Use of Stability Modeling to Support Accelerated Biologicals and Vaccines Development and Real-Time Stability Supply

Didier Clénet – Bioprocess R&D, Marcy l'étoile - France

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Accelerated Predictive Stability biologicals and vaccines

- 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.

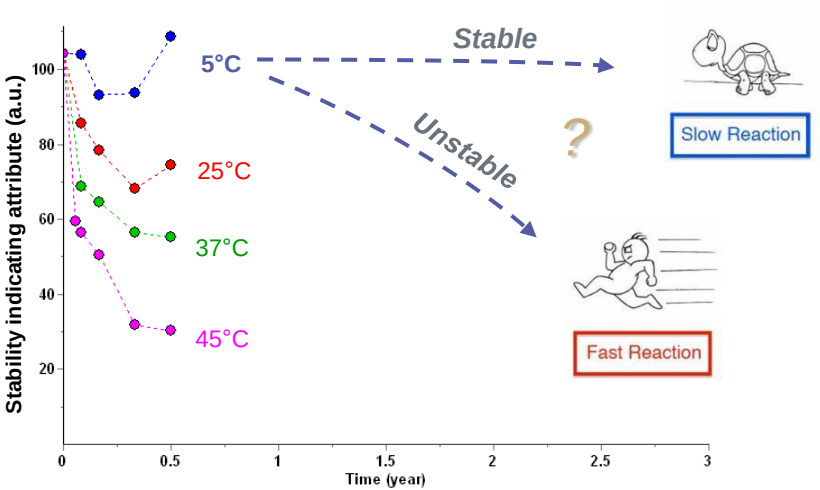
- In these circumstances, it is more logical that benefit vs scientific risk-based thinking is applied. In cases of incomplete data sets, making use of **prior knowledge** and **accelerated stability studies** to base their claims on shelf life, exploiting **modeling approaches**, will be critical for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

- This will also simplify **Post approval changes** such as **shelf-life extension**, which are likely to occur to ensure vaccine large scale availability and supply sustainability

Accelerated Predictive Stability (APS)

Background

Accelerated Predictive Stability (APS)



- Describe progress of stability indicating attributes using “good modeling practices”
  - Irrespective of the complexity of degradation pathways of products [1]
  - Using advanced kinetics models for fitting stability data obtained at accelerated temperatures and the recommended storage condition for one-step and multi-step reactions [2-3]

Kinetic model – Arrhenius based

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

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

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[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*

From first order to advanced kinetics... a long journey

Advanced kinetics from empirical to sophisticated reactions

- 1889 - **Arrhenius**: Dependence of the reaction rate on temperature
- 1944 - **Prout-Tompkins**: Elaboration of the kinetic model of autocatalytic reactions
- 1971 - **Sestak-Bergren**: General kinetic equation combining main possible rate limiting steps (movement of phase boundary, nucleation, diffusion, autocatalysis).
- 1999 - **Oliva** et al.: The degradation kinetics of human insulin fitted by Prout-Tompkins autocatalytic model. The reaction proceeds in one step according to the equation A+B ➡ 2B+C
- 1997 / 2008 - **Finke-Watsky**: Prion aggregation kinetics described by two-step model of nucleation and autocatalytic growth
- 2014 - **Roduit** et al.: Modified kinetic analysis of sparse data, kinetic model selection procedure based on Akaike and Bayesian information criteria and prediction bands provided by the Bootstrap method.
- Since 1980* - Two-step profiles often mentioned to described complex bioproduct degradations with an initial rapid drop followed by a long gradual decrease phase

One-step kinetics

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

Two-step kinetics

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

$$\frac{d\alpha}{dt} = r.A_1.\exp\left(-\frac{E_{a1}}{RT}\right).(1-\alpha_1)^{n_1}.{\alpha_1}^{m_1} + (1-r).A_2.\exp\left(-\frac{E_{a2}}{RT}\right).(1-\alpha_2)^{n_2}.{\alpha_2}^{m_2}$$

* *Precausta et al., **1980**, Allison et al., **1981**, Mariner et al., **1990**, Roduit et al., **2014**; Hansen et al., **2016**; Clénet, **2018**; Neyra et al., **2021**, Campa et al., **2021***

Good Modeling Practices for Stability Predictions of Products

- From simple to more sophisticated kinetics. Screening of large number of kinetic models as a general rule.
- For vaccines*, biotherapeutics, polymers, adjuvants, synthetics, …

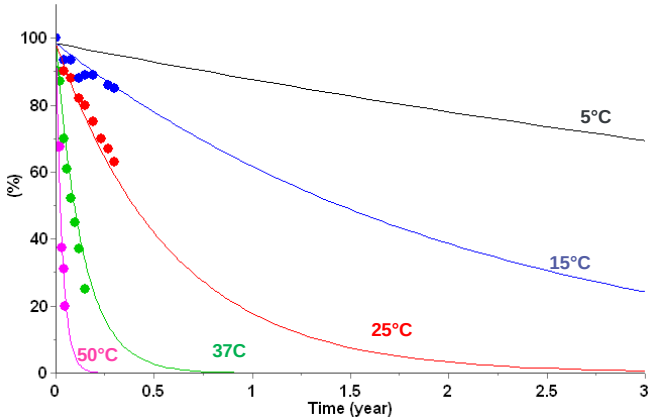
Single step, 1st order reaction

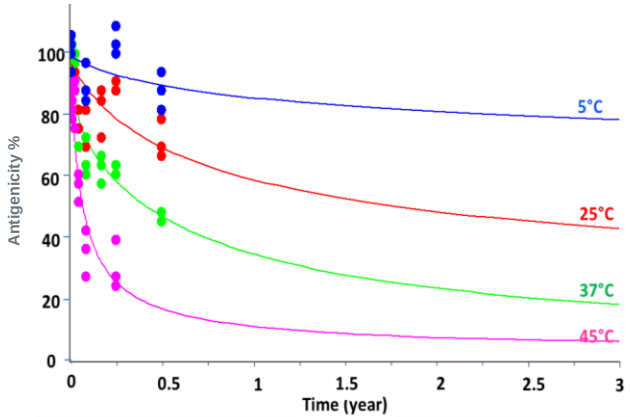
$$\frac{d\alpha}{dt} = \exp(20.7) \cdot \exp\left(-\frac{92{,}6.10^3}{RT}\right) \cdot (1-\alpha)^1$$

- Model complexity +

Competitive two-step reaction

$$\frac{d\alpha}{dt} = 0.41 * 1.08E8 * exp\left(-\frac{83.2E3}{RT}\right) \cdot (1-\alpha)^4 + 0.59 * 1.68E31 * exp\left(-\frac{229.5E3}{RT}\right) \cdot (1-\alpha)^2$$

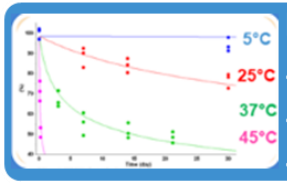




*A. Moriconi et al., Vaccine **2020**, D. Clénet, Eur. J. Pharm. **2018**

Good Modeling Practices for Stability Predictions of Products

1



Predictive Stability Study

- Incubate samples at 3 (or more) different temperatures, i.e. 5°C, 25°C, 37°C, … for months
- Perform periodic analyses to get at least 20 or 30 experimental data points
- Favor replicates

2

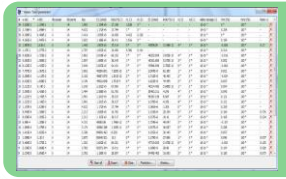
Arrhenius, 1st order, Autocatalytic, Prout-Tompkins, Avramy-Erofeev, Sourour-Kamal, …

