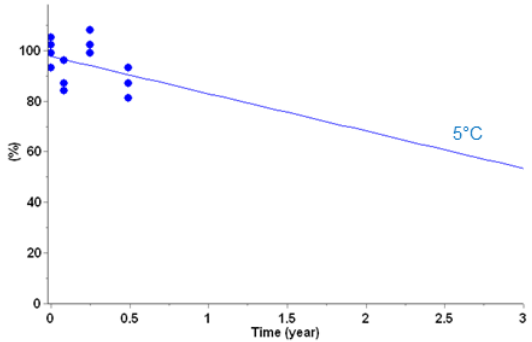
** C. Campa et al., Vaccines, **2021**, M. Huelsmayer et al., Scientific Reports, **2023***

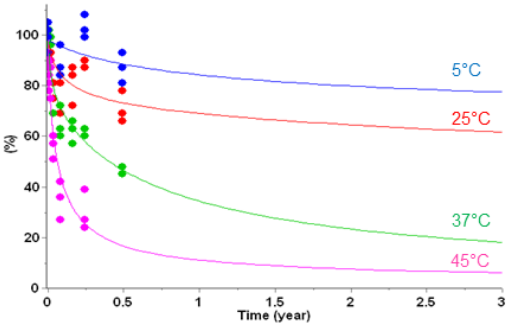
AKM – Estimation of shelf-life

- Taking benefit of stability data obtained at different temperatures and advanced kinetics to estimate realistic shelf-life of products

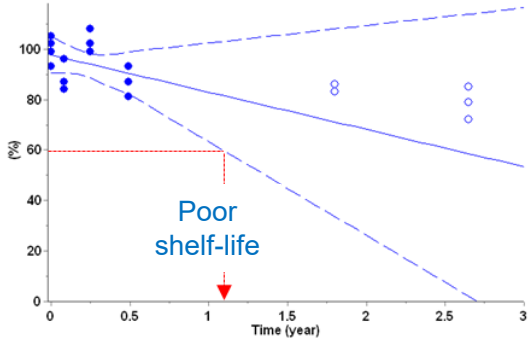
ICH linear regression (5°C)

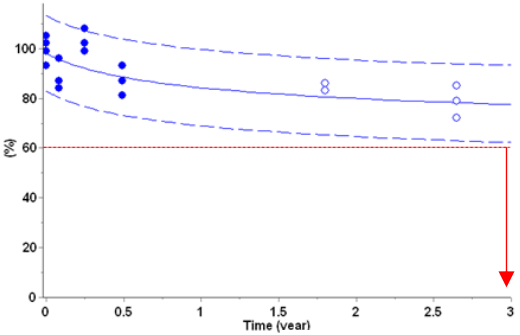
AKM (5°C, 25°C, 37°C, 45°C) *





Lower acceptance criteria





3-years at 5°C

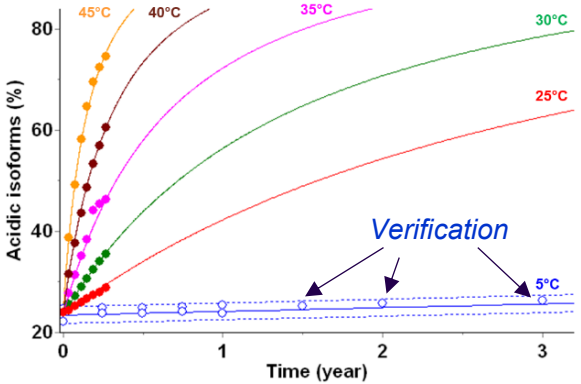
Realistic shelf-life

* C. Campa et al., Vaccines, **2021**

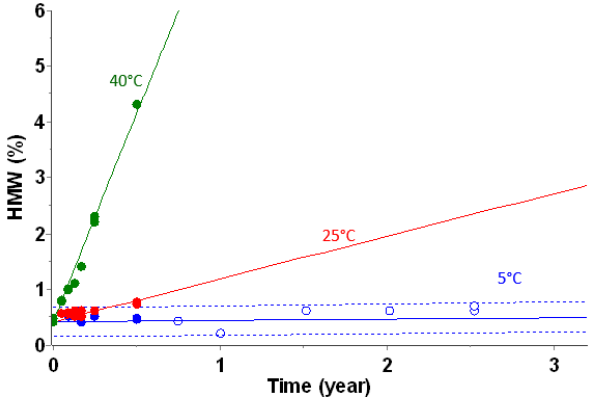
AKM – Predicting stability of CQA of biotherapeutics and vaccines in liquid and freeze-dried pharmaceutical forms

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

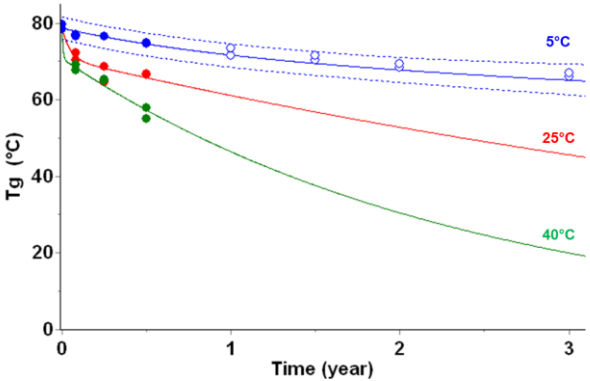
abbvie - liquid mAb
Acidic isoforms



NOVARTIS – liquid mAb
HMW



sanofi - freeze-dried mAb
Glass transition temp.



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Predictive stability using AKM – Main applications

Shelf-life estimation / extension

2

in case of process change, process techno transfer...

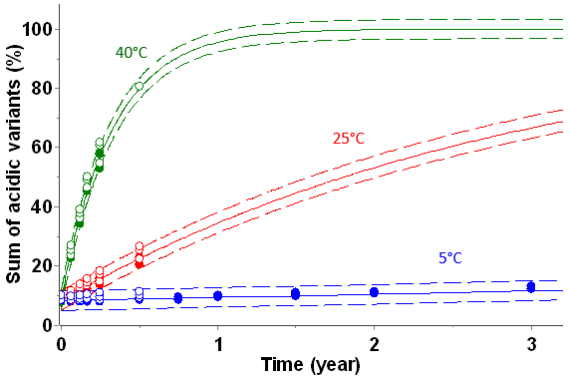
Comparability studies

Impact of temperature excursions

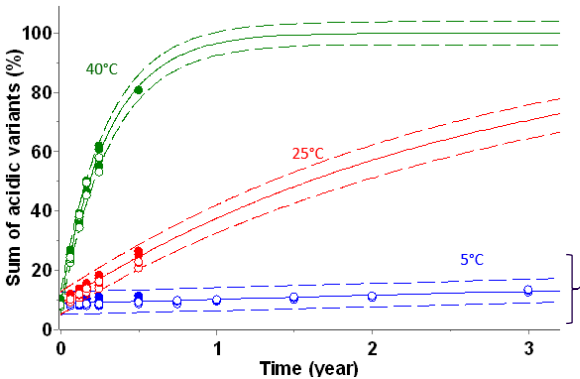
AKM – Batch-to-batch comparisons for clinical batches

