Best practices for determining and updating storage temperature and shelf-life Workshop

December 9, 2020

Agenda

- Introductions, meeting overview and rules – 5min
- Principles and practices of vaccine stability and manufacturing modeling –Tim Schofield – 20 min
- Case study: A vaccine’s journey from factory to field – Renske Hesselink, CEPI – 20min
- Case study: nOPV lessons learned – Erman Tritama, Bio Farma – 20min
- Industry Position: Best practices for updating stability data – Didier Clénet and Chrissy Richards, Sanofi – 30min
- WHO assessment of stability data to ensure programmatic suitability for LMIC – Carmen Rodriguez Hernandez, WHO – 20 min
- Meeting close – 5 min

Introduction

- Meeting organizers & purpose of the meeting
- How to handle questions – 1) Meeting Chat; 2) “Raised hand”
- Mechanism for determining future workshop topics

- **Vials & DP Capacity available for COVID-19 Vaccines**
  - ❖ CEPI has secured vials and DP capacity to support >2BN doses of COVID-19 vaccine
  - ❖ Offered this capacity to partners and have allocated capacity to each partner who has requested it
  - ❖ Some capacity remains; unallocated vial capacity as well as DP capacity (non-live product only). We are interested in understanding if this could be helpful to anyone's COVID-19 vaccine production response.
  - ❖ Aware of additional DS capacity that has not been partnered
  - ❖ If you have any interest in these vials or DP/DS capacity, please contact sustainable.manufacturing@cepi.net. We would be happy to collaborate to see how we may fill your needs.

Future Workshops – Response Requested

We will insert the following workshop topics in the meeting chat. Please vote for a January workshop by “liking” the comment in the chat.

1. Best practices for updating stability data offline
2. Best practices for Tech Transfer
3. Post approval changes
4. *No additional workshops needed*

If you are unable to access the chat and would still like to vote, you can email Julia.Kuhn@gatesfoundation.org

Principles and practices of vaccine stability and manufacturing modeling

TIM SCHOFIELD
OWNER & CONSULTANT
CMC SCIENCES, LLC

9TH BEST PRACTICES FOR DETERMINING AND UPDATING
STORAGE TEMPERATE AND SHELF LIFE WORKSHOP

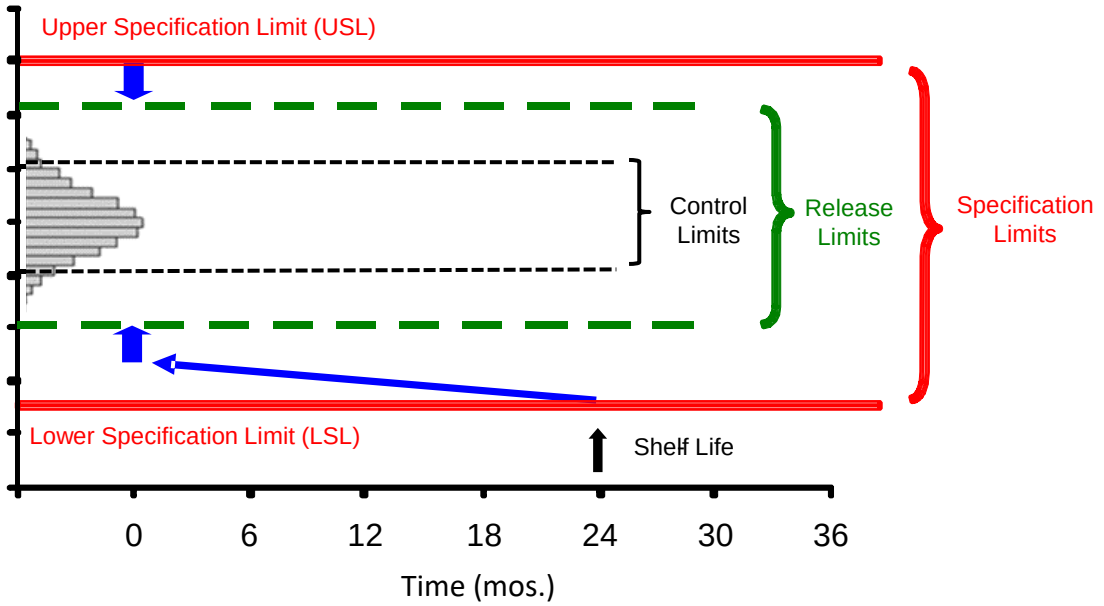
DECEMBER 9, 2020

Outline

- A basic release model
- Manufacturing modeling
- Some tradeoffs in stability and manufacturing modeling
- Benefits of modeling
- Summary

A basic release model
For potency

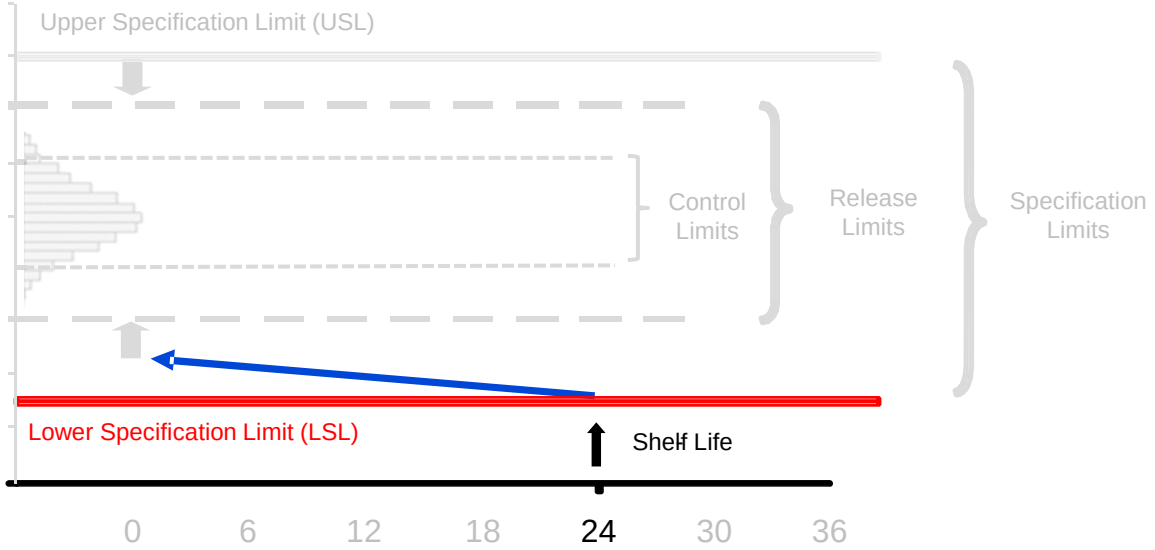
- A model which ensures safe and effective vaccine throughout its designated shelf life



- Clinically/scientifically justified lower (LSL) and/or upper (USL) ***specification limits***
- ***Release limits*** calculated to ensure quality at release and throughout shelf-life
- ***Control limits*** formulated to help manage process consistency

General principles of modeling

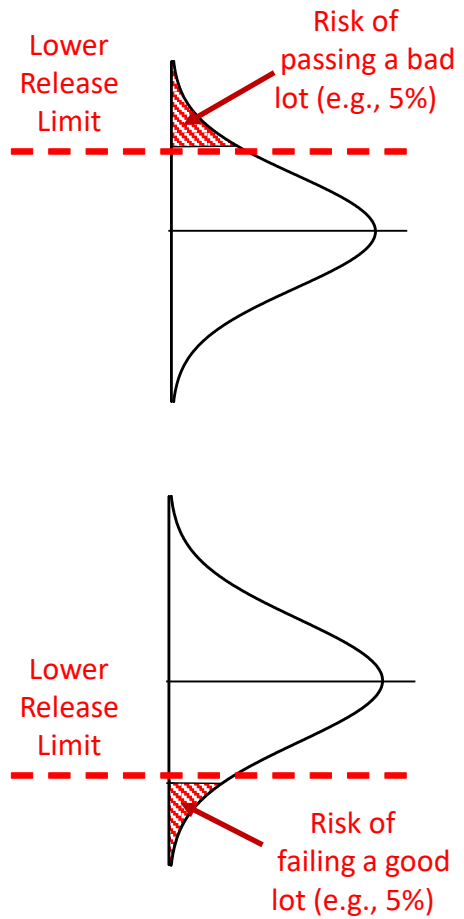
- The model for a lower release limit (LRL)
  - Includes adjustment for the *estimated loss*: $LSL + |Slope| \cdot Shelf\ Life$



  - However, the ***risk*** that a lot released at this level will fall below the ***lower specification limit (LSL)*** at end of shelf life is ***≥50%***

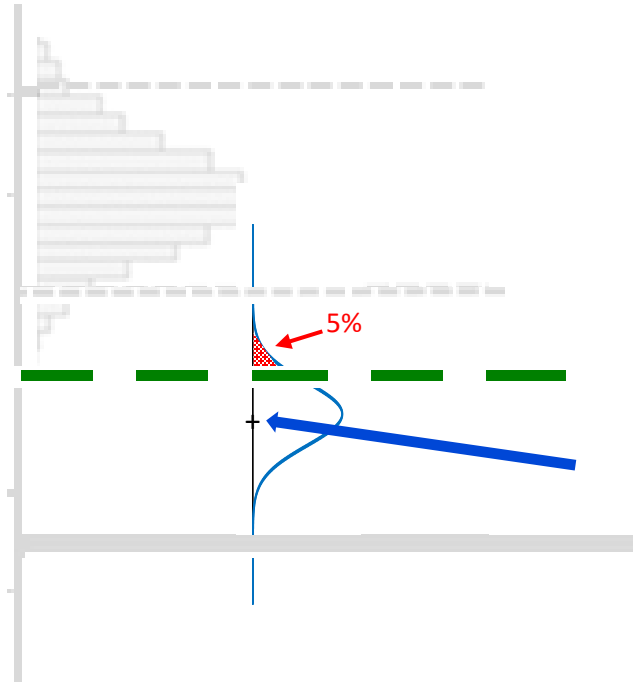
General principle of modeling (cont.)

- Risk can be managed by accounting for uncertainty
  - Uncertainty is the statistical error associated with estimation
- Risk can be depicted as an area under a curve depicting uncertainty
- There are two risks associated with release testing
  - Consumer's risk – the risk of releasing a "bad" lot
  - Manufacturer's risk – the risk of failing a "good" lot
- These can be used in models to limit risks (increase confidence)



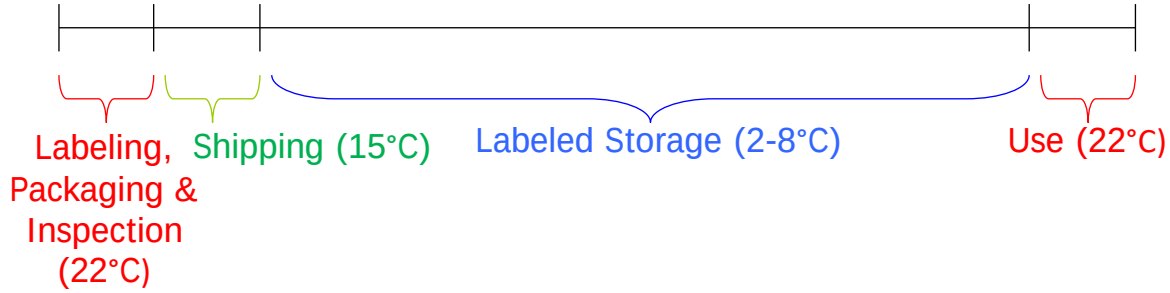
General principles of modeling (cont.)