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, …)

$$\frac{d\alpha}{dt} = A.\exp\left(-\frac{E_a}{RT}\right).(1-\alpha)^n \quad , \ldots \quad \frac{d\alpha}{dt} = A_1.exp\left(-\frac{E_{a1}}{RT}\right).(1-\alpha)^{n_1}.\alpha^{m_1} + A_2.\exp\left(-\frac{E_{a2}}{RT}\right).(1-\alpha)^{n_2}.\alpha^{m_2}$$

3

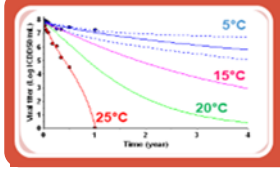


Identify best kinetic model(s)

- The more appropriate model(s) are identified according to several statistical parameters (quality of fit - RSS, model comparison scores - AIC and BIC).

$$BIC = N\ln\left(\frac{RSS}{N}\right) + K\ln(N)$$

4



Determine accuracy of predictions - predictive bands

- Run statistical analysis (boostrap) to obtain realistic prediction intervals (PB 95%)
- Long-term stability (shel-life)
- Impact of temperature excursions

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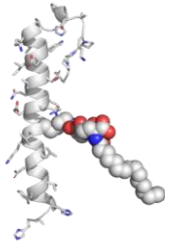
* *Clénet, **2020**, Roque et al., **2021**, Campa et al., **2021***

Accelerated Predictive Stability (APS)

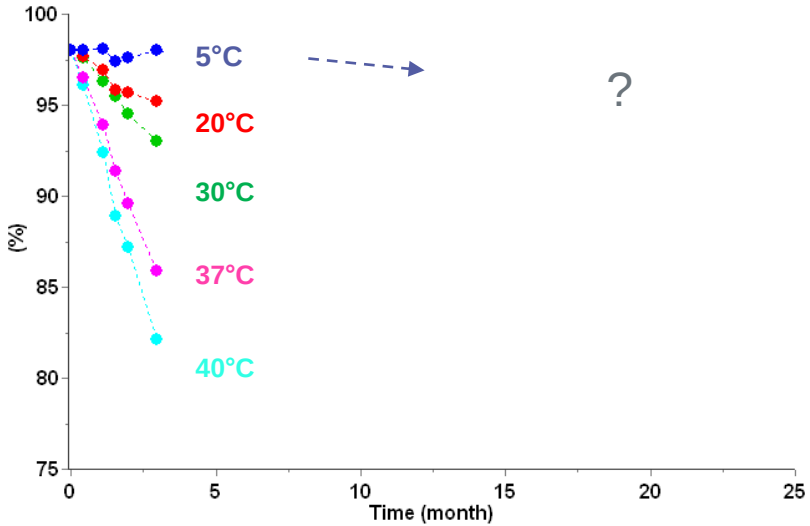
Use cases

Shelf-life predictions based on 3-months data

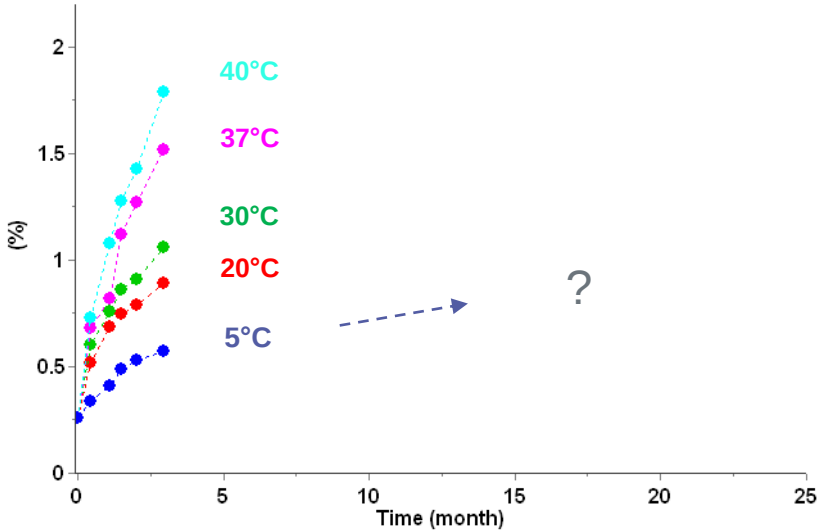


Case study #1: a peptide including two main attributes (purity and HMWP)

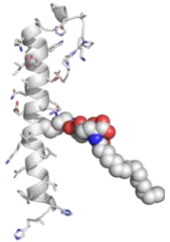
Target: ≥ 90% **purity** after 24 months (5°C)



Target: ≤ 2% **HMWPs** after 24 months (5°C)



Shelf-life predictions based on 3-months data

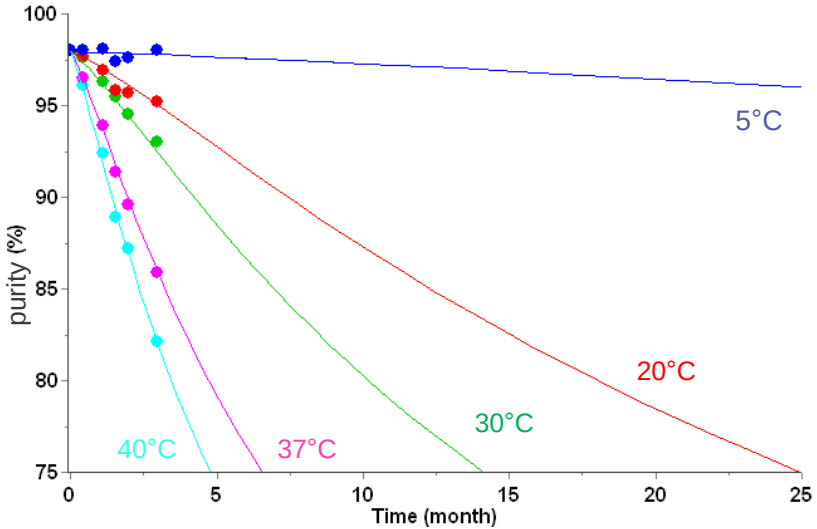


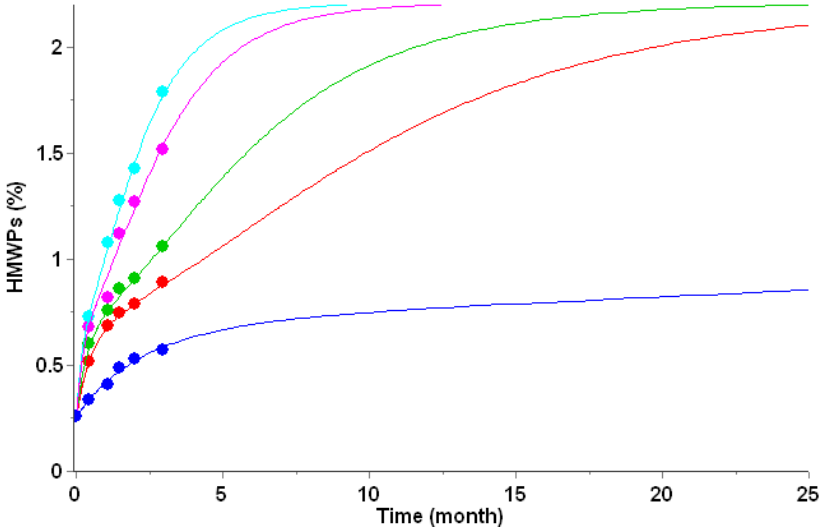
Case study #1: a peptide including two main attributes (purity and HMWP)