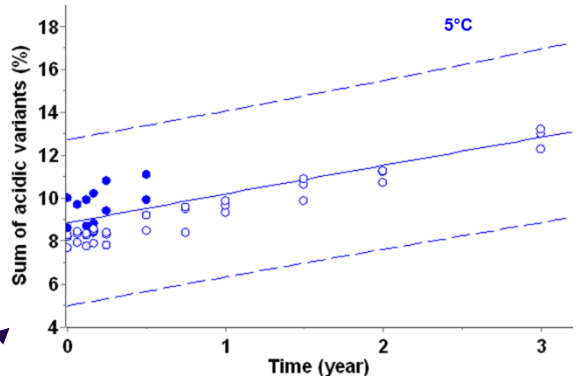
- Cross comparisons of experimental stability data and prediction intervals (kinetic model) for a biotherapeutic (mAb)
- Verification of the clinical batch model was achieved by comparing associated predictions at 5 °C with real stability data of the technical batch

Stability data of **3 clinical batches** (open circles) compared with 3 technical batches (filled circles and lines)



Stability data of **3 technical batches** (open circles) compared with 3 clinical batches (filled circles and lines)





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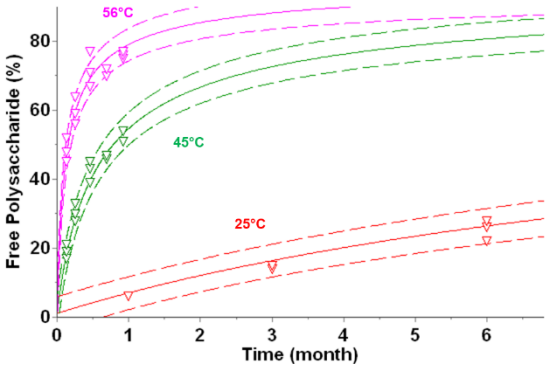
** M. Hueslmeyer et al., Scientific Repots,* ***2023***

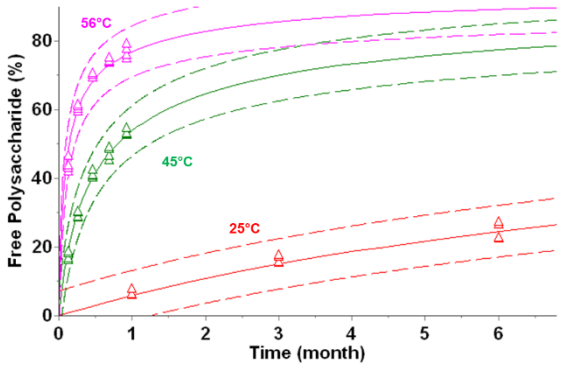
AKM – Batch-to-batch comparisons for scale-up production

- Cross comparisons of experimental stability data and prediction intervals (kinetic model) for a Polysaccharide-Protein conjugate vaccine
- Long-term stability (i.e., up to 4 years) at 5 °C was accurately predicted for batches at both scales

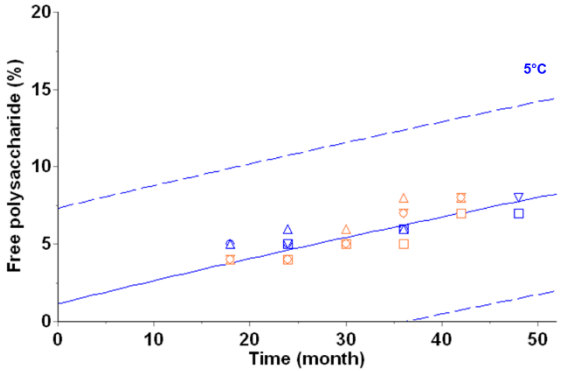
Stability data of **small-scale batch** (triangles) compared with large-scale batch kinetic model (lines)



Stability data of **large-scale batch** (triangles) compared with small-scale batch kinetic model (lines)



Cross comparisons of experimental data and model predictions up to 4-years



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** M. Hueslmeyer et al., Scientific Repots, **2023***