- There are two estimates associated with calculation of a lower release limit
  - The estimated loss over shelf life – from *stability studies*
  - The estimated potency at release – from the *release assay*
- These can be combined with the estimated loss to limit the consumer's risk of receiving a subpotent lot at end of shelf life
  - Usually, 5% risk which is consistent with the ICH use of a 95% confidence interval for shelf life determination



General principles of modeling (cont.)
WHO Guidelines

- *WHO Guideline on Stability Evaluation of Vaccines* (2006)
  - A more comprehensive release model is illustrated which accounts for losses accrued from manufacture through end of shelf life



  - Note 1: 1st order kinetics rates are concentration independent; there's no need to perform "sequential stability" to model the LRS
  - Note 2: ***WHO Extended Controlled Temperature Conditions (ECTC)*** is a special case of the WHO model:

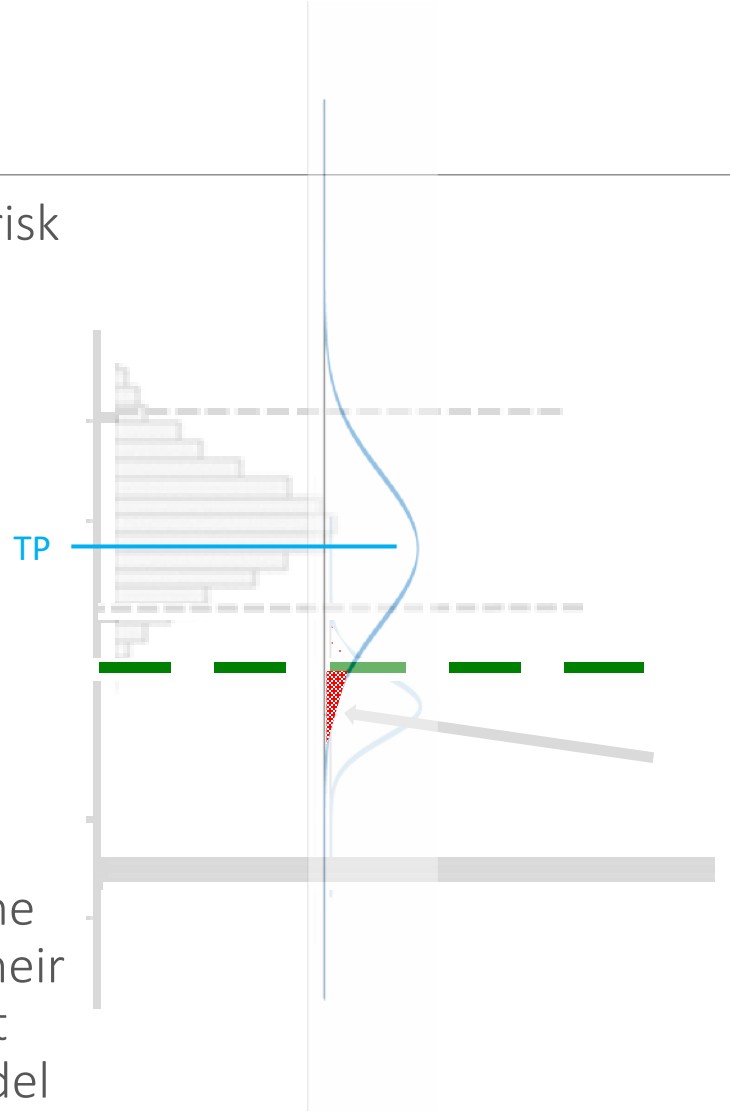
> ". . . a single exposure to at least 40 °C for a minimum of 3 days just prior to administration."

General principles of modeling (cont.)

- A release model *requires a true specification* – i.e., a limit on quality, not on manufacturing variability
- A release model rewards effort
  - Through stability study and assay designs
- A manufacturing model can be built upon this which uses similar principles including limiting *manufacturer's risk*

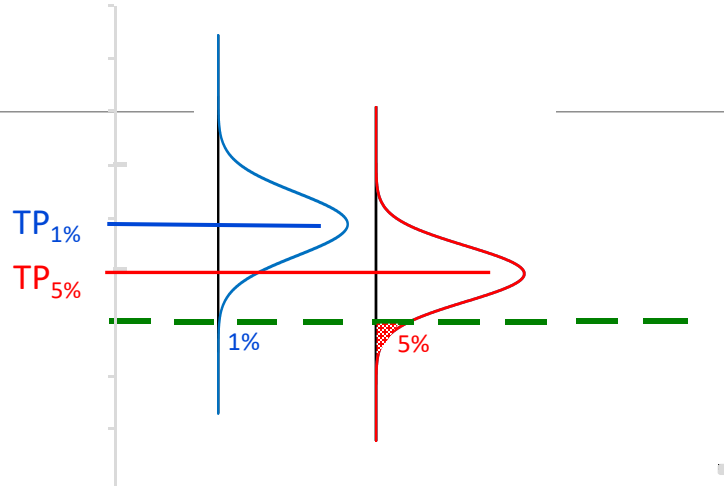
Manufacturing modeling

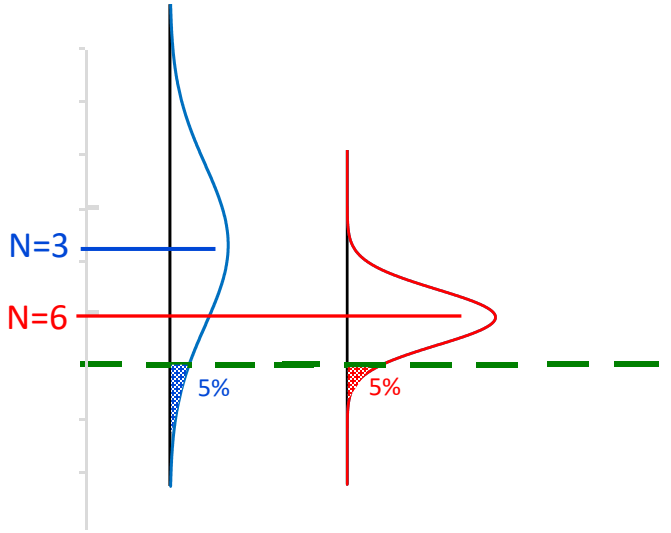
- Vaccines are overfilled to control manufacturer's risk (i.e., risk of an out-of-specification potency at release)
- A simple overfill model
  - Bulk vaccine is diluted to a *target potency (TP)* based on bulk potency determination
    - Two estimates in the model: (1) estimated bulk potency; and (2) estimated release potency
  - Like the release model TP can be determined to reduce the risk of failing the release limit
- More generally, a manufacturing model is the same as a release model and includes step losses and their uncertainties, and IPC's resulting in an adjustment (e.g., dilution) – in the same way as the WHO model



Some tradeoffs in stability and manufacturing modeling

- The target level (and thus the overfill) can be reduced by assuming greater consumer and/or manufacturer risks
  - Tradeoff between product failure and bulk capacity
  - *Low risk/low capacity* versus *high risk/high capacity*
- The target level can be reduced through greater investment in study and assay designs
  - Long-term decrease in capacity ***(N=3)*** versus one-time investment *(N=6)* in testing





Some tradeoffs in stability and manufacturing modeling (cont.)

- A cost/benefit analysis can be performed to evaluate the optimum levels of stability and manufacturing options
  - Noting cost of less capacity due to higher overfill

Option (Cost)	Risk Factor	Comment
Low consumer's risk (α x $$$)	Efficacy	Fixed high benefit
Low manufacturer's risk (β x $$$)	Capacity	Balance overfill versus failed lots
Reduced exposure conditions ($$)	Efficacy & Capacity	Manufacturing and supply chain costs; benefit of efficacy and lower overfill
Study and assay design ($)	Efficacy & Capacity	One-time cost

  - Budget modeling can include these options, their co-dependencies, and additional factors (e.g., costs due to hospitalization, etc.)

Benefits of modeling

- A risk management approach
- Driver of technical and study development
- Facilitates capacity management
- Effective use of development data
- Encourages use of prior knowledge

Summary

- Stability and manufacturing modeling can be used to manage both the risk to vaccine subjects of receiving unsafe or ineffective vaccine, and the risk to manufacturers of failing to meet the release specification
- Tradeoffs among exposure conditions, CMC designs, and manufacturer's risk can be evaluated to optimize vaccine quality and supply
- Development and quality decisions can be informed more broadly by clinical and public health considerations

Thank you!

tim@cmcsciences.com

Questions?

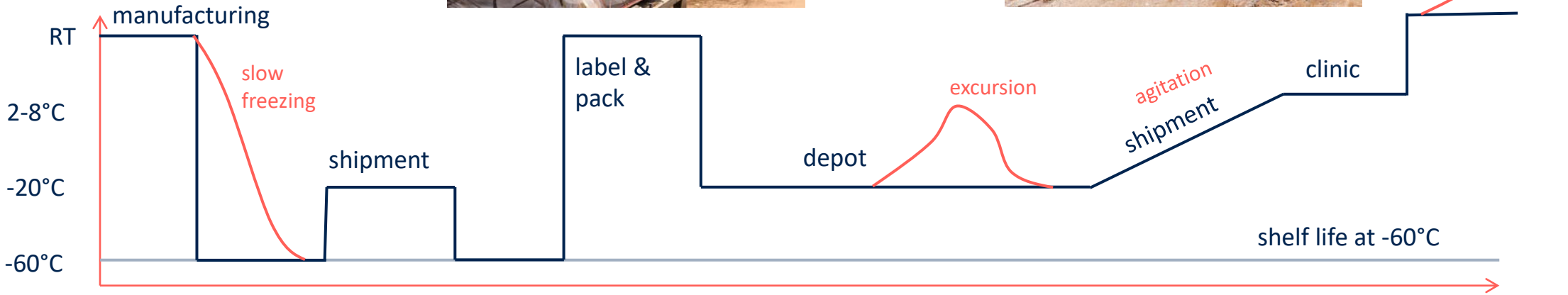
A vaccine's journey from factory to field

Renske Hesselink, CMC Lead, CEPI

CEPI

Stability workshop, Manufacturing SWAT Team, 09 December 2020

The journey of a Drug Product



- A Drug Product experiences many conditions on its journey to the patient, some planned and some unplanned:
  - Shelf Life defined at certain temperature(s) or range(s)
  - But also: slow temperature transitions, excursions, shipment and handling, agitation, light, in-use…
  - How to test and control product stability at all these conditions?

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Surprises from the field

"We accidentally unplugged the fridge on Friday evening in which the vaccine was stored over the weekend, can we still use the doses?"

"The lowest detected temperature during shipment on dry ice was -87°C, is that ok?"

"We took the temperature monitors out of the shipment right when it arrived. But between that and putting the vaccine into the cold storage, there was a period of 30 minutes during which the pallet was exposed to room temperature"

"For the vaccination, we take the doses out of the fridge and bring them to room temperature in advance. How long is the vaccine stable at this temperature? Can we put it back into the fridge and use it later?"

"The vaccine was accidentally left in daylight for several hours, what shall we do with it?"

"We prepare the syringes in one part of the clinic and transport them on a cart, this is fine, right?"