Best kinetic models describing reaction progresses as function of time and temperatures

$$\frac{d\alpha}{dt} = 3.85E23.\exp\left(-\frac{86.1E3}{RT}\right).(1-\alpha)^{0.17}.\alpha^{0.101}$$

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





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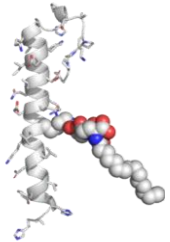
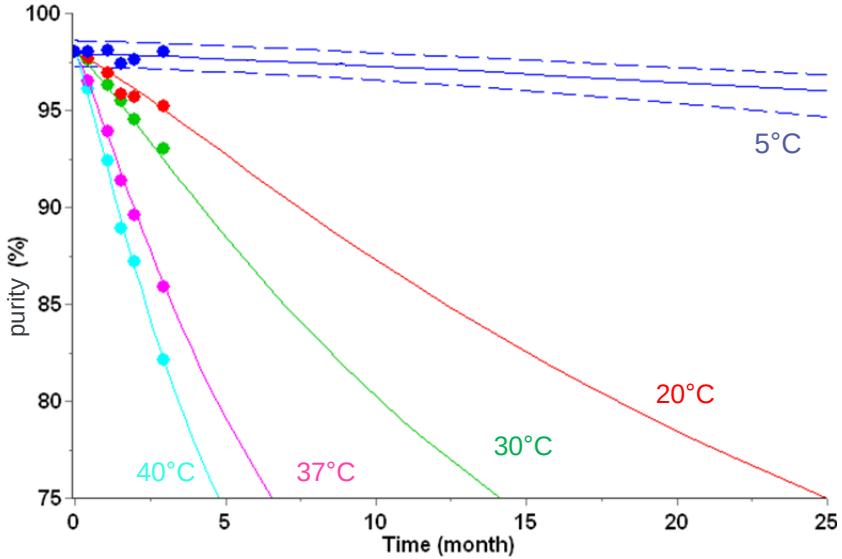
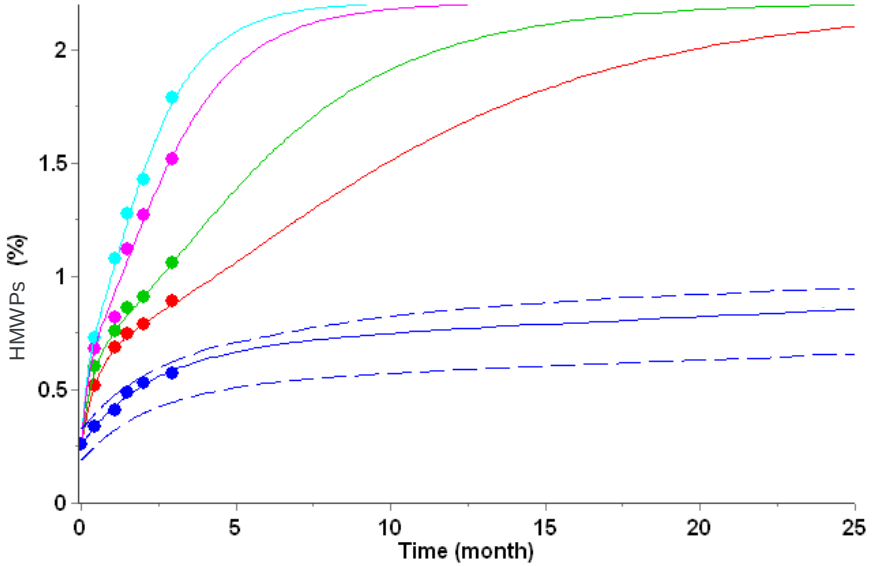
Shelf-life predictions based on 3-months data



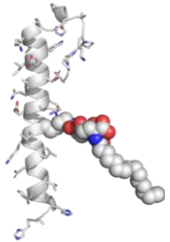
Case study #1: a peptide including two main attributes (purity and HMWP)

Accuracy of long-term prediction determine by bootstrap confidence interval (dashed-lines)



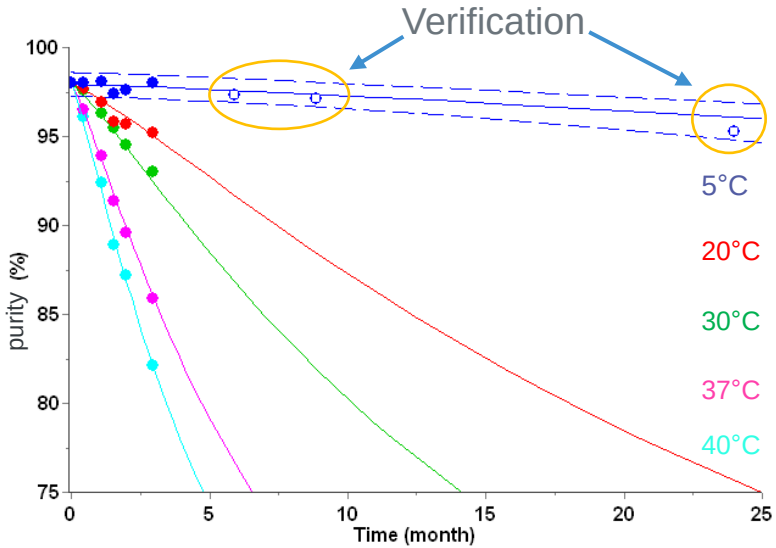


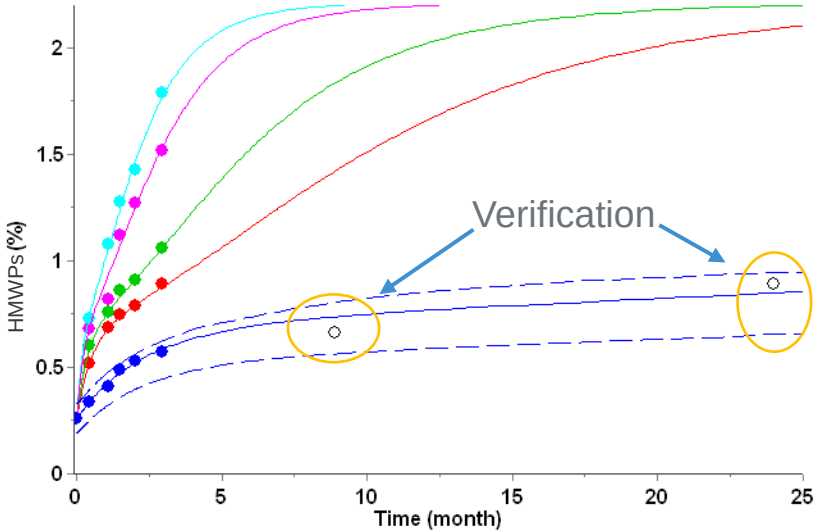
Shelf-life predictions based on 3-months data



Case study #1: a peptide including two main attributes (purity and HMWP)

Experimental long-term data correctly predicted within 95% prediction bands*
→ low risk to fail for shelf-life





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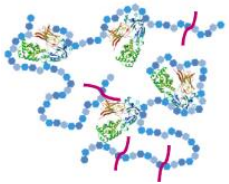
* A. Evers et al., Pharmaceutics, **2021**, submitted