Predictive stability using AKM – Main applications

Shelf-life estimation / extension

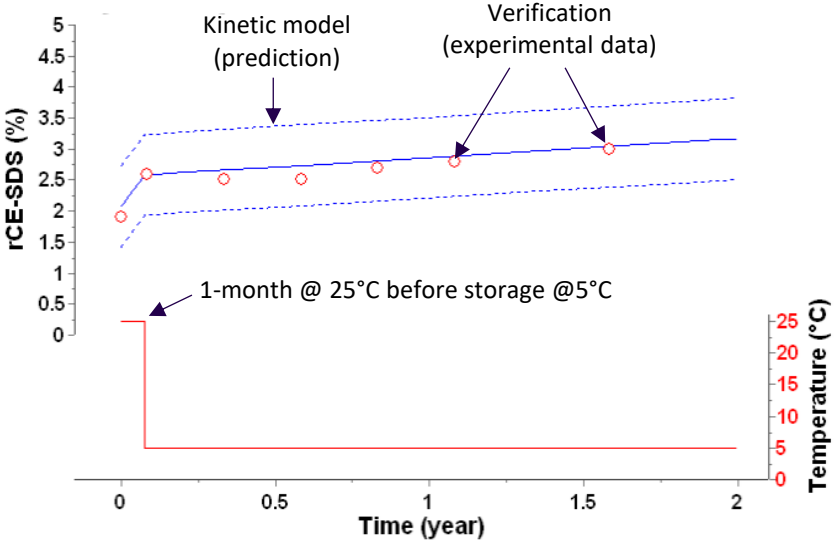
Comparability studies

3 **Impact of temperature excursions**

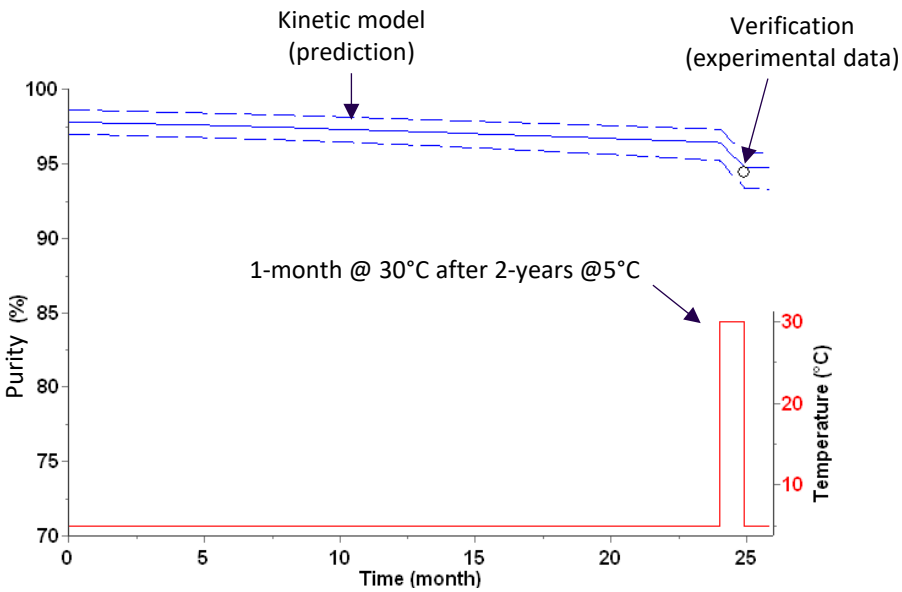
AKM – Impact of temperature excursions

- Taking advantage of kinetic models developed with stability data at different temperatures to simulate impact of cold-chain breaks
- Purity predictions are shown with prediction intervals while experimental data determined at the end of temperature excursions, and not used for kinetic modeling, are displayed as open circles.

Fusion protein



Therapeutic peptide



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** M. Hueslmeyer et al., Scientific Repots, **2023***

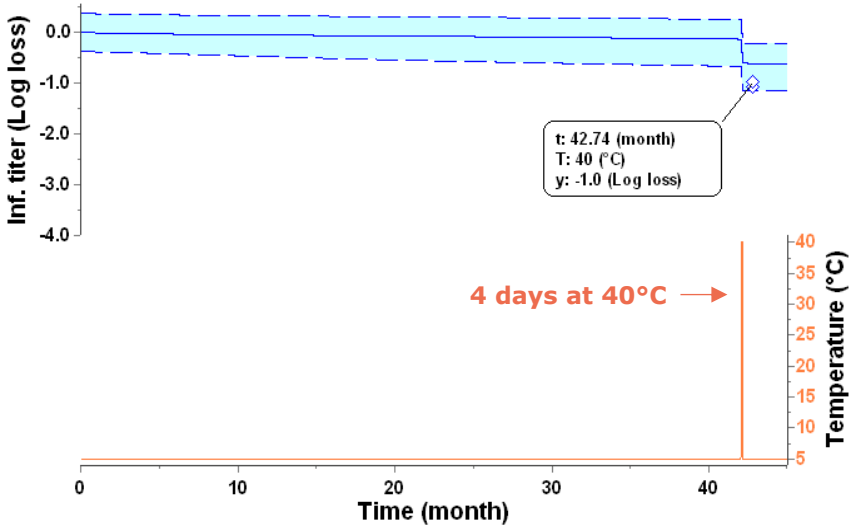
*** A. Evers et al., Pharmaceutics, **2022***

AKM – Impact of temperature excursions

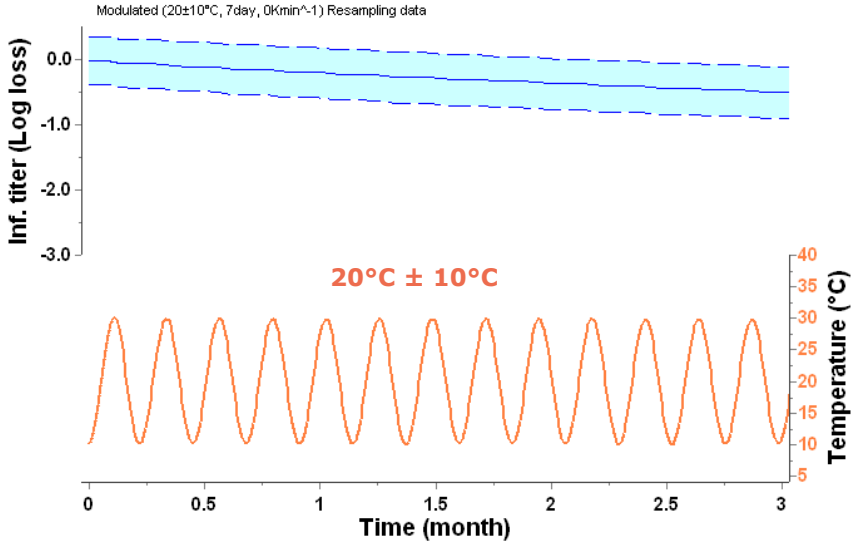
- Kinetic model developed using stability data covering 5°C – 40°C and up to -3.0 Log CCID50 loss
- Stability prediction for any time-temperature profiles in this temperature range and level of degradation

Virus-based vaccine

Excursion at end of shelf-life



Cycling temperature



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** D. Clenet et al., submitted, **2026***

Agenda

01 Introduction – Stability Modeling background

02 Advanced Kinetic Modeling - Main Applications

03 **Stability Modeling – Regulatory landscape**

04 Conclusions and perspectives

Advanced Kinetic Modeling - Relationship with regulators

- Over last few years, AKM has already been used **to simulate the stability of several parameters (CQA)** for a **wide range of bioproducts** and has already been presented to several National Regulatory Authorities to support new stability claims for biotherapeutics with positive outcomes (**FDA** in US, **CDE** in China, **EMA** in Europe, **BGTD** in Canada, **ANSM** in France, **MEB** in Sweden, **TGA** in Australia, **COFEPRIS** in Mexico, etc.)

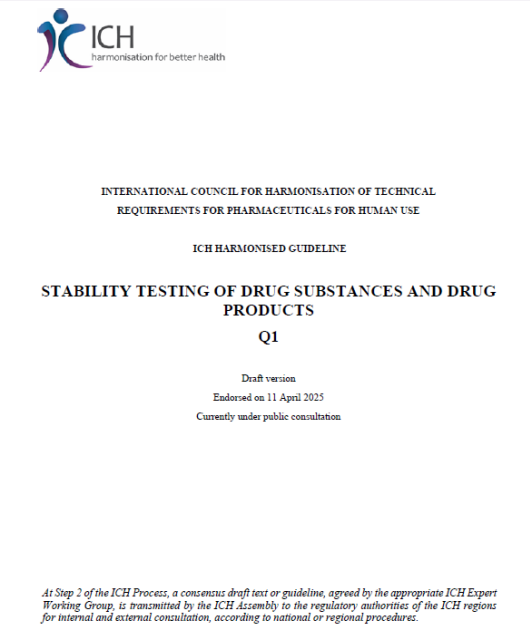
- AKM example version for **ICH constituency review** has been assimilated into the Q1 revision packaged.

- AKM discussed in several external trade and technical associations: PhRMA, EFPIA, IQ, PDA, BIO, CEPI …

- 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.