- During transportation and storage, technical issues like temperature excursions can (and will!) occur
- We recommend to integrate / simulate this in stability studies, to allows proper answering of questions and complaints from the field
- This will also substantiate the data from Vaccine Vial Monitors (VVM)

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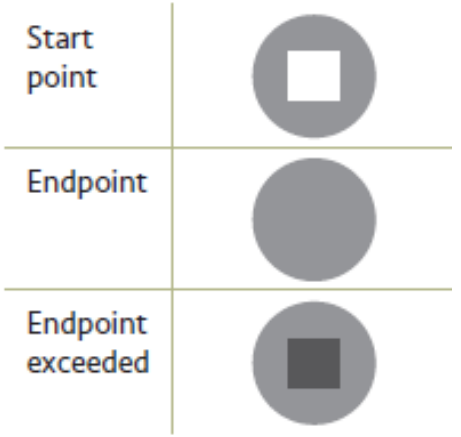
How to test (un)planned conditions?

- Understand and model stability and degradation → effect of conditions can be predicted by model
  - Advantage: good understanding of degradation routes and rates at different temperatures, accurate modelling of the effect of certain stress
  - But: requires large dataset and good methods

$$\frac{d\alpha}{dt} = A_1 \exp\left(-\frac{E_1}{RT}\right)(1-\alpha)^{n1}\alpha^{m1} + A_2 \exp\left(-\frac{E_2}{RT}\right)(1-\alpha)^{n2}\alpha^{m2}$$

- Test worst-case conditions or determine edge of failure → anything inside this range is acceptable
  - Advantage: actual stresses applied, not dependent on model
  - But: exact excursion conditions not tested, may discard vaccine doses too quickly out of caution

- Vaccine vial monitor (VVM)
  - Advantages: registers cumulative heat exposure of specific vial, preventing both undue wastage and accidental use of degraded vaccines
  - But: vaccine needs to fall into one of the VVM categories; temperature is not the only stress
  - VVM recommended for WHO PQ, but may be waived initially for COVID-19 vaccines (*WHO 'Considerations for Evaluation of COVID19 Vaccines, 25 November 2020*)



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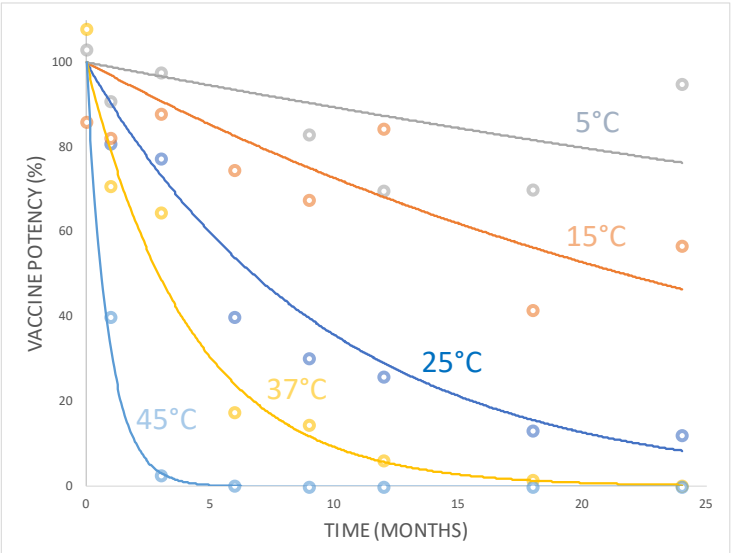
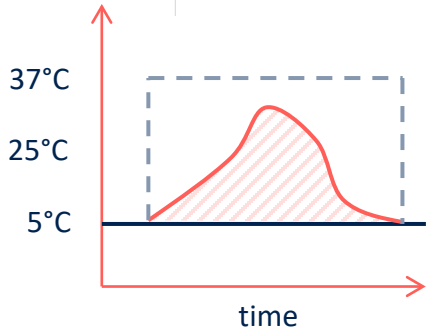
Arrhenius modeling

- Arrhenius equation describes the temperature-dependence of reaction rates
- Vaccine degradation is often a complex process with multiple reactions occurring simultaneously, dominant degradation pathway may differ per condition → more complex form of Arrhenius equation required

Arrhenius model can:

- Predict real-time from accelerated stability
  - Still needs to be confirmed with real-time data
- Calculate impact of temperature excursion according to exact profile
  - Without model, conservative approach is taken to assume worst-case may be too strict
- Determine batch-to-batch consistency or impact of process changes
  - Stability part of comparability
  - The same temperature-dependence of degradation indicator that batches behave similarly

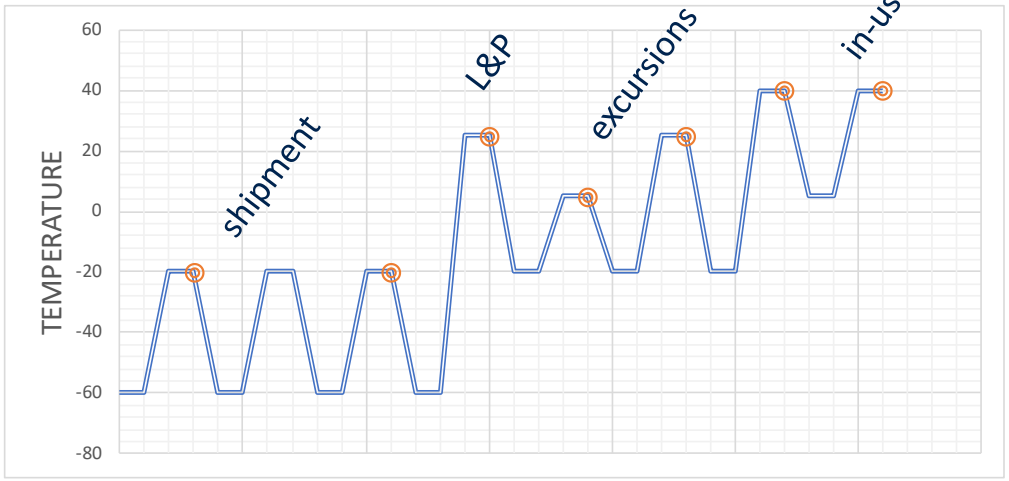




rates is strong

Test multiple excursions

- Instead of modeling and predicting, the effect of multiple temperature changes and excursions can be directly tested
  - Test worst-case scenario with several sampling points in between
  - Consider both planned (for shipment, labelling, administration) and unplanned excursions
- Why ship at -20°C?
  - Shipment on dry ice may result in excursions to < -80 °C
  - Container-closure integrity breach may occur at these
    CCI needs to be tested at ultralow temperatures
- In-use stability
  - Consider region: ‘room temperature’ is not always the same



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Temperature is not the only stress

- Product may also be exposed to agitation, freezing stress, light exposure…
- Light: ICH Q1B on photostability testing prescribes exposure to at least 1.2 million lux hours illumination and 200 watt hours/square meter UV energy
  - This can be quite damaging for biologics, especially UV light
  - However, secondary packaging usually fully protects against light
- Direct light exposure: during manufacturing and administration
  - Manufacturing exposure controlled and tested (e.g. max hold times)
  - Administration conditions less controlled
  - If product is light sensitive → control measures may be needed

Illuminance (lux)	Example
120,000	Brightest sunlight
20,000	Shade illuminated by entire clear blue sky, mid-day
10,000–25,000	Typical overcast day, mid-day
3000	Winter day with cloudy sky
400	Sunrise or sunset on a clear day (ambient illumination)
400–10,000	Indoor artificial lighting
400–10,000	Indoor lighting with window-filtered daylight

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Conclusions

- A Drug Product will experience many planned and unplanned conditions before reaching the vaccinee: temperature, freezing, agitation, light, contact materials, administration
- It is important to understand the degradation routes of the product and its sensitivity to various stresses
  - Modelling
  - Direct testing
  - VVM
  - Consider all stresses and cumulative effects
  - Develop strong post-approval stability program

"Vaccines do not save lives, vaccinations do" – the vaccine needs to make the journey to the patient while staying safe and efficacious

Photo: Gavi/ GMB Akash

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Questions?

nOPV2 Lessons Learned

Stability Workshop

December 9, 2020

Erman Tritama, PhD

Presentation Overview

- nOPV2 background
- Lessons Learned
  - Strategic goal for manufacturing
  - Stability data submitted and WHO response
  - Impacts of limited stability data
  - Implications for COVID-19 vaccine manufacturers

nOPV-2: Background

Objective:

- Reduce the risk of vaccine associated paralytic poliomyelitis (**VAPP**) and circulating vaccine derived polioviruses (**cVDPV**)

Status:

- Designed to improve genetic stability and decrease the risk of loss of attenuation relative to the parental Sabin 2 strain
- First-in-human study initiated in 2017. Phase II studies in adults and children/infants completed in 2019
- Oral live vaccine designed for outbreak response
- Important tool to help achieve Polio eradication
- Achieved WHO Emergency Use Listing (EUL) on Nov. 13, 2020

Strategic Goal for Manufacturing

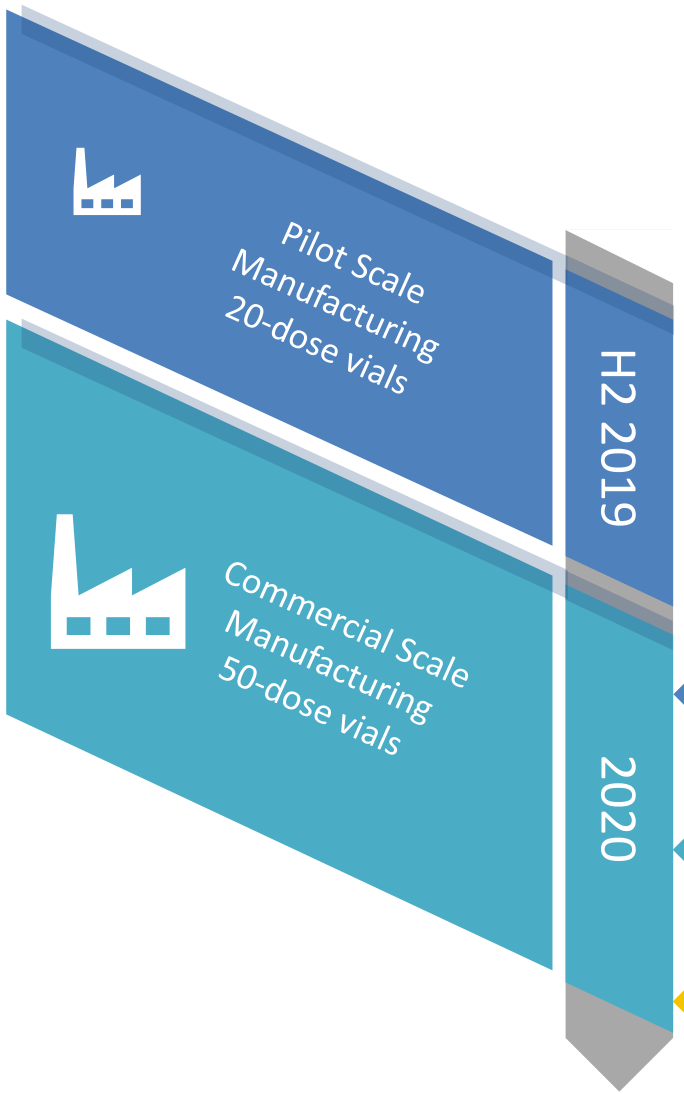
Need: Supply nOPV2 to be supplied as quickly as possible to address the Public Health Emergency of International Concern (PHEIC) declared by WHO

Strategic Goal: Maximize doses available & use of limited filling capacity

Achieved by

- Completing scale-up from Pilot Scale to Commercial Scale Manufacturing in < 10 months
- Implementing change from 20- to 50-dose vial to maximize filing capacity

Stability Data Submitted and WHO Response



Initial EUL Submission
Pilot Scale
Feb. 2020

Second EUL Submission
Commercial Scale
Aug. 2020

EUL Approved
Nov. 2020

Stability Data Included in Initial EUL Submission (Pilot Scale, 20-dose vials)

- 36 months real time stability (10 ds/vial) & 3 months (20 ds/vial)
- 8 months accelerated stability at 2-8°C (10 ds/vial) & 1 months (20 ds/vial)
- 14 days accelerated stability at 25C (10 ds/vial) & 24 days (20 ds/vial)
- 48 hrs accelerated stability at 37C (10 ds/vial) & 48 hrs (20 ds/vial)

Stability Data Included in Second EUL Submission (Commercial Scale, 50-dose vials), including response to LoQ

- real time stability data – 3 month
- accelerated stability at 2-8°C – 1 month
- Accelerated stability at 25 C – 14 days
- Accelerated stability at 37 C – 48 hours
- Supported by data from Pilot Plant (10, 20, 50-dose vials)
  - 10-dose vial (clinical lot) real time stability - 36 months
  - 10-dose vial sequential stability – 34 month at -20 and 3 months at 2-8 C
  - 50-dose vial real time stability - 6 months
  - 50-dose vial accelerated stability at 2-8°C - 7 months
  - 50-dose vial accelerated stability at 25 C – 14 days
  - 50-dose vial accelerated stability at 37 C – 48 hours

EUL Approved Shelf Life and Storage

- 12-month shelf life
- Storage period of 3 months at 2-8°C

WHO Response

- Data provided does not support requested shelf life of 36 months or 6 months of storage at 2-8°C
- Material produced in Pilot Plant (incl. clinical lots) not representative of Commercial material

For reference mOPV2 Package Insert states, ”Vaccine is potent if stored at not higher than -20 C until the expiry date indicated on the vial. It can be stored for up to six months between +2 C and +8 C.”