Stability predictions for a polysaccharide-based vaccine



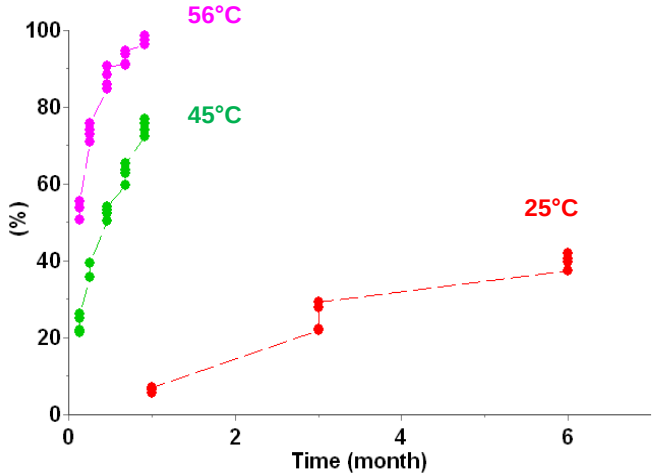
- Case study #2: Free polysaccharide percentage not detectable (< LoQ) during the first 6-months storage at 5°C
- Advanced kinetic model developed using experimental data at accelerated stability conditions at 25°C, 45°C and 56°C could accurately predict rate of free polysaccharide emergence over 4-years at 5°C

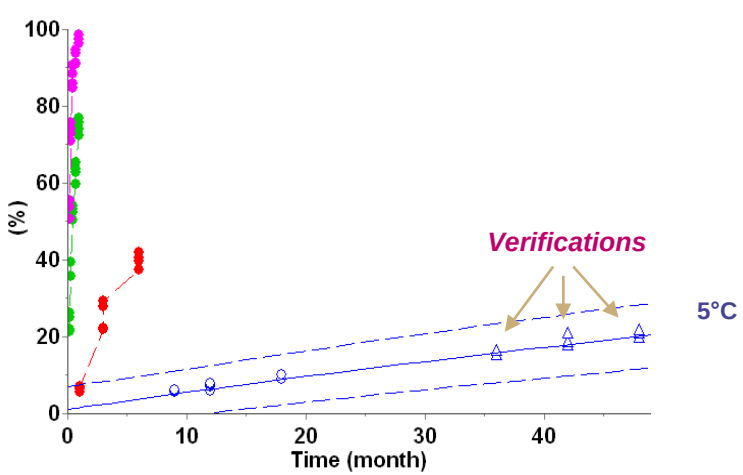
Short-term stability data

$$\frac{d\alpha}{dt} = 1.5E13 * exp\left(-\frac{121.3\ x\ 10^3}{RT}\right)(1-\alpha)^2$$

Kinetic Modeling

Long-term stability prediction





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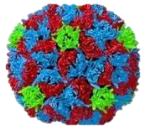
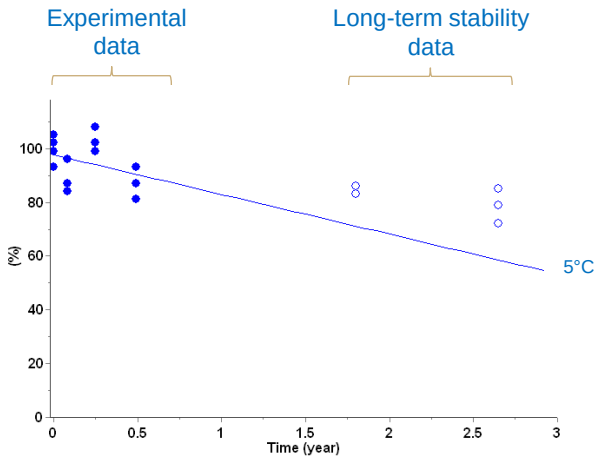
[6] C. Neyra et al., Int. J. Pharm. **2021**

Stability predictions for an inactivated virus-based vaccine



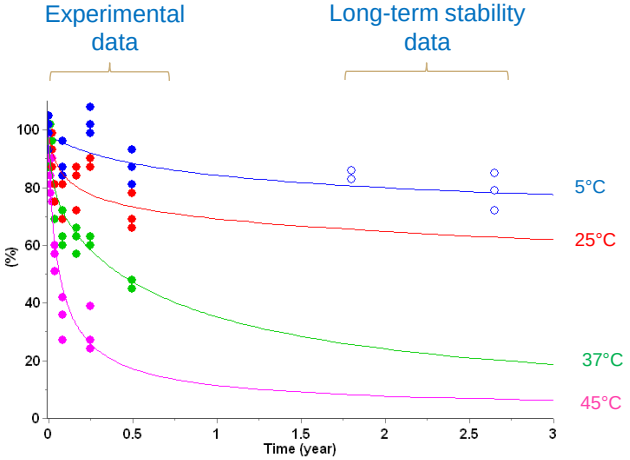
- Antigenicity determined by ELISA as a key stability indicating attribute for a virus-based vaccine [#]

Classical linear regression based on 6 months experimental data at 5°C.



$$[x]_t = 97.662 - 1.231 * t$$

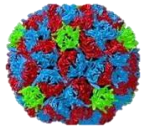
Best kinetic model based on 6 months experimental data at 5°C, 25°C, 37°C, 45°C.



$$\frac{d\alpha}{dt} = 0.409 * 1.08E8 * exp\left(-\frac{83.2E3}{RT}\right).(1-\alpha)^4 + 0.591 * 1.68E31 * exp\left(-\frac{229.5E3}{RT}\right)(1-\alpha)^2$$

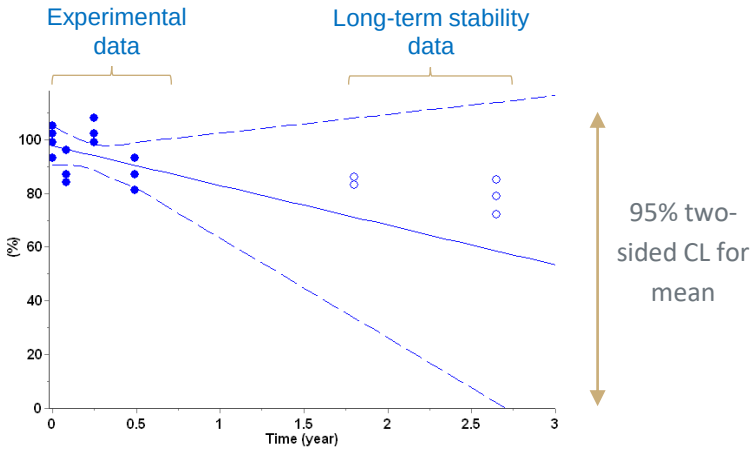
[#] C. Campa et al., Vaccines **2021**

Stability predictions for an inactivated virus-based vaccine



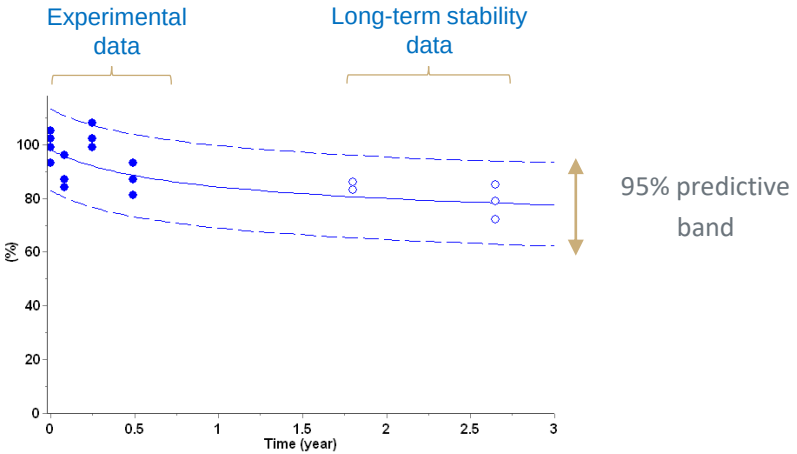
- Focus on 5°C storage temperature, two-step kinetic model and bootstrap prediction interval were required to accurately predict 3 years stability[#]