*C. Campa et al., Vaccines, **2021**, A Lennard et al., J. Pharm. Sc., **2024**, D. Skomski et al., J. Pharm. Sc., **2025***

ICH stability guidelines revision now includes new predictive product Stability Modelling approaches



ICH
harmonisation for better health

INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

STABILITY TESTING OF DRUG SUBSTANCES AND DRUG PRODUCTS

Q1

Draft version

Endorsed on 11 April 2025

Currently under public consultation

At Step 2 of the ICH Process, a consensus draft text or guideline, agreed by the appropriate ICH Expert Working Group, is transmitted by the ICH Assembly to the regulatory authorities of the ICH regions for internal and external consultation, according to national or regional procedures.

Old ICH guidelines on product stability (designed in 2003)

- Shelf-life estimation methods were designed for small molecules in mind, suggesting the use of too simple linear regression.
- They can fail to adequately describe the complex stability behavior of bioproducts, which frequently involve complex and multi-step reactions
- No predictive stability approach

Predictive stability recommendations through EFPIA, PhRMA and academics

New ICH Q1 drafted version released for comments (April 2025)

- First time ever, predictive product stability approach acknowledged as alternative and complementary to real time stability studies when limited long-term stability data available
- Thermo-kinetic modelling (AKM) is now considered in a dedicated section to "enhanced stability modelling" and in Annex 2.
- AKM examples that were agreed on by the EWG will be part of the training also be published on the ICH website and is considered as critical to correct interpretation of the guideline.

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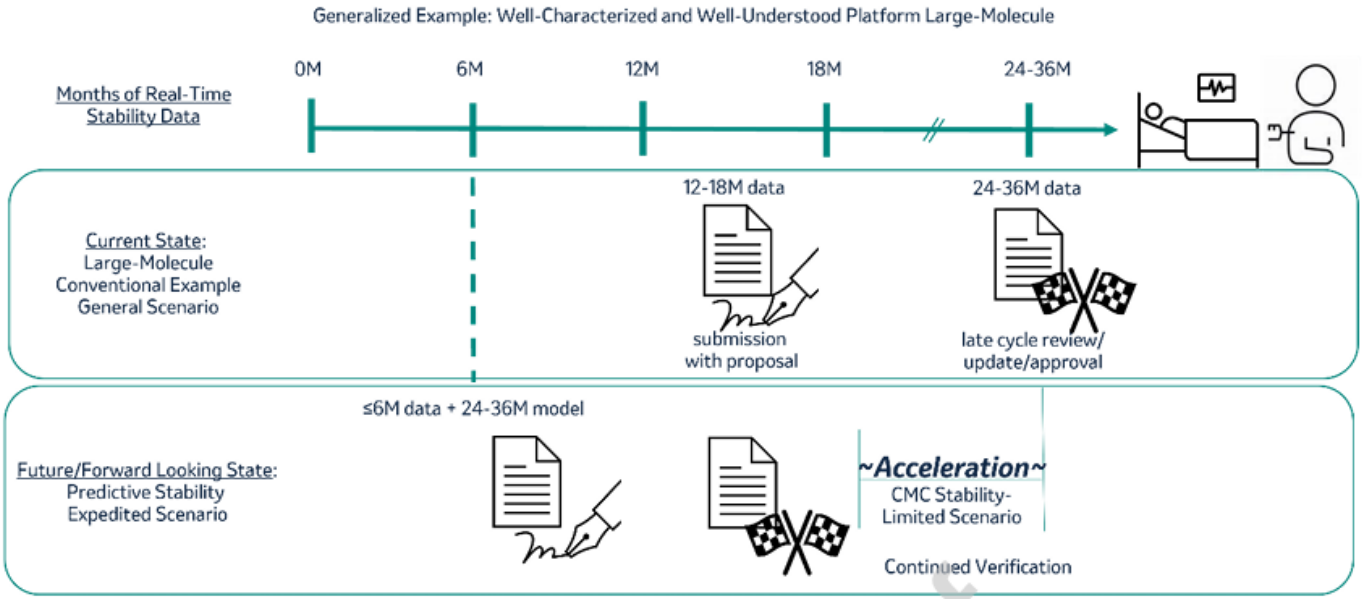
AKM approach perspectives and opportunity to accelerate time to patient ?

From a patient-centric standpoint, risk-based stability, predictive stability modelling hold the potential to accelerate patient access to new life-saving treatments (by potentially 3-6+ months as per industry survey) as well as extend shelf-life, improve selection of more stable molecules, optimize processes and address storage condition management, derisking cold-chain supply.



Stability Modeling – Regulatory landscape

Table 1
Regulatory Engagement for Predictive Stability in Biologics and Vaccines - Historical Example Case Studies (preceding revisions to ICH stability series industry guidelines). Partly adapted from prior publications.

Description of Case Study	Phase	Modality	Territory	Regulatory Outcome
support shelf-life determination beyond the available long term stability data	Commercial (REGEN-COV)	biologics (2-antibody cocktail)	various global health agencies incl US FDA/EMA (10 agencies)	Full acceptance under emergency use
shelf-life determination without full real-time stability data	Commercial	recombinant protein vaccine	EMA, US FDA, Health Canada	Acceptance / positive feedback
extend shelf-life for a Phase 3 clinical batch [a]	clinical	inactivated virus vaccine	Thailand	Full acceptance (no follow up questions)
de-risk impact of high temperature excursions [b]	commercial	multi-valent adjuvant vaccine	EMA	Full acceptance of new model-informed acceptance criteria (no follow up questions)
de-risk temperature excursions [c]	commercial	live attenuated vaccine	Brazil	Full acceptance (no follow up questions)
Phase 1 formulation selection justification [d]	clinical	live attenuated vaccine	US FDA	Acceptable justification (no follow up questions)
understanding degradation process [e]	commercial	mRNA	EMA[82]	Acceptable justification
support process/site change [f]	lifecycle	biologics (monoclonal antibody)	unspecified	Full acceptance (no follow up questions)
support a drug substance site change	lifecycle	biologics (monoclonal antibody)	US FDA (BLA)	Partial acceptance (permissible as supporting information but no relief on DS/DP stability package)

[a] 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.
[b] 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 at 5°C (recommended storage condition).
[c] Stability Modeling used 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.
[d] 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.
[e] Data on the degradation rate was provided and shown to demonstrate Arrhenius behavior, with first order kinetics. The stability profiles were demonstrated to be

Stability Modeling – Biotherapeutic post-approval change

This use case demonstrates how AKM was pivotal for a biotherapeutic (mAb) in de-risking High Molecular Weight (HMW) challenges and securing EMA acceptance for specification extension.