Impacts of limited stability data

Issue	Comments
28 million doses labeled at risk with 36-month shelf life and PI stating 6 months at 2-8°C • Do not match parameters in EUL approved label and PI • Only 10 months shelf life remaining at EUL	• Local NRA will be responsible for product release • WHO, UNICEF, and GPEI will monitor to ensure all doses distributed are used or returned prior to expiry
Additional 130 million doses filled, but not labeled • Current shelf-life is limited for these vials	• Submit additional stability data in a rolling fashion to WHO PQ to extend shelf life and storage
Need for nOPV2 as soon as possible, but important to maximize shelf life	• Halted filling of frozen bulk to preserve shelf life • Need to carefully manage supply for filling, labeling, and shipping. Most entities will be unable to conduct “just-in-time” filling.

Implications for COVID-19 Vaccine Manufacturers

- **Assume all facilities will be held to commercial GMP standards:**
  This applies for emergency use authorization / emergency use listing
- **Assume data from small-scale/clinical lots or pilot scale facilities may not be accepted to support EUL:**
  Scale to commercial GMP scale as soon as possible
- **Accelerated stability data may not be acceptable even for well-understood vaccines (such as OPV):**
  Start real time stability studies early in development with GMP commercial scale product
- **Work with regulators to align on requirements at outset & throughout development:**
  Better inform plans, align on changes and submission expectations:
  - Confirm with WHO PQ and relevant NRA whether inclusion of manufacturing date rather than expiry date could be acceptable (leverage online portal or other means for updates)
  - Confirm with WHO PQ that label on vial and package will be in English only. Package insert can be in multiple languages
  - Ensure relevant NRAs have a process for emergency use licensure and emergency use export/import

Questions?

Best practices for updating stability data

Didier Clénet, Christine Richards

Sanofi Pasteur

on behalf of Vaccines Europe/ IFPMA

COVAX Workshop: “Best practices for determining and updating storage temperate and shelf- life”

9 Dec 20

Outline

- Relevance of stability consideration for COVID vaccines supply (industry perspective)
- Stability modeling as a tool to ensure fast supply of vaccines & examples from real life
- Vaccine specificities and commonalities vs biotherapeutics
- WHO- CEPI- Needs from Industry

Relevance of stability considerations for COVID vaccines supply (industry perspective)

- 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.

Relevance of stability considerations for COVID vaccines supply (industry perspective)

- 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

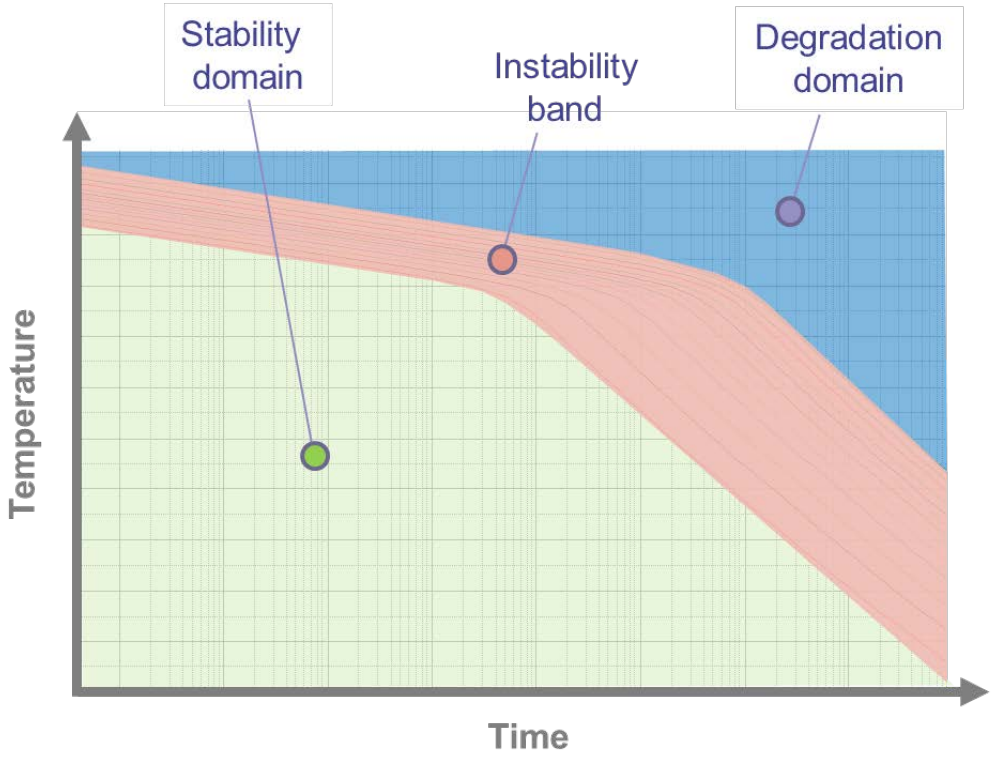
Accelerated Predictive Stability biologicals and vaccines

Key questions

- How long can antigen be kept native?
- How fast can antigen reach a denaturation state?
  - In days/months/years?
- What is the more appropriate storage condition?
  - Freezer, cold chamber, ambient temperature…
- How can we leverage accelerated stability studies to accurately predict shelf-life at the intended storage conditions?
  - Changes in stability over time at low temperature might not be significant until many months of data has been collected. Impractical in a pandemic situation
- What about temperature excursions during storage and shipments?

Stability modeling

Building an accurate stability design space [1]



Accelerated Predictive Stability biologicals and vaccines

- **Describing degradation rates of vaccines**

Kinetic model

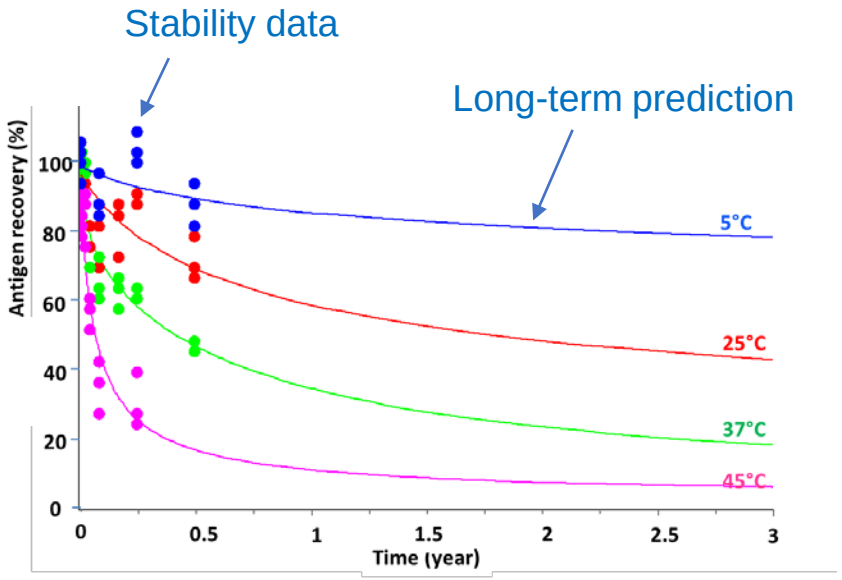
$$\frac{d\alpha}{dt} = \underbrace{k_1 . A_1 . exp\left(-\frac{E_{a1}}{RT}\right) . (1-\alpha)^{n_1} . \alpha^{m_1}}_{\text{1-step}} + \underbrace{k_2 . A_2 . \exp\left(-\frac{E_{a2}}{RT}\right) . (1-\alpha)^{n_2} . \alpha^{m_2}}_{\text{2-step}}$$

$d\alpha/dt$	Reaction rate
α	Reaction progress
T	Temperature (K)
t	Time
R	Universal gas constant
Kinetic parameters	
A	Pre-exponential factor
E	Activation energy
n	Order of the reaction
m	Reaction order for autocatalytic type component
k	Contribution of the reaction rates of the first and second stages of the overall reaction rate

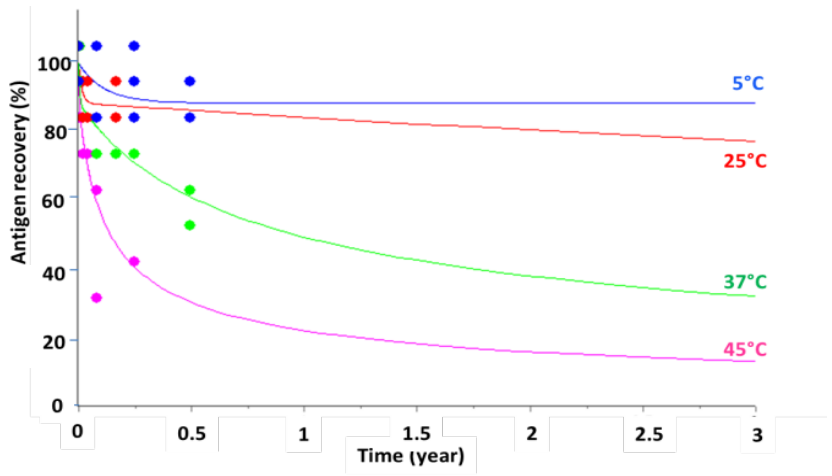
- **Taking advantage of advanced kinetics and statistics**
  - Non-linear regression methods adjusting kinetic parameters on stability data obtained under recommended storage conditions (+5°C ± 3°C) and under accelerated conditions (+25°C ± 2°C and +37°C ± 2°C)
  - Applying « good modeling practices » to describe degradation rates of vaccines, independently of the complexity of degradation pathways [2-4]