Classical linear regression to predict long-term stability at 5°C



$$[x]_t = 97.662 - 1.231 * t$$

Two-step kinetic model to predict long-term stability at 5°C



$$\frac{d\alpha}{dt} = 0.409 * 1.08E8 * exp\left(-\frac{83.2E3}{RT}\right).(1-\alpha)^4 + 0.591 * 1.68E31 * exp\left(-\frac{229.5E3}{RT}\right)(1-\alpha)^2$$

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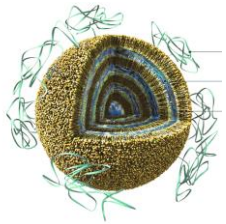
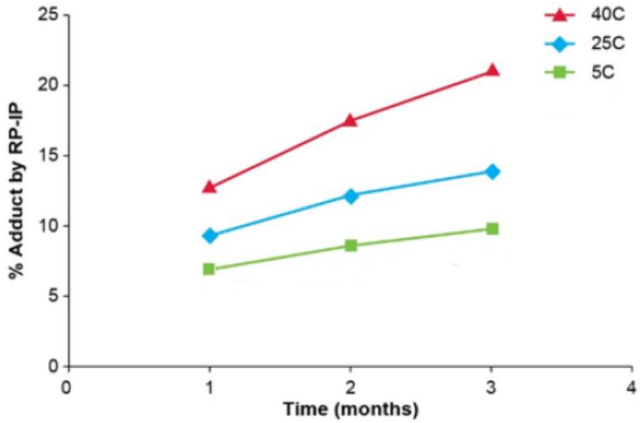
[#] *C. Campa et al., Vaccines* ***2021***

Stability predictions for mRNA vaccines



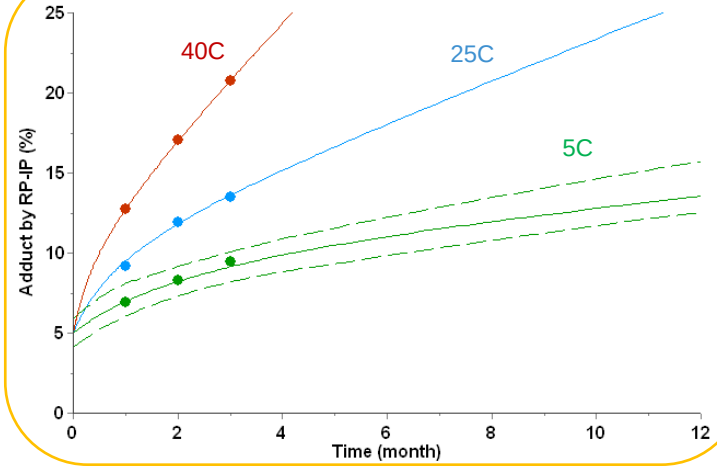
- Case study #3: Moderna investigated the **loss of mRNA purity to adduct formation** (preprint*)
- RP-IP HPLC integrity analysis was applied to mRNA extracted from an **mRNA-LNP**, a late eluting-peak (LP) was detected by HPLC that was not observed by CE.
- An mRNA-LNP formulation was stored for three months at different temperatures (40°C, red; 25°C, blue; 5°C, green), and sampled at 1, 2, and 3 months for analysis by RP-IP HPLC

3-months stability data - Formation of adduct*



Kinetic Modeling

1-year stability predictions (kinetic model)



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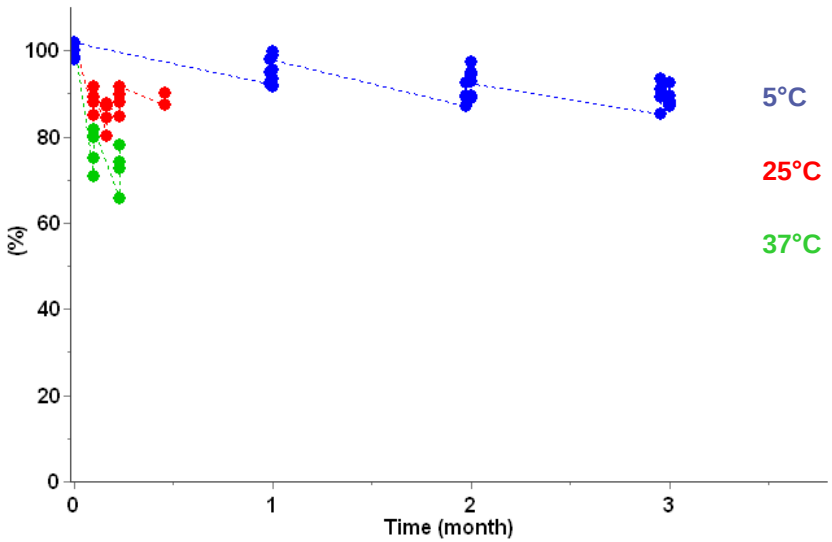
* *M. Packer et al. A novel mechanism for the loss of mRNA activity in lipid nanoparticle delivery systems,* ***2021***

Stability predictions for a virus-based vaccine

- Antigenicity as a key stability indicating attribute
- Short-term stability data at 5°C, 25°C and 37°C for several representative batches



Stability modeling best practices

- Screening of kinetic models
- Ranking and selection of best model(s)
- Stability predictions with predictive bands

Stability predictions for a virus-based vaccine

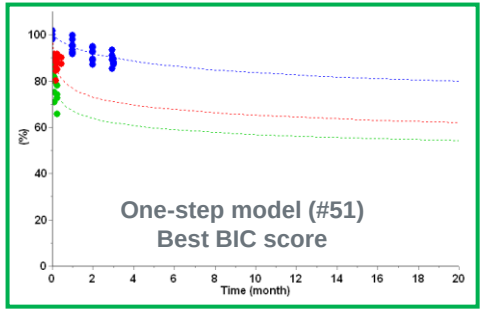
Best models

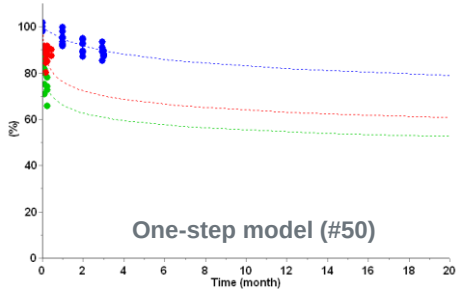
Model ranking

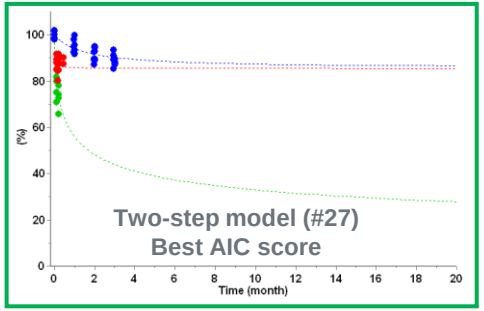
			Statistics Parameters				Parameters Step 1				Parameters Step 2				
#			w AIC (%)	w BIC (%)	Nb param	Nb points	Rss	E1 (J/mol)	ln(A1*s) (-)	n1 (-)	m1 (-)	E2 (J/mol)	ln(A2*s) (-)	n2 (-)	m2 (-)	Ratio v1
51	☑	—— -	2.052E-1	29.333	3	70	737.402	1.228E+5	35.785	15 *	0 *	-	-	-	-	-
50	☑	-----	1.972E-1	28.189	3	70	738.24	1.2E+5	34.549	14 *	0 *	-	-	-	-	-
27	☑	——	19.701	8.722	6	70	584.054	1.478E+5	48.795	2 *	0 *	5.73E+5	207.544	5 *	0 *	0.145
26	☑	— - -	15.625	6.918	6	70	587.934	1.467E+5	48.291	2 *	0 *	5.679E+5	205.477	4 *	0 *	0.146
2	☑	—---	9.294	4.115	6	70	596.725	1.307E+5	41.04	1 *	0 *	6.386E+5	232.589	0 *	0 *	0.137
6	☑	·····	9.28	4.109	6	70	596.751	5.841E+5	211.424	0 *	0 *	1.306E+5	40.99	1 *	0 *	0.863
13	☐		8.841	3.914	6	70	597.579	1.431E+5	46.677	2 *	0 *	4.59E+5	163.046	2 *	0 *	0.15