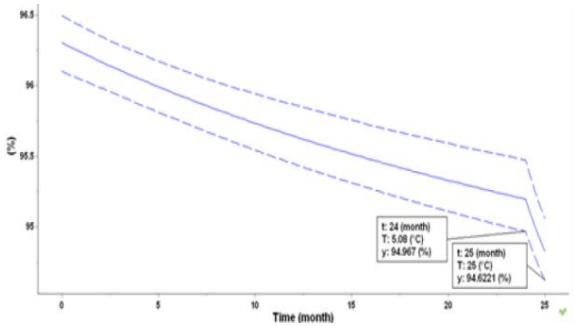
- Challenge: post-change batches showed faster HMW aggregation *vs*. pre-change, risking OOS at release and end-of-shelf-life.

Type II variation assessment

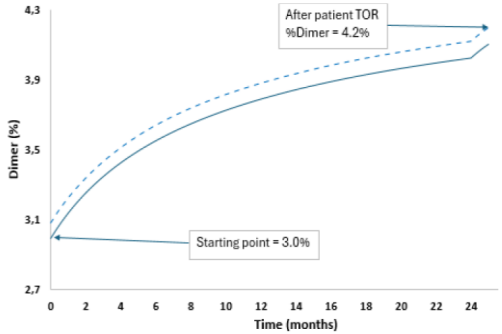
- AKM Solution: Enabled predictive modeling of HMW evolution, supporting a scientifically justified spec extension. The AKM modeling supported establishing end-of shelf-life specification limits for main peak purity setting and end-of-shelf-life specification limit for the dimer.
- EMA Outcome: "*A kinetics modelling approach is used to derive threshold for the dimer and main peak purity for C2P2 DP up to the end of shelf-life.* ***This approach is deemed reasonable*** *and the resulting proposed changes in the acceptance criteria are considered modest*." Specifications changes "approvable". HMW no longer a blocking point.

EMA feedback: Advanced Kinetics Modeling approach is considered "reasonable" and the change in HMW specifications is "approvable."

Main peak (%) stability modeling of DP PPQ dosages 150 mg – 300 mg



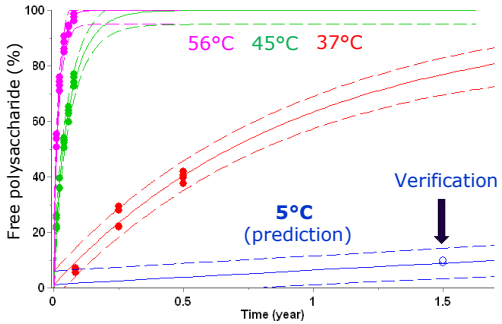
Dimer (%) stability modeling of DP PPQ dosages 150 mg – 300 mg

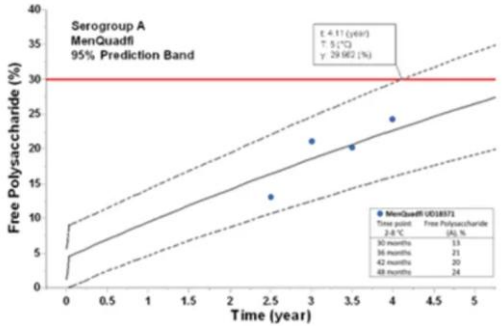


Stability Modeling – Polysaccharide-based vaccine

Type II variation [B.II.f.1.c]: Change in storage conditions

- when the stability studies have not been performed in accordance with an approved stability protocol. This variation is to include an SmPC claim for **temporary temperature excursion up to 25°C for 72 hours**, from the standard storage conditions.
- AKM Solution: Developing a kinetic model to simulate such an excursion
- We had one lot studied for 4 years. The kinetics modelling allowed to be confident in the quality of MenQuadfi with temperature excursions until expiry.
- A variation was submitted and approved in the EU and UK to support a time-out-of-fridge claim for end users. This was enabled by predictive stability modelling based on 6 months of data, providing confidence in good vaccine quality and avoiding 4+ years of additional stability studies with 2 more lots.
- The **EMA approved the variation with just the 1 lot stability data** (dossier section 3.2.P.8.1, and 3.2.P.5.1). **UK** accepted the same variation with temperature excursion with 1 lot. **TGA** accepted the same variation after we shared the kinetic model conclusion as a response to questions, provided we commit to adding 2 more lots with temperature excursions studied until expiry of 4 years. **CBER** did not accept and asked for 3 lots in temperature excursion studies (at new higher production scale).





At Sanofi, a dedicated AKM program is in place to support all products with stability modeling

04

Modalities

Vaccines, Recombinant, Synthetics, mRNA

06

App. Types

Shelf- Life determination / extension, process change, tech transfer, process derisking & more

> 35

Active Cases

Number of use cases in implementation

> 20

Cases in pre-scoping

Number of use cases in assessment of business impact, HA acceptance POS, technical feasibility, AKM regulatory strategies building…

+54%

YoY Active cases Growth

Year-over-year increase vs. 2025 portfolio

90%

Health Authorities Acceptance

Overall rate of HA positive feedbacks on AKM (prior to submission, post submission)

Patient Benefits:

- Time to development saving
- Time to registration acceleration (3-9 months) as stability studies (mostly on product development critical path)
- Market shortage derisking (up to 2 years)
- …

Others Benefits:

- Cost avoidance
- Cost saving
- Supply derisking
- Decrease of process changes dev. timelines
- …

TIME TO REGISTRATION ACCELERATION
Up to 8 months

DEVELOPMENT TIMELINES SAVING
Up to 9 months

AKM uses cases are selected with high business impact within a cross-function organization involving CMC, Quality, Reg. Aff. up to HA engagement

- N. Mansois (CapGemini), M. Matthews, P. Mehta, E. Walsh, I. Geneste, B. Niederhaus, L. Chinn, D. Hurlin, S. Petit, A. Huth, Y. VanHaelst, W. Roche, P. Ballesta (CapGemini), H. Achard (CapGemini), M. Gerasimov, C. Neyra, M. Gentric, E. Coppens, S. Ramesh, S. Perrin, E. Vetter, O. Faure, A. Grandjean, P. Showhan, C. Airiau, N. Rahman, … *and all the Sanofi stability modeling user-group members*

- M. Huelsmeyer (Abbvie), D. Kuzman (Novartis), J. Weusten (MSD), A. Evers and D. Skomski (Merck), C. Campa (GSK), A. Lennard (Amgen), A. Ji (Genentech), S. Roberts (Novonordisk), …

- B. Roduit (AKTS), C. Borgeat (AKTS), L. Natalis (Pharmalex), P. Lebrun (Pharmalex), K. Waterman (Freethink)

This work was funded by Sanofi. Didier Clénet is a Sanofi employee and may hold shares and/or stock options in the company