Case study #1: Inactivated virus

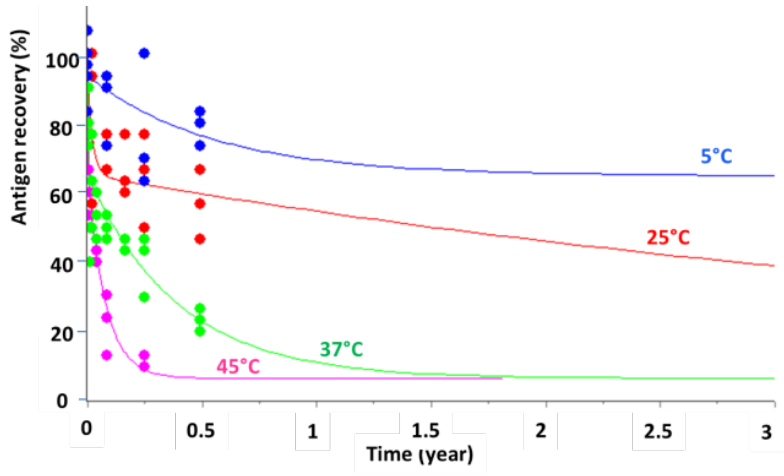
- Antigenicity determined by ELISA as a key stability indicating attribute for a polio vaccine
- 3 years of stability predicted based on 6 months data [5]



Serotype 1



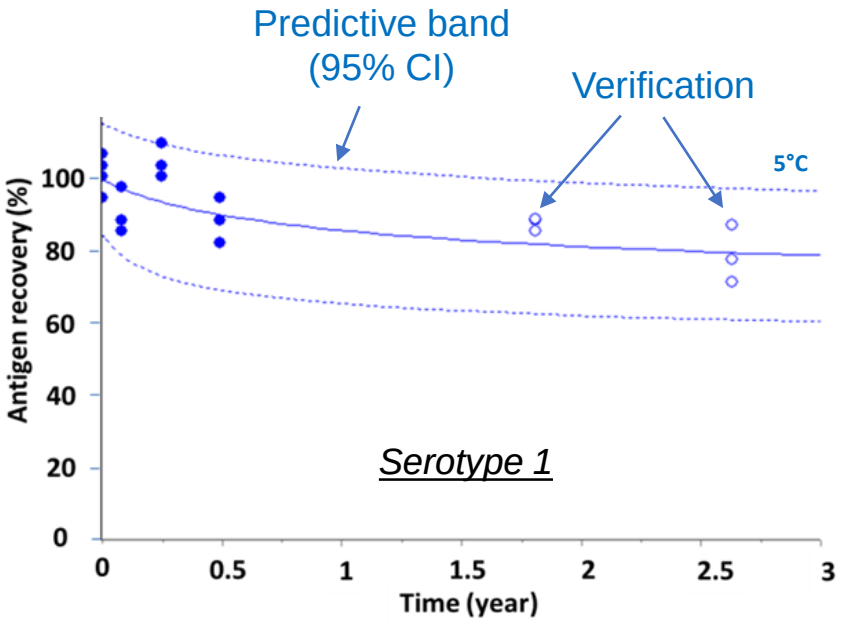
Serotype 2

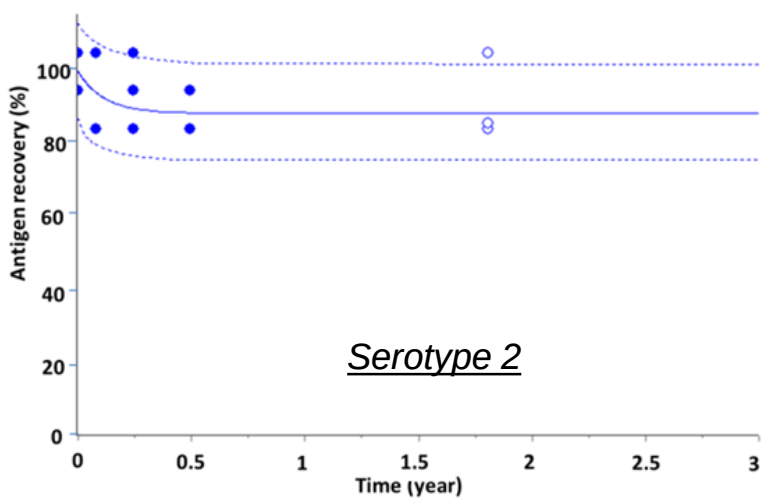


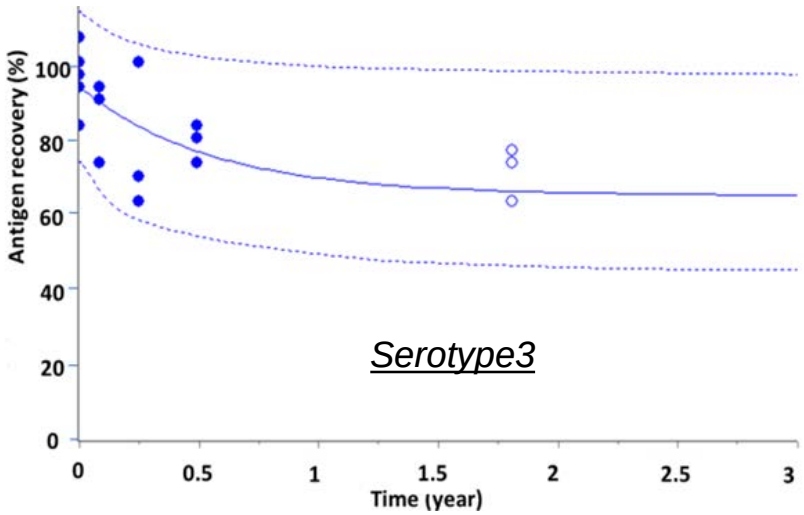
Serotype3

Case study #1: Inactivated virus

- Focus on 5°C storage temperature, predictive bands (95% CI) were determined for 3-years predictions by using bootstrap analysis
- Long-term stability of serotypes was conveniently predicted
- Confidence intervals can be integrated into the model by, for example, using bootstrap analysis
- Predictive bands contain experimental data determined after ~2 years for verification of models [5]



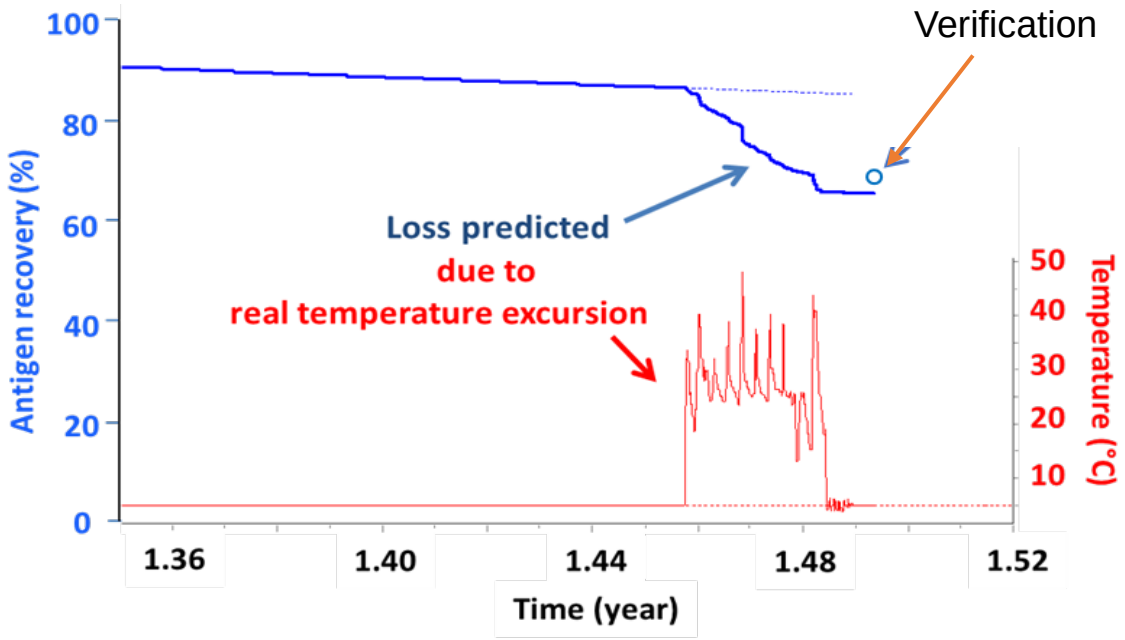




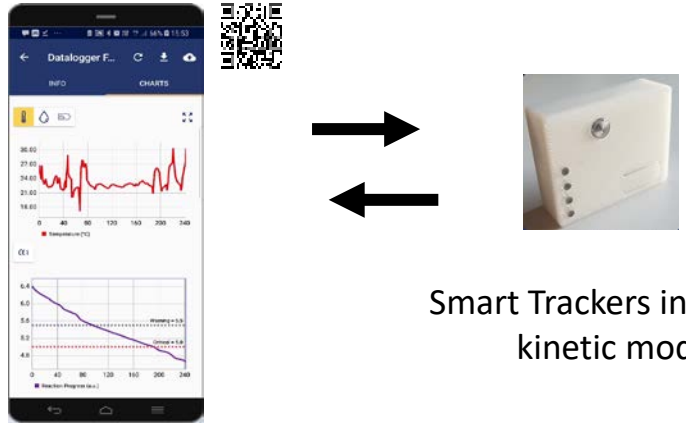
Case study #1: Inactivated virus

- Model can be used for a variety of purpose : from shelf-life prediction to impact of cold chain issues
- Example : loss of antigenicity during experimental shipments by car or by flight without refrigerated conditions was predicted with high accuracy (error of predictions ≤ 5%) [5]

Product in a cold chamber (2–8 °C) then 10 days travel at ambient temperature during shipment



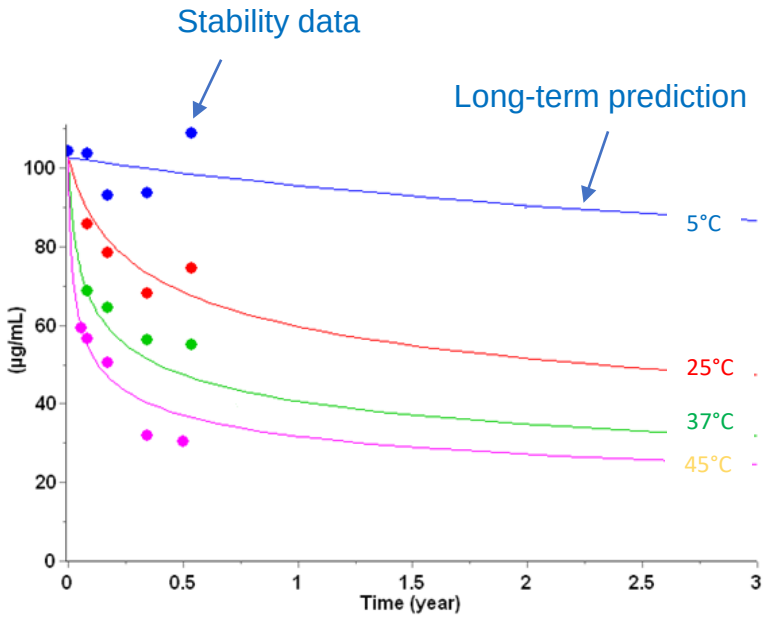
Monitoring in real-time the quality of vaccines during storage periods and shipments [4;6]