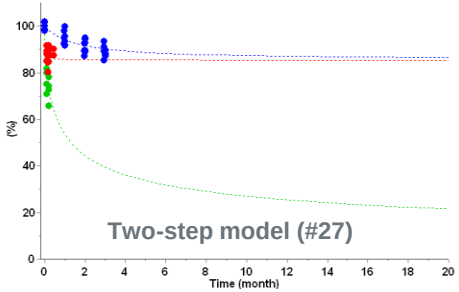
One-step

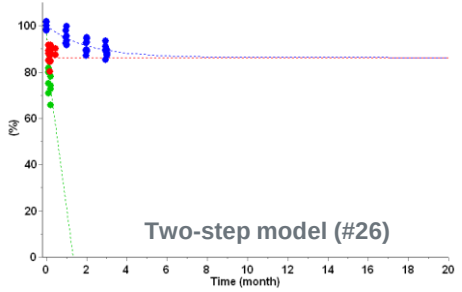
Two-step

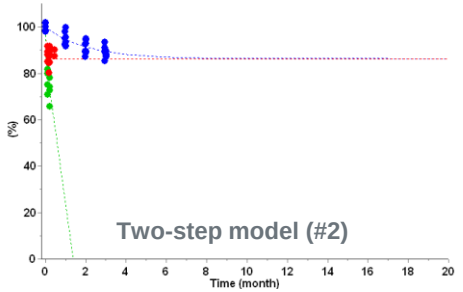












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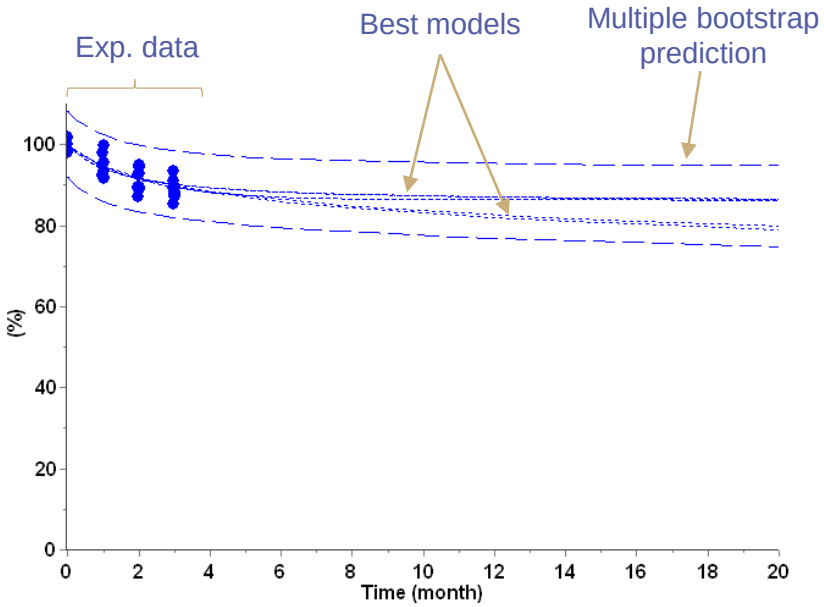
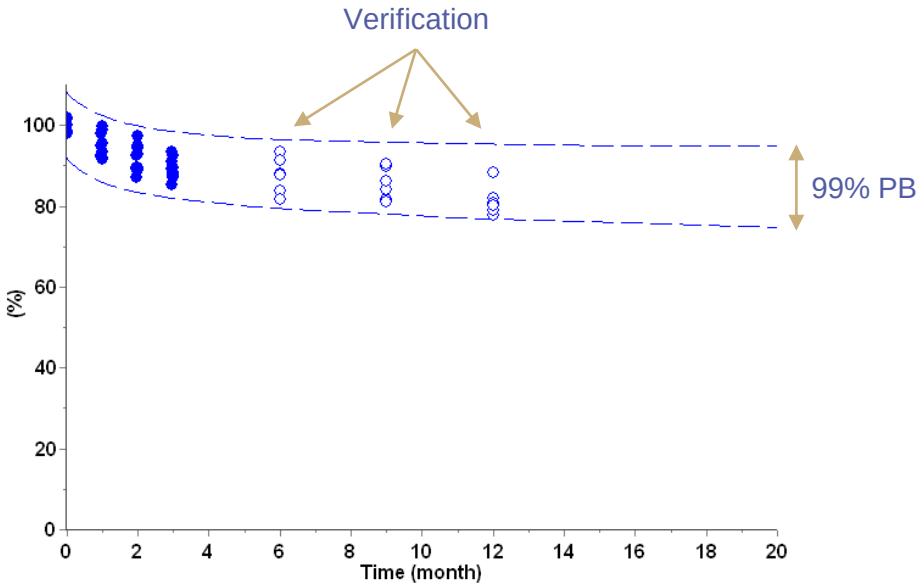
Stability predictions for a virus-based vaccine

- Best accuracy of long-term prediction using multiple bootstrap weighted by AIC/BIC scores





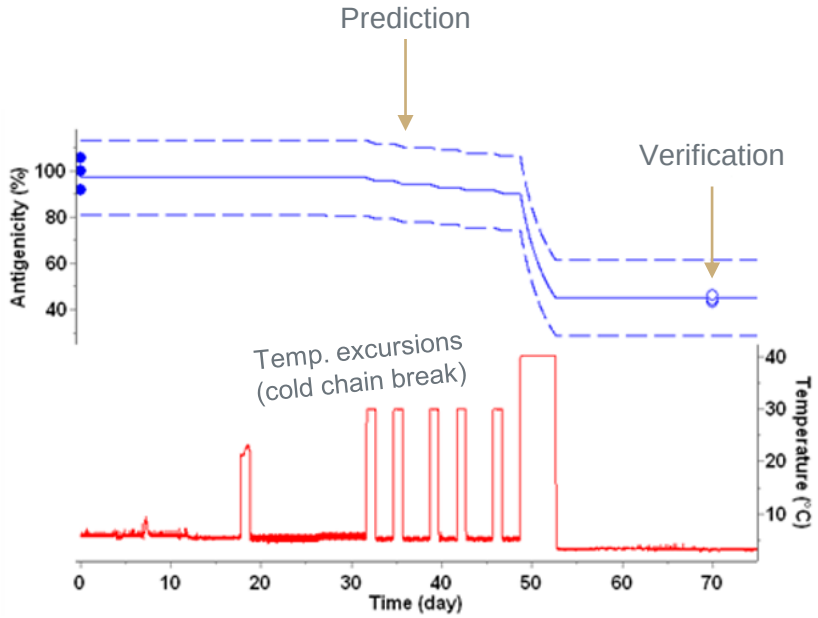
Accelerated Predictive Stability (APS)