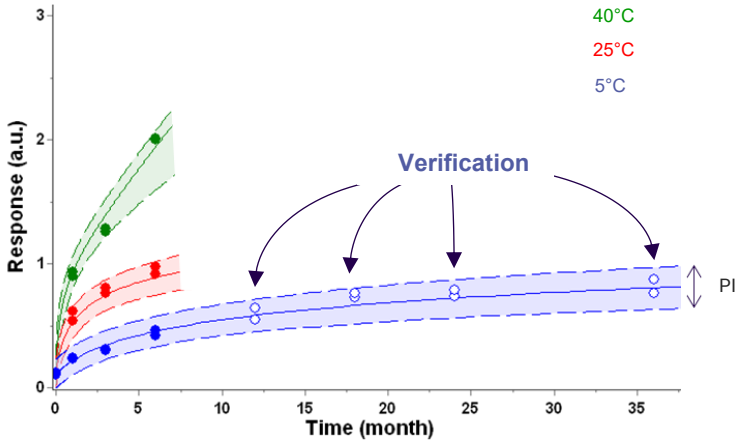
Back-up

List of Publications / Range of Critical Quality Attributes (CQAs)

Modality	Critical Quality Attributes (CQAs)	Citations/References
Biologics	high molecular weight (HMW%), mAb impurity, acidic/basic variants species and acidic isoforms, fragments, potency, glass transition temperature, dimers, N-terminus pyroglutamate% and other free fatty acids	1. Lennard, A, Zimmermann B, Clenet D, Molony D, Tami C, Oliva Aviles C, Moran A, Pue-Gilchrist P, Flores E, Stability Modeling Methodologies to Enable Earlier Patient Access, J.Ph.Sci., *in press*, **2024** 2. M. Dillon, J. Xu, G. Thiagarajan, D. Skomski, A. Procopio, Predicting the Long-Term Stability of Biologics with Short-Term Data, Molecular Pharmaceutics **2024** 21 (9), 4673-4687 3. Huelsmeyer M, Kuzman D, Bončina M, et al. A universal tool for stability predictions of biotherapeutics, vaccines and in vitro diagnostic products. *Sci Rep*. **2023**;13(1):10077. 4. Kuzman D, Bunc M, Ravnik M, Reiter F, Žagar L, Bončina M. Long-term stability predictions of therapeutic monoclonal antibodies in solution using Arrhenius-based kinetics. *Sci Rep*. **2021**;11(1):20534 5. Bunc M, Hadži S, Graf C, Lah J, Bončina M. Aggregation Time Machine: A Platform for the Prediction and Optimization of Long-Term Antibody Stability Using Short-Term Kinetic Analysis J. Med. Chem. **2022**, 65, 3, 2623–2632 6. Doshi N, Martin J, Tomlinson A. Improving Prediction of Free Fatty Acid Particle Formation in Biopharmaceutical Drug Products: Incorporating Ester Distribution during Polysorbate 20 Degradation. Mol Pharm. **2020** Nov 2;17(11):4354-4363. doi: 10.1021/acs.molpharmaceut.0c00794. Epub 2020 Oct 8.
Vaccines	potency, antigen recovery, antigen purity, antigenicity determined by ELISA, vaccine depolymerization, adduct formation in LNP formulated mRNA vaccine, acetone quantity	1. Huelsmeyer M, Kuzman D, Bončina M, et al. A universal tool for stability predictions of biotherapeutics, vaccines and in vitro diagnostic products. *Sci Rep*. **2023**;13(1):10077. 2. Campa C, Pronce T, Paludi M, et al. Use of Stability Modeling to Support Accelerated Vaccine Development and Supply. Vaccines. **2021**;9(10):1114 3. Neyra, C., Clénet, D., Bright, M., Kensinger, R. & Hauser, S. Predictive modeling for assessing the long-term thermal stability of a new fully-liquid quadrivalent meningococcal tetanus toxoid conjugated vaccine. Int. J. Pharm. 609, 121143 (**2021**). 4. Moriconi A, Onnis V, Aggravi M, et al. A new strategy for preparing a tailored meningococcal ACWY conjugate vaccine for clinical testing. *Vaccine*. **2020**;38(23):3930-3933. 5. Roque, C., Ausar, S. F., Rahman, N. & Clénet, D. in Quality by Design—An Indispensable Approach to Accelerate Biopharmaceutical Product Development (ed PDA) 169–199 (**2021**) 6. Clénet D, Hourquet V, Woinet B, Ponceblanc H, Vangelisti M. A spray freeze dried micropellet based formulation proof-of-concept for a yellow fever vaccine candidate. Eur J Pharm Biopharm. **2019**;142:334-343. 7. Clénet, D. Accurate prediction of vaccine stability under real storage conditions and during temperature excursions. Eur. J. Pharm. Biopharm. 125, 76–84 (**2018**). 8. Clénet D, Imbert F, Probeck P, Rahman N, Ausar SF. Advanced Kinetic Analysis as a Tool for Formulation Development and Prediction of Vaccine Stability. J Pharm Sci. **2014**;103(10):3055-3064. doi:10.1002/jps.24117 9. Roduit, B., Hartmann, M., Folly, P., Sarbach, A. & Baltensperger, R. Prediction of thermal stability of materials by modifed kinetic and model selection approaches based on limited amount of experimental points. Termochim. Acta 579, 31–39 (**2014**).
ADCs (Antibody Drug Conjugates)	HMW%, acidic/basic variants, purity, potency	1. M. Dillon, J. Xu, G. Thiagarajan, D. Skomski, A. Procopio, Predicting the Long-Term Stability of Biologics with Short-Term Data, Molecular Pharmaceutics **2024** 21 (9), 4673-4687
Peptides	HMW% and purity of therapeutic peptides	1. Evers A, Clénet D, Pfeiffer-Marek S. Long-Term Stability Prediction for Developability Assessment of Biopharmaceutics Using Advanced Kinetic Modeling. *Pharmaceutics*. **2022;14(2)**:375.
mRNA-based products	HMW% and purity of therapeutic peptides	1. Scaccia A, Saade C, Ballesta P, Rieger M, Clénet D, Predicting Stability of conventional and mRNA-based vaccines, VaccinInsights, Vaccine Insights 4 (**2025**) 27–39. 2. Kis Z., Stability Modelling of mRNA Vaccine Quality Based on Temperature Monitoring throughout the Distribution Chain, Pharmaceutics, vol. 14, 430, **2022**.

AKM – Good Modeling Practices

- Model verification and validation usually include comparison of experimental stability data (at longer-term) and prediction (i.e. prediction interval) of the model.
- **Validation**: "Held out" stability data can be used for the purpose of evaluating and affirming the performance of the chosen model.
- **Ongoing Verification**: The process of checking the model fit on accruing real-time stability data that were collected <u>after</u> model adoption, as part of ongoing monitoring to check that the model is still valid as new data are being collected.



- Risk management via ongoing verification by comparing the predicted data with real-time stability to address regulatory concerns and build confidence in the robustness of modelling approaches

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Why Revise the ICH Stability Guidelines?