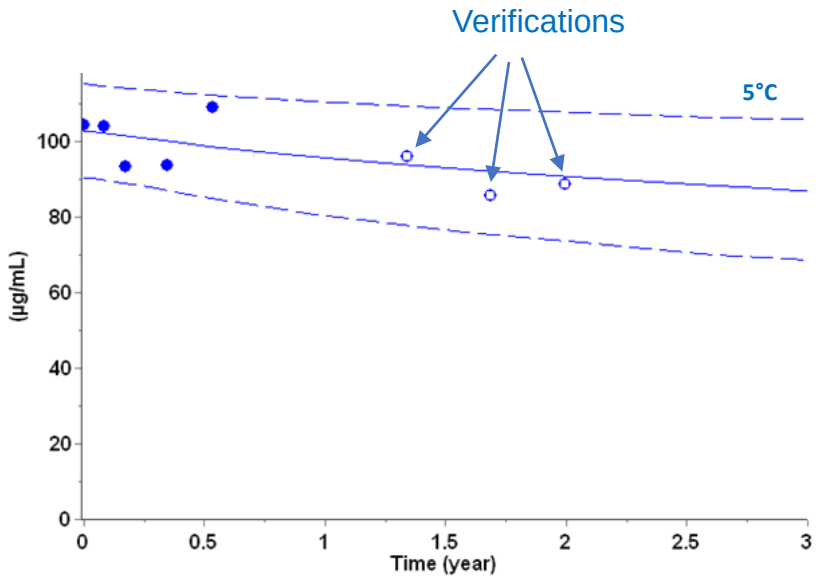


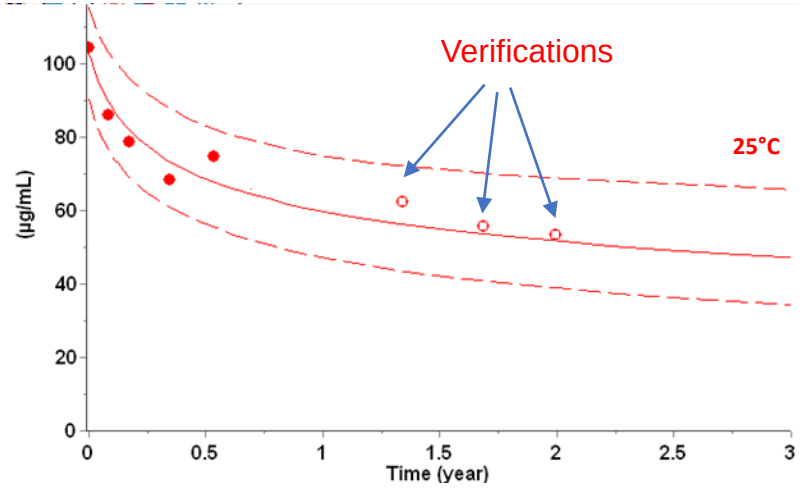
Smart Trackers integrating kinetic models

Case study #2: Protein-based vaccine

- Purity of the pneumococcal histidine triad protein D (PhtD) antigen determined by HPLC as a key stability indicating attribute
- 6 months stability data used for 3-years stability predictions at +5°C and +25°C
- Real 2-years stability data were accurately predicted, validating the kinetic model [7]

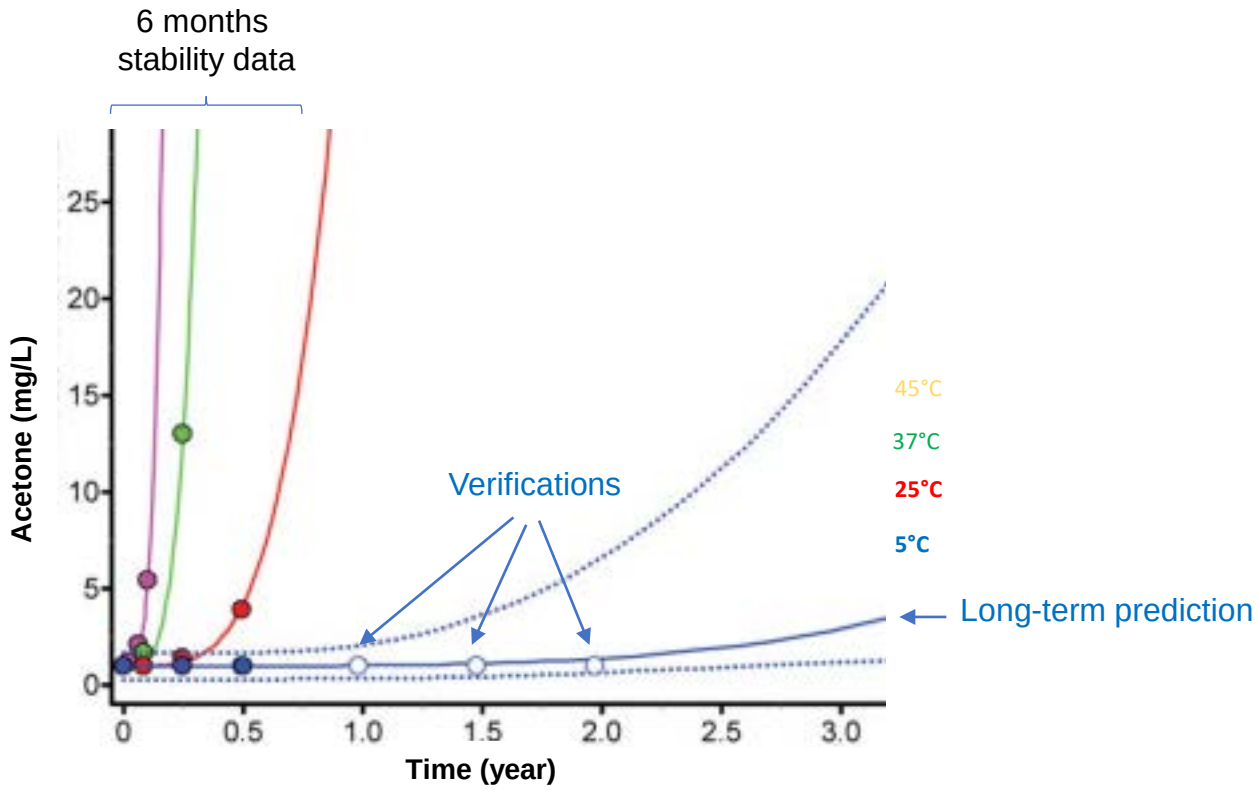






Case study #3: Emulsion-based adjuvant

- One of the major degradation products accumulating in the formulation as a result of oxidation of oil is acetone, considered as a stability indicative key attribute
- 6 months accelerated stability data were used to predict 3-years stability predictions at +5°C
- Real stability data for 2 years were accurately predicted, validating the kinetic model [7]



Accelerated Predictive Stability biologicals and vaccines

Main conclusions

- **Kinetic-based modeling approach was successfully used for:**
  - Stability predictions of protein and virus-based vaccines and emulsion-based adjuvant
  - Expiry date estimation of vaccines stored under recommended storage conditions
  - Evaluation of the impact of temperature excursions (cold chain breaks) during storage or shipments
- **Development of kinetic models describing well degradation of vaccines**
  - Ensured by the use of “good modeling practices” combining advanced kinetics and statistical analysis of stability data obtained under recommended storage conditions (+5°C) and under accelerated conditions (+25°C and +37°C)

Stability modeling and Regulators

- Various **Health Authorities** in Europe (France, Belgium, Germany), North America (Canada), South America (Brazil, Mexico) and Australia:
  - Are already aware of these methods for predicting shelf life and SL extensions
  - For various vaccines (multivalent, virus-based vaccines)

- Even if such modeling approaches are (still) not strictly described in the official guidelines (ICH, WHO), they are aligned with nonlinear regression methods mentioned inside and kinetic models can usually be proposed as supplementary data in dossiers

- Up to now, general feedback from the regulatory agencies is positive, since we take time to explain the approach and share examples/publications

- **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 by ICH QDG)

Accelerated Predictive Stability biologicals and vaccines

References

1. Stability modeling to predict vaccine shelf-life and evaluate impact of temperature excursions from the “cold chain”, D. Clénet, A. Saulnier, Poster, International Society for Vaccines, annual congress, Institut Pasteur, Paris, France, 5th-7th October **2017**

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

3. Stability Modeling in QbD: Accelerating Formulation Development and Predicting Shelf Life of Products, C. Roque, S.F. Ausar, N. Raham, D. Clénet, submitted for a PDA book dedicated on Quality by Design, **2020**

4. Accelerated Predictive Stability for Vaccines, D. Clénet, STP Pharma Pratique, July-August, **2020**

5. Accurate prediction of vaccine stability under real storage conditions and during temperature excursions, D. Clénet, Eur. J. Pharm. Biopharm., 125:76–84, **2018**

6. Continuous monitoring of shelf lives of materials by application of data loggers with implemented kinetic parameters, Roduit, B., Luyet, C. A., Hartmann, M., Folly, P., Sarbach, A., Dejeaifve, A., Dobson, R., Schroeter, N., Vorlet, O., & Dabros, M. Molecules, 24(12), 2217, **2019**

7. Advanced Kinetic Analysis as a Tool for Formulation Development and Prediction of Vaccine Stability, D. Clénet, F. Imbert, P. Probeck, N. Rahman, S.F. Ausar, S.F., J. Pharm. Sci. 103:3055–3064, **2014**

Vaccine specificities and commonalities vs biotherapeutics

- The presented data demonstrate that the use of advanced modelling approaches, along with the increased use of platform knowledge, make stability modelling a robust approach for vaccine stability assessment.

- Following the same principles, these approaches are increasingly being accepted for biotherapeutics.

- 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.

WHO- CEPI- Industry reflections*

- Using modelling and/or extrapolation)/platform data. This approach is specific to the type of vaccine and product. Therefore, it would be agreed upfront with the reference country through official consultation. The consultation outcome would then be shared and applied by reliance by other NRAs.

- Using stability data generated on clinical, small scale, or engineering batches in place of commercial batches in the initial licence, as was indicated in the EMA/FDA report on early access quality approaches

- Allowing data generation under normal conditions on the final process/final scale to become confirmatory rather than pivotal

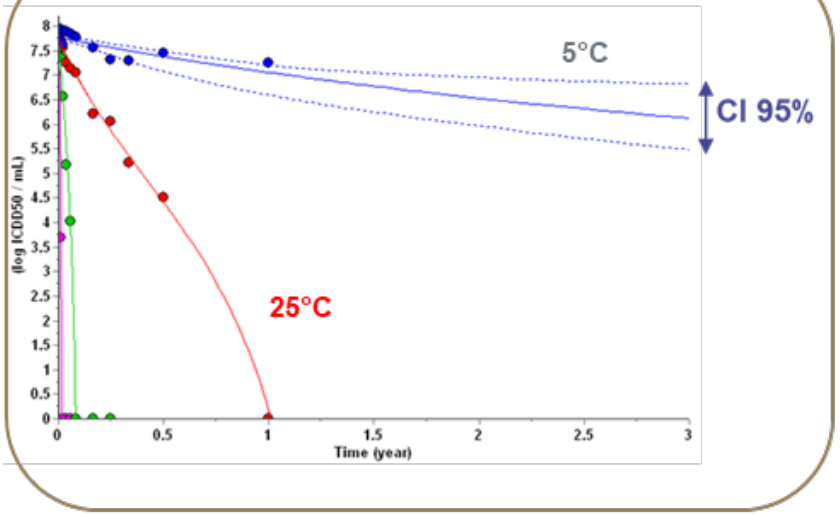
* *see also WHO CONSIDERATIONS FOR EVALUATION OF COVID19 VACCINES- Points to consider for manufacturers of COVID19 vaccines (Version 25 November 2020)*