Real-time Stability Monitoring of Vaccines

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

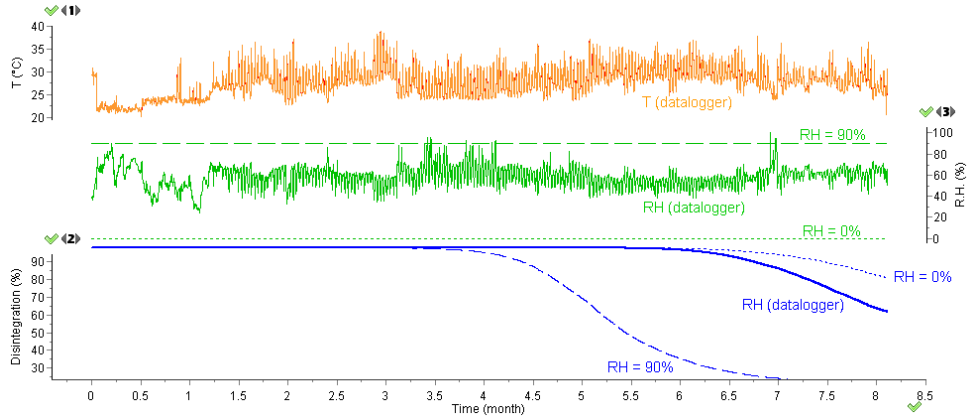
Shelf-life card integrating kinetic models



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

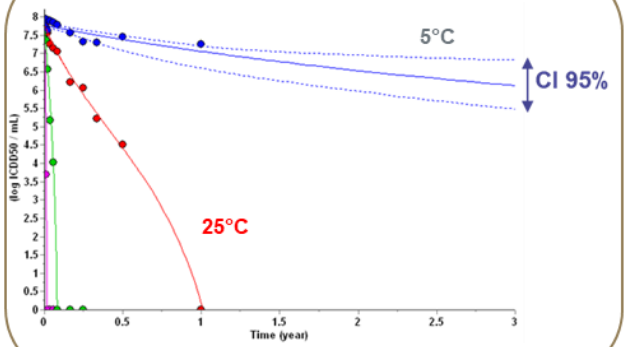
Real-time Stability Monitoring of Products

- Electronic time-temperature devices integrating kinetic models (temperature / humidity)
- Predicts stability of product quality attributes for all time/temperature conditions (including excursions) during storage or shipments



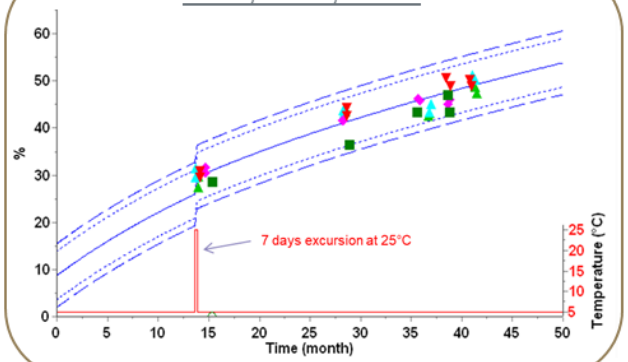
Once kinetic model identified… Various key applications

Shelf-life estimation

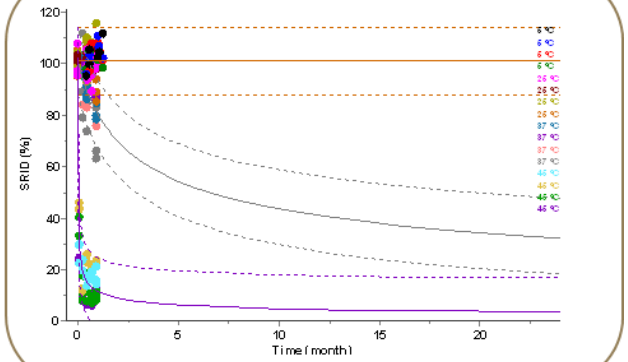


Excursions of temperature

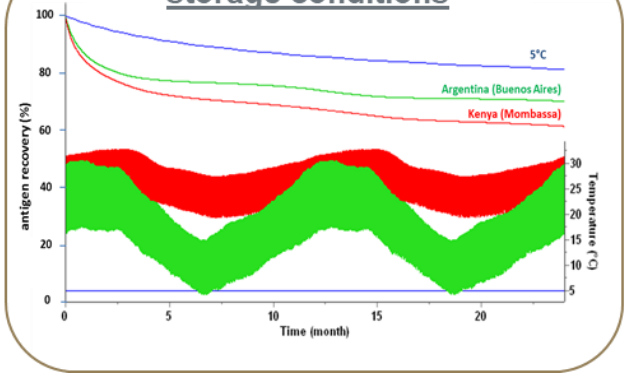
TOR, CTC, VVM



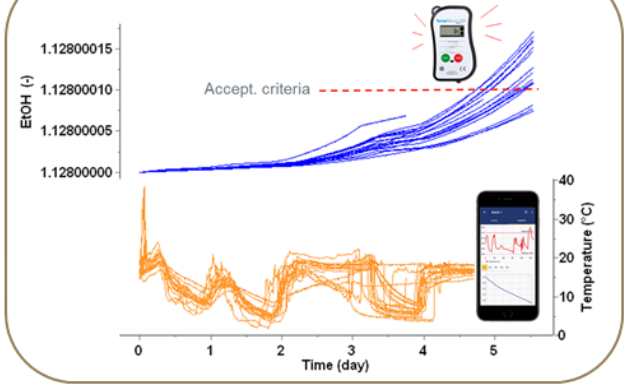
Batch-to-batch comparison



Recommend appropriated storage conditions



Real-time shelf-life monitoring



Accelerated Predictive Stability (APS)

Relationship with regulators

What about stability modeling with regulators

- The presented data demonstrate that the use of advanced kinetic modelling approaches, along with the increased use of platform knowledge, make stability modelling a robust approach for vaccine stability assessment.
- Specific thermostability issues of vaccines, as well as the high supply risks, make stability prediction approaches a particularly urgent topic to integrate into international guidance's.
- Following the same principles, these approaches are increasingly being accepted for biotherapeutics*
- Even if such modeling approaches are (still) not strictly described in the official guidelines (ICH, WHO), they could be considered part of nonlinear regression methods mentioned in the guidance. ICH guidelines can be improved with the inclusion of these matured modeling approaches.
  - An EFPIA working group is working on a proposal for the Stability Testing ICH Q1 (ICH New Topic Proposal)
- Various Health Authorities in Europe, North America, South America and Australia are already aware of these methods for predicting shelf life and SL extensions for various vaccines (multivalent, virus-based vaccines)
- To date, general feedback from the regulatory agencies is positive as a result of the detailed explanation provided by us of the approach and the scientific literature/use-cases shared

* D. Kusman et al, Sci. Rep., **2021**

Reasons to believe- Regulators/ Industry reflection on stability predictions

- Stability modeling (mostly as generated from prior knowledge) is under **discussion by Regulators (EMA/FDA) and Industry** since some years (EMA/ FDA early access workshop 2018) and is now in the EMA draft toolbox.