Final Concept Paper

Targeted Revisions of the ICH Stability Guideline Series (Guidelines ICH Q1A-F, ICH Q5C)

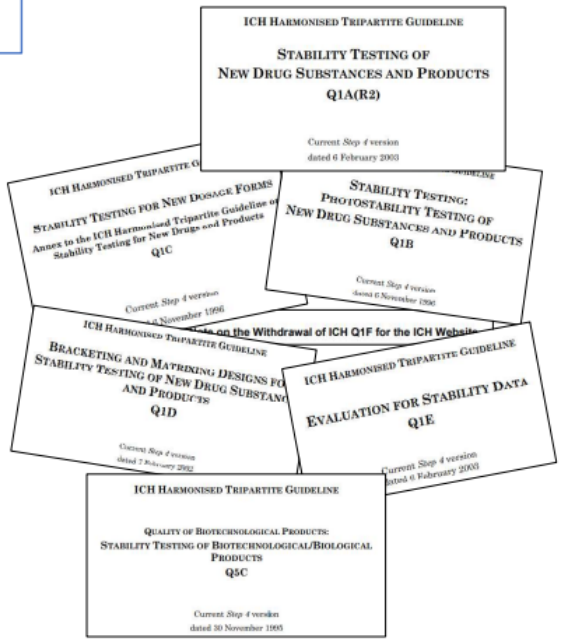
Endorsed by the Management Committee on 15 November 2022

Revision of the ICH Stability Guideline Series Q1A-Q1F and Q5C is recommended to:

a) Streamline the series by combining the various guidelines into a single guideline focused on core stability principles;
b) Promote harmonised interpretation by addressing potential gaps and areas of ambiguity;
c) Address additional technical issues, including relevant stability strategies and innovative tools that strengthen the application of risk management;
d) Consider inclusion of new topics, such as stability considerations for advanced therapies.

The envisioned result is a combined guideline, ICH Q1, with integrated annexes that address specific topics beyond the core principles on stability recommendations and to address product type specific recommendations, as required.

It is also recommended to update and supplement current training material.



Background in Thermo-Kinetics

Standard kinetics to describe irreversible reactions A → B

What we know since…

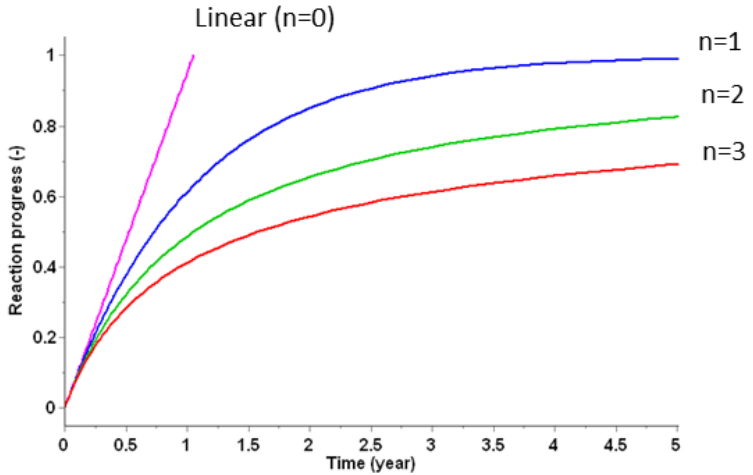
1889 – Arrhenius: linear and non-linear regressions - Reaction rate of a one-step reaction (A → B) depend on temperature

Reaction rate: $\frac{d\alpha}{dt} = A.\exp\left(-\frac{E_a}{RT}\right).(1-\alpha)^n$

Frequency factor

Activation energy

Order of the reaction



Background in Thermo-Kinetics

AKM describes progress of stability indicating attributes using truncated Šesták–Berggren equation, regardless of the complexity of degradation pathways of products considering single or multi-step reactions

- Then, **one-step** and **two-step models** must be considered to describe from simple to more sophisticated kinetics.
- **Decelerating** (e.g. nth-order: f(α)=(1-α) n), **accelerating** (e.g. power law) and **sigmoidal**-type reactions with accelerating period at the beginning and decelerating near the end.
- Note that restricted versions of such equations can be proposed (e.g., assuming 1st-order n=1 only and without autocatalytic type contribution, m=0), since they were demonstrated in specific cases (**prior knowledge**, ...).

Commonly applied kinetic models	Reaction models f(alpha)
PT: Prout-Tompkins	(1-α)α
Fn: nth order	(1-α)^n
F1: first order	(1-α)
F2: second order	(1-α)^2
F3: third order	(1-α)^3
P1: power law	α^0
P2: power law	2 α ^(1/2)
P3: power law	3 α ^(2/3)
P4: power law	4 α ^(3/4)
Pn: power law	n α ^(1-1/n)
An: Avrami-Erofeev	n (1-α) [-ln(1-α)]^(1-1/n)
A2: Avrami-Erofeev	2 (1-α) [-ln(1-α)]^(1/2)
A3: Avrami-Erofeev	3 (1-α) [-ln(1-α)]^(2/3)
Rn: n contracting	n (1-α)^(1-1/n)
R2: contracting cylinder	2 (1-α)^(1/2)
R3: contracting sphere	3 (1-α)^(2/3)
D2: 2-dimensional diffusion	[-ln(1-α)]^-1
D3: 3-dimensional diffusion	1.5 [1-(1-α)^(1/3)]^-1 (1-α)^(2/3)

One-step model

Frequency factor; Activation energy; Order of the reaction; Autocatalytic contribution of the reaction

$$\frac{d\alpha}{dt} = A.\exp\left(-\frac{E_a}{RT}\right).(1-\alpha)^n.\alpha^m$$

Two-step model

Add a second step

$$\frac{d\alpha}{dt} = A_1.\exp\left(-\frac{E_{a1}}{RT}\right).(1-\alpha)^{n_1} \oplus A_2.\exp\left(-\frac{E_{a2}}{RT}\right).(1-\alpha)^{n_2}.\alpha^{m_2}$$

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Modeling complex degradation pathways of bioproducts

Two-step models can be required to accurately describe thermostability of bio products

$$A \xrightarrow{k_1, \Delta H_{R1}} B + C$$

$$A \xrightarrow{k_2, \Delta H_{R2}} D + E$$

$$\frac{\mathrm{d}\alpha}{\mathrm{d}t} = k_1(1-\alpha) + k_2(1-\alpha)$$

$$\frac{d\alpha}{dt} = \underbrace{0,8 * 9.8E5.\exp\left(-\frac{75,7E3}{RT}\right).(1-\alpha)^1}_{\text{stage 1}} + \underbrace{0,2 * 1,1E3.\exp\left(-\frac{51,9E3}{RT}\right)}_{\text{stage 2}}$$

"Two-phase degradation profiles, with initial rapid drop followed by a long gradual decrease phase, have already been described during accelerated stability studies of several peptides, in vitro proteins and viruses.