Accelerated Predictive Stability biologicals and vaccines

Back-up

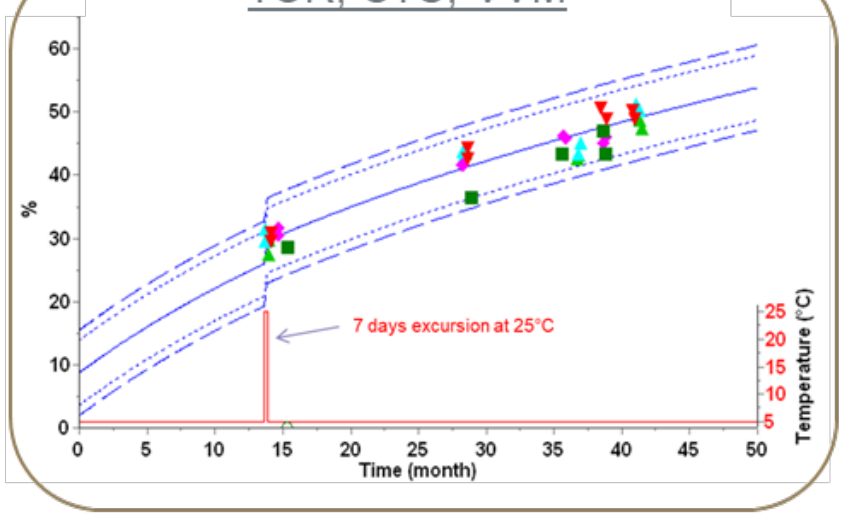
Once kinetic model identified… Various applications emerge

Shelf-life estimation

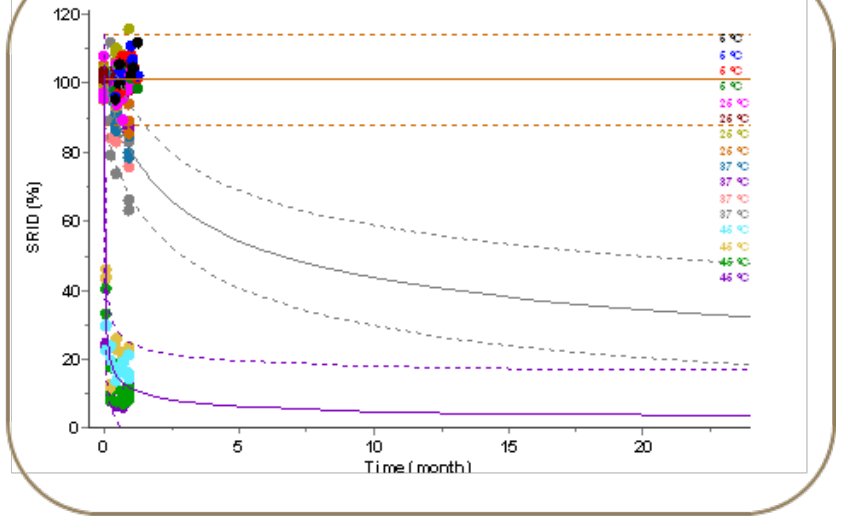


Excursions of temperature

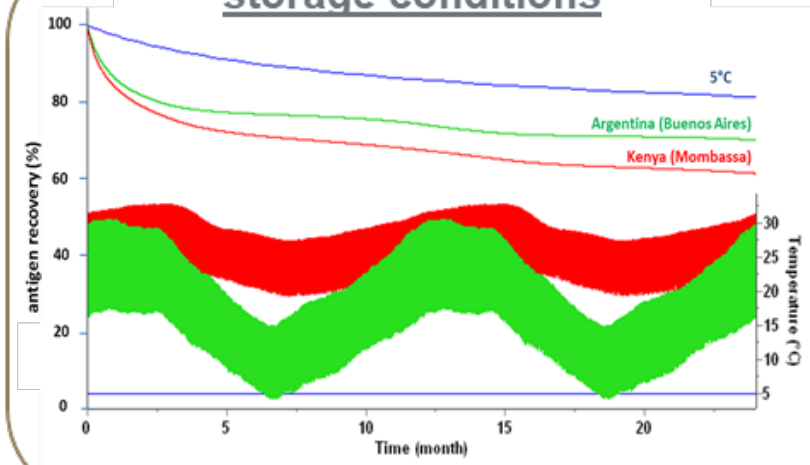
TOR, CTC, VVM



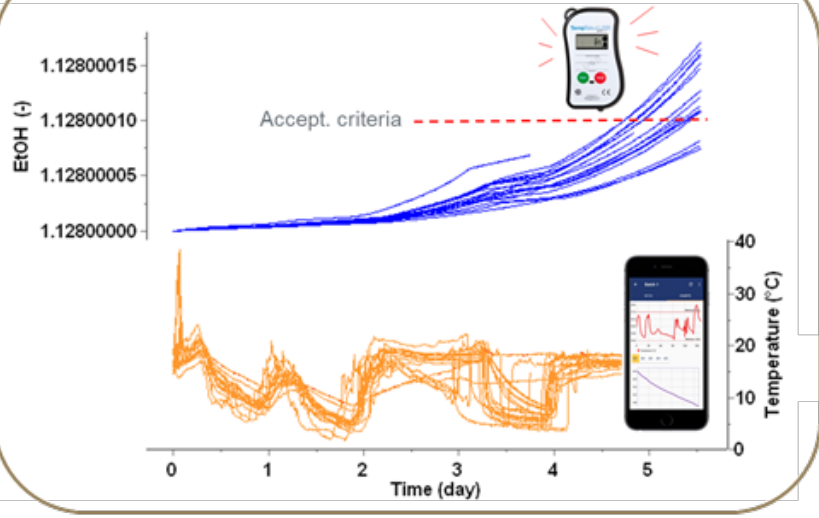
Batch-to-batch comparison



Recommend appropriated storage conditions

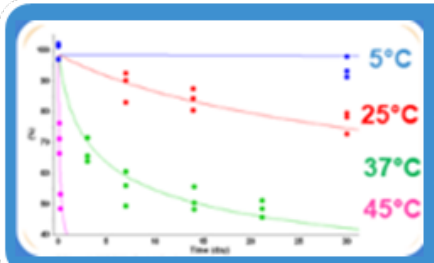


Real-time shelf-life monitoring



Good Modeling Practices for Stability Predictions

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

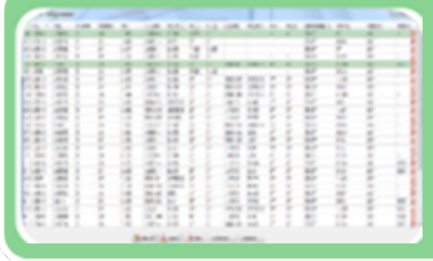
Arrhenius, 1st order, Autocatalytic, Prout-Tompkins, Avramy-Erofeev, Sourour-Kamal, …

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

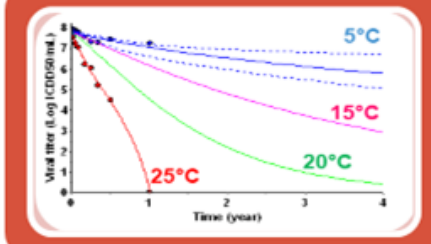


Identify the more appropriate kinetic model

- The model describing best the reaction progress is identified according to various statistical parameters (quality of fit by RSS, model comparison scores by AIC, BIC, …)

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

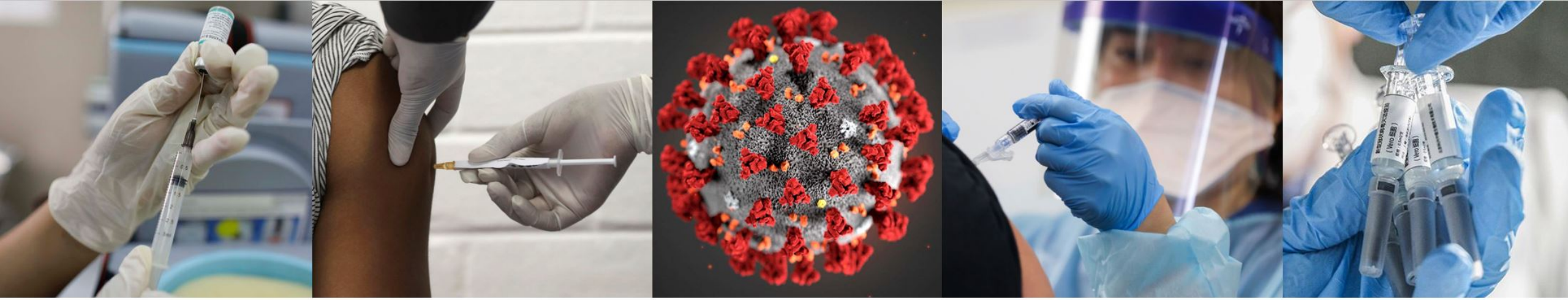
4



Determine accuracy of predictions (confidence interval)

- Use the selected model to predict reaction progress under any time / temperature domains (isotherm, non-isotherm, excursions of temperature, datalogger profiles during shipments, …)
- Predictive bands (95% conf. interval) are obtained by appropriated statistical analysis (boostrap, …)

Questions?

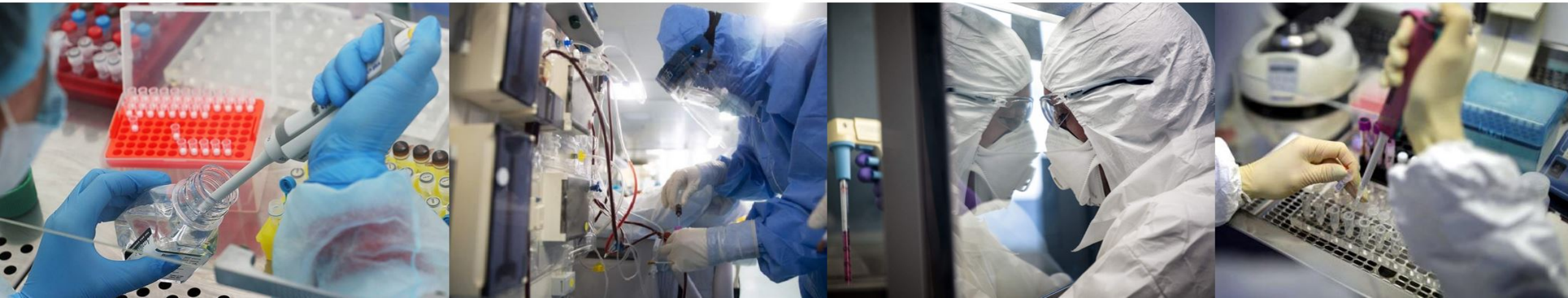


WHO assessment stability data to ensure programmatic suitability

09 December 2020

COVAX Workshop: “Best practices for determining and updating storage temperate and shelf- life”

Carmen Rodriguez Team lead vaccines PQ
Department of Regulation and Prequalification (RPQ)



Goal & objectives

Goal of this WHO work: to optimize access & availability to safe, efficacious, quality-assured COVID-19 products by further aligning regulatory processes

Objectives of today's presentation:

- Explain added value of PQ to ensure supply chain in LMIC
- Stability data requirements
- Challenges/way forward

Purpose of WHO PQ

- A service provided to UN purchasing agencies.
- Provides independent opinion/advice on the quality, safety and efficacy of vaccines for purchase
- Ensures that candidate vaccines are suitable for the target population and meet the needs of the programme
- Ensures continuing compliance with specifications and established standards of quality

Stability review: added value WHO assessment

Aspects	Guidelines	Outcome	Supply chain in countries
Regulatory		**Shelf life and storage condition**	▪ Stability profile: Cold chain requirements/ suitability for use under field conditions, shelf life and remaining shelf life at time of shipment ▪ Packaging: Volume of cold space required, primary and secondary packaging characteristics ▪ Applicability of WHO Multidose vial policy ▪ Ensure applicability of an adequate vaccine vial monitor (VVM) type ▪ Compliance with WHO Guidelines on International Packaging and shipping of vaccines
Programmatic suitability		**Suitability in LMIC**	

WHO considerations for evaluation of Covid 19 vaccines*.