- **Cross- company proven experience** (e.g., Vaccines Europe task force) on reliability of stability modeling when following some key modeling best practices

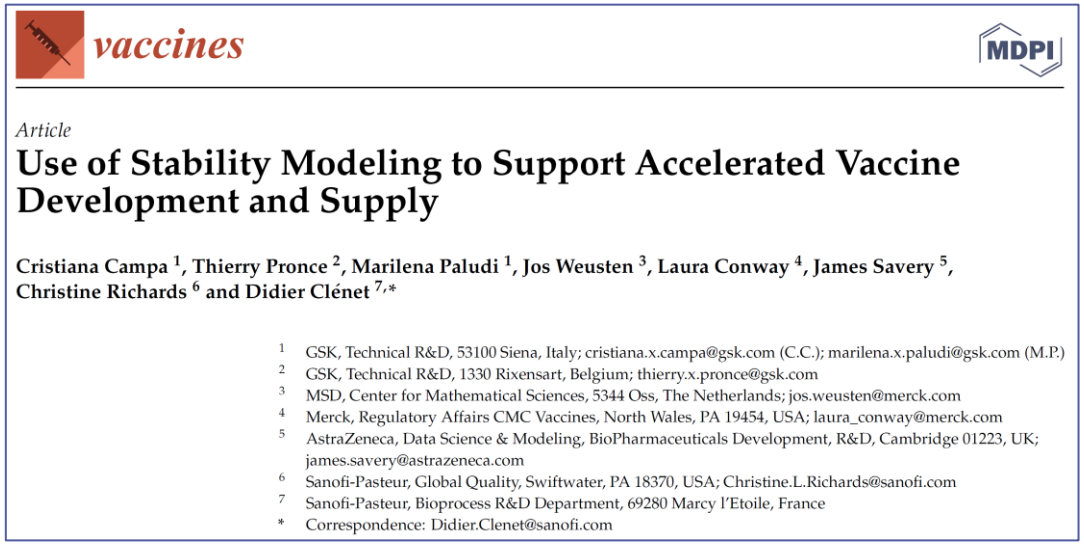
  - *Appropriate kinetic models can be used to accurately predict long-term stability of different vaccines types, mostly using product- specific accelerated data.*

  - *When kinetic models of vaccine are appropriately developed, the use of electronic time-temperature devices integrating such models would be able to inform, in real time, the level of vaccine degradation -from their production to their use.*

from the Draft toolbox guidance on scientific elements and regulatory tools to support quality data packages for PRIME marketing authorisation applications
https://www.ema.europa.eu/en/documents/scientific-guideline/draft-toolbox-guidance-scientific-elements-regulatory-tools-support-quality-data-packages-prime_en.pdf

Accelerated Predictive Stability biologicals and vaccines

- **Vaccine Europe: Stability Taskforce comprised of modeling, stability and CMC experts from across industry**
  - To determine the proposed vaccine shelf life in the absence of real time stability data on the commercial batches - Asks of the Regulatory Advisory Group (RAG) and publication just submitted in Vaccines



vaccines

MDPI

Article

Use of Stability Modeling to Support Accelerated Vaccine Development and Supply

Cristiana Campa [1], Thierry Pronce [2], Marilena Paludi [1], Jos Weusten [3], Laura Conway [4], James Savery [5], Christine Richards [6] and Didier Clénet [7,*]

1 GSK, Technical R&D, 53100 Siena, Italy; cristiana.x.campa@gsk.com (C.C.); marilena.x.paludi@gsk.com (M.P.)
2 GSK, Technical R&D, 1330 Rixensart, Belgium; thierry.x.pronce@gsk.com
3 MSD, Center for Mathematical Sciences, 5344 Oss, The Netherlands; jos.weusten@merck.com
4 Merck, Regulatory Affairs CMC Vaccines, North Wales, PA 19454, USA; laura_conway@merck.com
5 AstraZeneca, Data Science & Modeling, BioPharmaceuticals Development, R&D, Cambridge 01223, UK; james.savery@astrazeneca.com
6 Sanofi-Pasteur, Global Quality, Swiftwater, PA 18370, USA; Christine.L.Richards@sanofi.com
7 Sanofi-Pasteur, Bioprocess R&D Department, 69280 Marcy l'Etoile, France
* Correspondence: Didier.Clenet@sanofi.com

Vaccines | Free Full-Text | Use of Stability Modeling to Support Accelerated Vaccine Development and Supply (mdpi.com)

Accelerated Predictive Stability biologicals and vaccines

- **Vaccine Europe task force**
  - C. Campa (GSK)
  - T. Ponce (GSK)
  - M. Paludi (GSK)
  - J. Weusten (MSD)
  - L. Conway (Merck)
  - J. Savary (AstraZeneca)
  - C. Richard (Sanofi)
  - D. Clénet (Sanofi)

- **EFPIA Stability**
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  - T. Gastineau (Sanofi)

- **Sanofi colleagues**
  - H. Achard
  - T. Alin
  - P. Ballesta
  - S. Pfeiffer-Marek
  - A. Evers (Merck)
  - E. Vetter
  - M. Luciani
  - C. Xi-Kramer
  - C. Airiau
  - C. Neyra
  - M. Rhynyk
  - F. Ausar
  - N. Rahman
  - O. Faure
  - D. Caudron
  - A. Bsila
  - S. Petit
  - E. Bardoux
  - … and all the stability modeling user-group members

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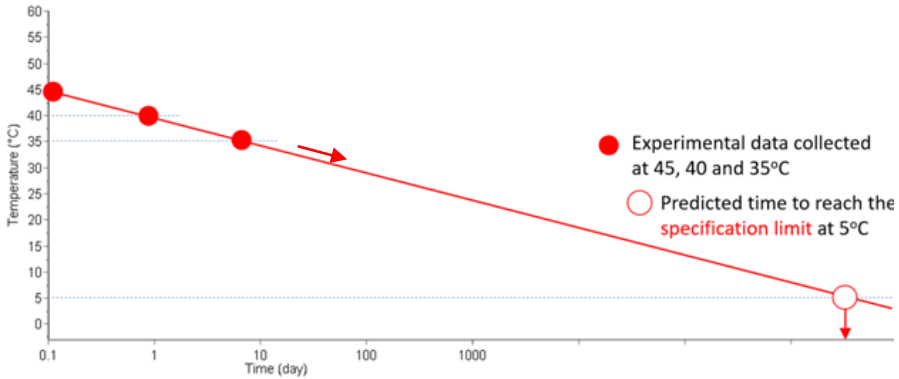
Accelerated Predictive Stability biologicals and vaccines

- **Back-up slides**

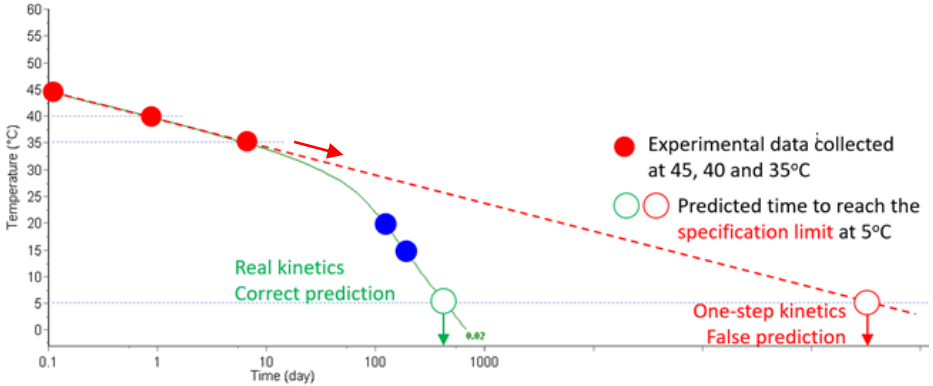
Stability predictions using isoconversional method

- 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**

Why discussion on stability is urgent for vaccines

- 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.**

*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

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6. B. Roduit, M. Hartmann, P. Folly, A. Sarbach, R. Baltensperger, Prediction of thermal stability of materials by modified kinetic and model selection approaches based on limited amount of experimental points, Thermochimica Acta, 579, 31–39, **2014**