The selection of two-step reactions model is purely based on the statistical analysis and goodness of fit with two major pathways of phenomenological kinetic model of the reaction rate, which are most likely built up from the sum of multiple reactions.

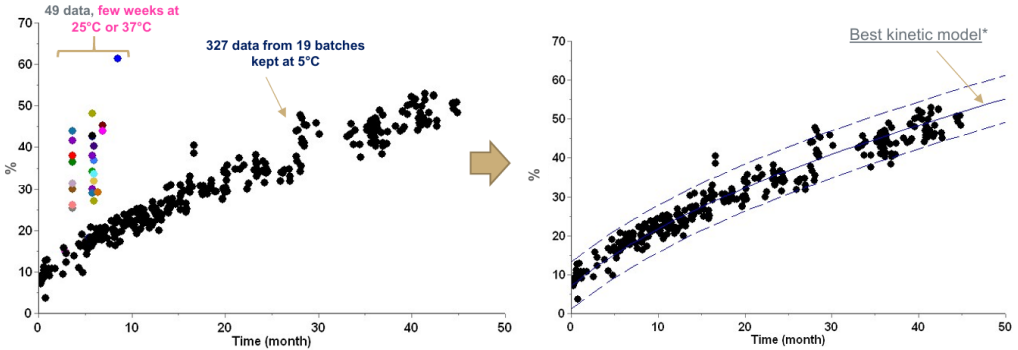
At that point, it is necessary to clearly underline that this result does not have a real mechanistic basis, but it rather only depicts a phenomenological mathematical model applied for fitting the reaction course."

Stability Modeling – multivalent polysaccharide-based vaccine

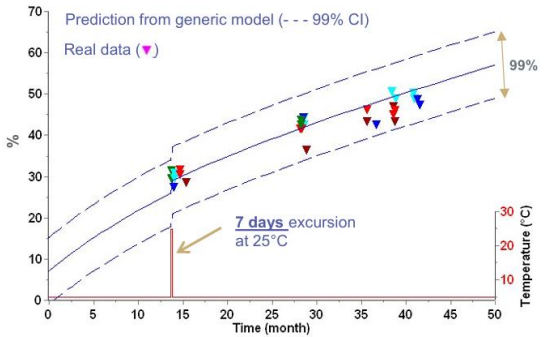
Type II variation to maintain a claim in the SmPC in case of Temperature excursion

- Stability data indicate that the vaccine components are stable at temperatures **up to 25°C for 72 hours**, while extending the Shelf Life of the Finished Product (from 36 to 48 months)
- AKM Solution: Developing a kinetic model to simulate such an excursion (described in CTD Dossier)
- Acceptance criteria still met when stored 48 months at +5°C with an incubation period of 7 days at +25°C, whenever the excursion occurs. Prediction verified with real-time stability data generated from 5 lots
- Variation submitted in Europe, through CP procedure (Rap: PEI/DE, Co-Rap: FAMHP/BE). Stab. modeling approach accepted provided that 1) available real time stability data are submitted and 2) the final data will be submitted when available (commitment)

1) Development of a generic kinetic model



2) Simulation of out-of-fridge scenario



Stability Modeling – live attenuated virus-based vaccine

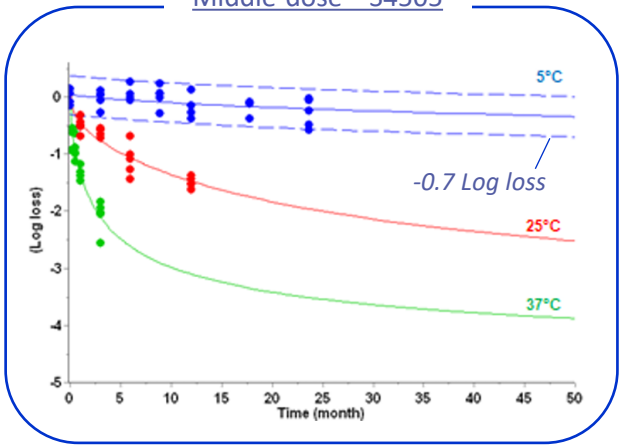
Selection of DP formulation for phase I

- Applying AKM to predict < 1.0 Log loss of CCID50 (infectious virus concentration) after at least 3 years at 5°C.

IND Ph. I submitted to the CBER

- Section 3.2.P.2.3 - Manufacturing Process Development - Formulations development*
- "The formulation candidate was evaluated at 1 L and 5 L scale. Stability studies and associated kinetic-based modeling approach were performed and indicated that the defined formulation is appropriate to ensure Drug Product quality and stability."
- For the middle-dose batch targeted at 5.0 Log/dose used in Phase I and to be used in Phase II clinical studies, considering lower 95% PI, the loss of infectivity was predicted at -0.7 Log loss up to 48 months.

Middle-dose – S4505



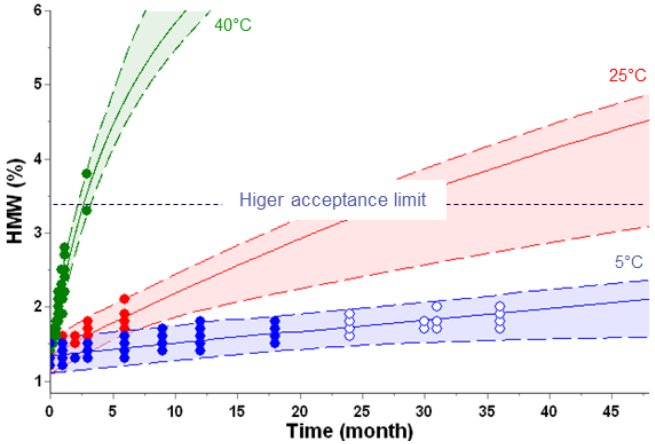
D. Clénet, V. Hourquet, B. Woinet, H. Ponceblanc, M. Vangelisti, A spray freeze dried micropellet based formulation proof-of-concept for a yellow fever vaccine candidate, Eur. J. Pharm. Biopharm., 132:334-343, **2019**

Stability Modeling – Post-approval change

Process change impact assessment – Introduction of a second filtration DP process across 3 DP sites

- Challenge: atypical results (HP-SEC, iCIEF) on 1 DP refiltered batch obtained during accelerated (6 months) and long-term stability (11 months). After investigation, it was confirmed that the root cause of atypical results are only due to the intrinsic method variability and not linked to the additional filtration.
- Furthermore, AKM enabled predictive modeling of low molecular weight LMW, iCIEF and high molecular weight HMW evolutions, supporting comparability study for pre- *vs*. post-change processes for main CQAs.
- **Agreement of HA after submission with stability data on the first 2 PPQ runs only** (1 month for EMA and 5 months for FDA).
- Multi-site validation approach validated by health autorities (1 PPQ run on each of the 3 DP sites).

1) Pre-change
historical PPQ batches (sites A, B, C)



2) **Post-change**