Main outcome	Submission requirements	Assessment process	Programmatic suitability & post approval monitoring
Storage conditions and shelf-life, (in-use storage conditions and shelf-life).	**Stability data for the vaccine produced at the scale intended for distribution**	• **scientific risk-based approach** to determine the proposed vaccine shelf life in the absence of real time stability data on the commercial batches • **Consideration of** platform stability data, prior knowledge from early clinical batches or statistical modelling may also be applied to forecast expiry of product.	• **storage at less than -20°C:** • **if storage below +2°C, period, a minimum period of storage between +2°C and +8°C is required** **Assistance with regards to infrastructure for vaccine storage and distribution at required temperatures.**

- **The summary should include results, from forced degradation studies and stress conditions, as well as conclusions with respect to storage conditions and retest date or shelf-life, as appropriate.**
- **Information on the analytical procedures used to generate the data and validation of these procedures should be included**

* Evaluation criteria https://www.who.int/medicines/regulation/prequalification/prequal-vaccines/resources/1_EOI-Covid-19_Vaccines.pdf?ua=1

Path forward

Challenge	Requirements	Solution
International Transportation		• ultra-low shipment supplement to the WHO shipping guidelines will be developed published in Q1 2021) • Shipping validation to show evidence that the amount of dry ice used is able to maintain the temperature inside the shipping container at between - 80 degrees to – 60 degrees for 48 hrs.
Containers		• Passive Insulated polystyrene boxes can be used with dry ice as the coolant. • Dry ice sublimates at about 3-5 kg per 24 hrs. so the weight of dry ice needs to be factored-in • For a 48 hr. trip for example it would be safe to have about 6-10 kg of dry ice

Path forward

Challenge	Requirements	Solution
Dataloggers		• Current WHO prequalified data loggers cannot perform at temperatures below -30 degrees. • WHO has been in touch with manufacturers of devices which can perform down to -80 degrees. • Specifications for ultralow data loggers available in Q1 2021
Vaccine vial monitor		• WHO has been in touch the VVM manufacturer and they are ready to develop VVMs of appropriate categories to suit the stability of ultralow temperature vaccines as needed • There are currently specifications for VVM1 and there is they have the capability to develop VVM0.5 and 0.25 as well

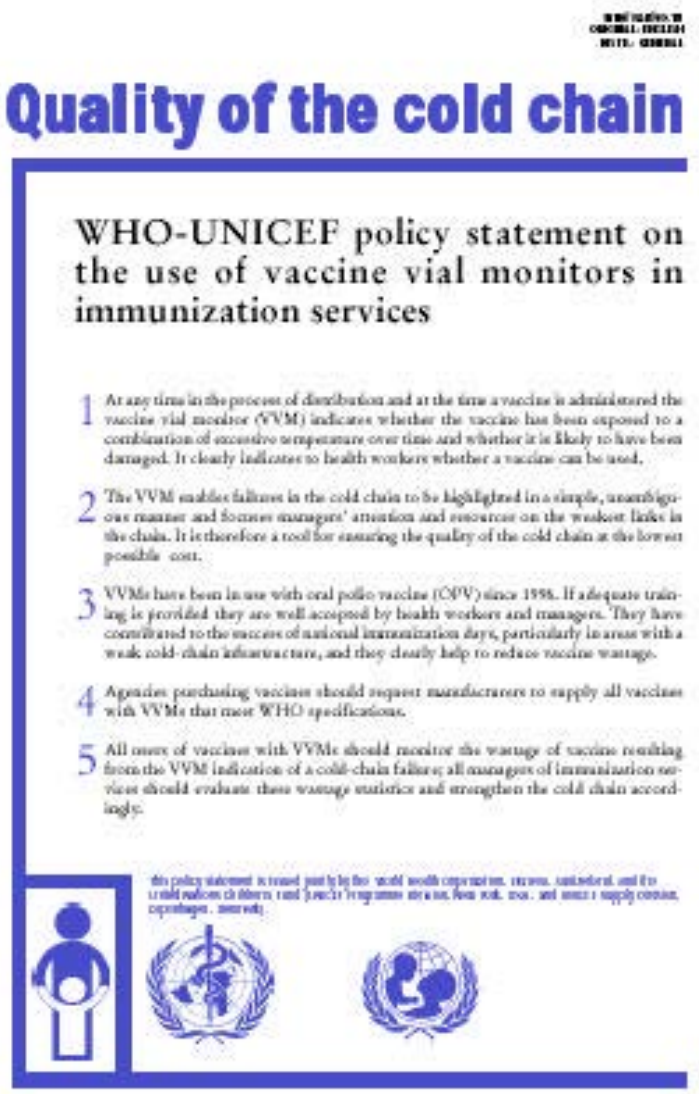
Selection of VVM category

Review of real time-real conditions stability data in addition to other conditions

- Temperature: 2-8°C, 25°C and 37°C
- Time: 3,6,9,12,18 and every 6 months afterwards

All tests performed to support shelf life

USE OF THE VACCINE UNDER THE RECOMMENDED STORAGE CONDITIONS



Quality of the cold chain

WHO-UNICEF policy statement on the use of vaccine vial monitors in immunization services

1 At any time in the process of distribution and at the time a vaccine is administered the vaccine vial monitor (VVM) indicates whether the vaccine has been exposed to a combination of excessive temperature over time and whether it is likely to have been damaged. It clearly indicates to health workers whether a vaccine can be used.

2 The VVM enables failures in the cold chain to be highlighted in a simple, unambiguous manner and focuses managers' attention and resources on the weakest links in the chain. It is therefore a tool for ensuring the quality of the cold chain at the lowest possible cost.

3 VVMs have been in use with oral polio vaccine (OPV) since 1998. If adequate training is provided they are well accepted by health workers and managers. They have contributed to the success of national immunization days, particularly in areas with a weak cold-chain infrastructure, and they clearly help to reduce vaccine wastage.

4 Agencies purchasing vaccines should request manufacturers to supply all vaccines with VVMs that meet WHO specifications.

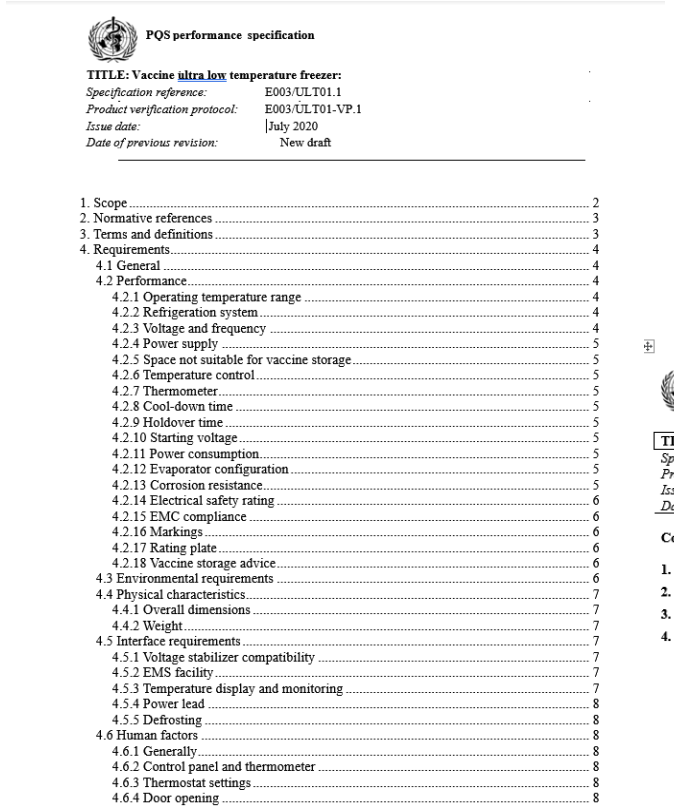
5 All users of vaccines with VVMs should monitor the wastage of vaccine resulting from the VVM indication of a cold-chain failure; all managers of immunization services should evaluate these wastage statistics and strengthen the cold chain accordingly.

Category	N° days to reach end point 37°C	N° days to reach end point 25°C	Time to end point at 5°C
VVM30	30	193	> 4 years
VVM14	14	90	> 3 years
VVM7	7	45	> 2 years
VVM2	2	N/A	225 days

Path forward: Country preparedness

- **Ultra-low temperature freezers:**
- WHO specifications for ULT freezers and associated power requirements, and transport cold boxes will be published in December 2020

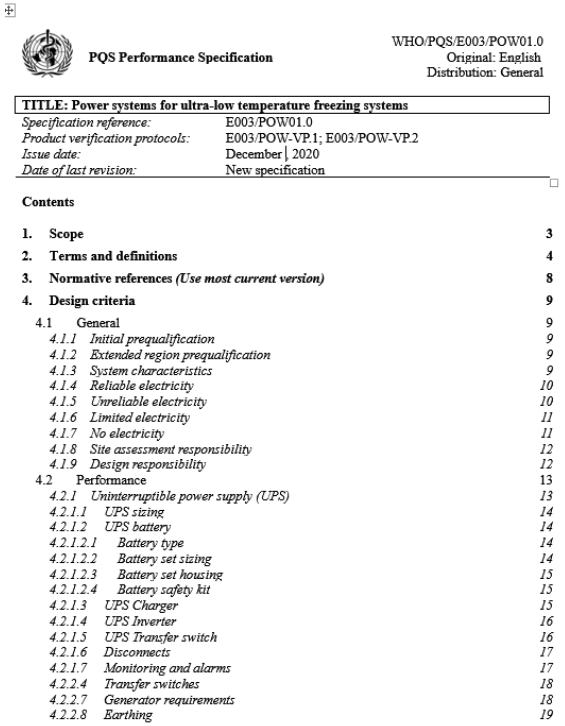
- **Training**
- Appropriate cold chain and vaccine management training package tailored to ultralow temperature vaccines for health workers will be needed, including training on safety and the provision of safety equipment such as gloves



PQS performance specification

TITLE: Vaccine ultra low temperature freezer:

Specification reference: E003/ULT01.1
Product verification protocol: E003/ULT01-VP.1
Issue date: July 2020
Date of previous revision: New draft



PQS Performance Specification

WHO/PQS/E003/POW01.0
Original: English
Distribution: General

TITLE: Power systems for ultra-low temperature freezing systems

Specification reference: E003/POW01.0
Product verification protocols: E003/POW-VP.1; E003/POW-VP.2
Issue date: December 2020
Date of last revision: New specification

Contents

Additional information:

Technical Report Series on Stability of vaccines TRS962 Annex 3

VVM performance specs WHO/PQS/E006/IN05.4

Procedure and Questions and Answers

https://www.who.int/medicines/regulation/prequalification/prequal-vaccines/EUL_PQ_Vaccines/en/

Target product profile

https://www.who.int/docs/default-source/blue-print/who-target-product-profiles-for-covid-19-vaccines.pdf?sfvrsn=1d5da7ca_5&download=true

Evaluation criteria and EOI. https://www.who.int/medicines/regulation/prequalification/prequal-vaccines/resources/1_EOI-Covid-19_Vaccines.pdf?ua=1

Roadmap https://www.who.int/publications/m/item/roadmap-for-evaluation-of-astrazeneca-azd1222-vaccine-against-covid-19

Contact: EUL@who.int

World Health Organization

WHO/Otto B.

WORKING TOGETHER

Department of Regulation and Prequalification, WHO

Thank you