

WHO Guidelines on Stability Evaluation of Vaccines

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WHO Guidelines on Stability Evaluation of Vaccines



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- Overview of WHO Guideline
- Stability quality attributes
- Basic principles of vaccine stability
- Stability during development
- Stability supporting licensure
- Post licensure stability evaluation
- Challenges to implementation

Overview of WHO Guidelines



- Acknowledges the importance of stability to the success of immunization programs worldwide
- Provides a scientific basis and guiding principles for evaluation of stability over the vaccine lifecycle
 - For the purpose of clinical trial monitoring
 - For licensing
 - For post licensure monitoring
- Adopted by the 57th meeting of the WHO Expert Committee on Biological Standardization, 23-27 October 2006



WHO/BS/06.2049 - Final
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GUIDELINES ON STABILITY EVALUATION OF VACCINES

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Adopted by the 57th meeting of the WHO Expert Committee on Biological Standardization, 23-27 October 2006. A definitive version of this document, which will differ from this version in editorial but not scientific details, will be published in the WHO Technical Report Series.

Overview of WHO Guidelines (cont.)



- Supported by implementation workshops
 - Seoul, Korea (Apr 2008)
 - Geneva, Switz. (Oct 2008)
- Workshop proceeding published in a special issue of *Biologicals*, November 2009, 37(6)

WHO/KFDA Joint Workshop on Stability Evaluation of Vaccines
April 23 - 25 2008, Seoul

IABS International Scientific Workshop CONFERENCE ANNOUNCEMENT

27-29 October 2008 - Geneva International Conference Centre (www.ctcg.ch/en)

Stability Evaluation of Vaccines

A Life Cycle Approach

Register on line at www.iabs.org/upcoming

The International Association of Biologicals (IABS), in association with the US National Institute of Allergy and Infectious Diseases (NIAID), UK National Institute for Biological Standards and Control (NIBSC), Germany's Paul Ehrlich Institut (PEI) and World Health Organization (WHO), is organizing an interactive conference to inform and assist regulators and industry in the implementation of the principles and approaches set out in the recently adopted WHO guidelines on the stability evaluation of vaccines.

The conference will hear from leading experts in the field, with contributions from the following (as speakers, panelists and sponsors):

<p>Monday 27th October</p> <p>Session 1</p> <ul style="list-style-type: none"> • WHO approach to stability evaluation of vaccines • Experiences from developing countries • Key issues to be addressed in the workshop <p>Session 2</p> <ul style="list-style-type: none"> • Goals of stability evaluation throughout the vaccine life cycle • Basic principles of stability • Quality problems of intermediates and final product <p>Session 3</p> <ul style="list-style-type: none"> • Studies supporting clinical and product development 	<p>Tuesday 28th October</p> <p>Session 4 (case study)</p> <ul style="list-style-type: none"> • Stability supporting product licensure • Cold chain break investigation process (Case Study) • Stability evaluation post licensure • Compatibility/stability plan (Case Study) • Continuous compatibility studies (Case Study) <p>Session 4</p> <ul style="list-style-type: none"> • Annual vaccines: Seasonal Influenza (Case Study) • Vaccines associated with high variable assays (Case Study) 	<p>Wednesday 29th October</p> <p>Session 5 (case study)</p> <ul style="list-style-type: none"> • Contract vaccine: Stability parameters defined by an external client case program for MMR-Vaccinia (Case Study) • Contract vaccine: DTaP-IV (Case Study) • Model format for stability report <p>Session 5</p> <ul style="list-style-type: none"> • Panel Discussion: <ul style="list-style-type: none"> (i) Compliance vs. Estimation Made easy & done (ii) Critical Minimum Specification & Release Specification (iii) Questions from the audience
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IABS: IABS, Pharmatier Consulting, Pharmatier, Bangkok, Ministry of Public Health, Thailand
 NIAID: Krasavak, Immunization, Vaccines and Biologicals Department, WHO
 PEI: Krause, Office of Vaccines, FDA
 WHO: Richard, IABS
 NIBSC: Head of Vaccines, Vaccines Section, Paul Ehrlich Institut
 PEI: Marie Perard, IABS
 WHO: Richard, IABS
 WHO: Shiu, Immunization, Vaccines and Biologicals Department, WHO
 WHO: South Africa
 WHO: Zoon, IABS, NIBSC

$$\ln(k) = a + b \cdot \text{Release} = \text{Spec} + b \cdot \text{Spec}$$

$$\text{Minimum Release Specification} = \text{Clinical Minimum} + \sum \hat{b}_i + z_{\alpha} \cdot \sqrt{\sum \hat{b}_i^2 S_{b_i}^2 + S_{\text{Assay}}^2}$$

Delegate fees: CHF250 non-commercial organizations; CHF350 commercial organizations; CHF100 discount for IABS members
 For further information please contact the conference secretariat at iabs@iabs.org



Stability Quality Attributes



- Stability quality attributes should include those properties which impact safety and/or efficacy
 - e.g., potency, sterility, etc.
- Note: all properties change over time; thus any parameter related to safety and/or efficacy should be part of the vaccine stability program
- Stability quality attributes should also include properties which impact stability over the course of shelf-life
 - e.g., increase in moisture over time for a lyophilized vaccine
- Similarly properties which impact stability should be part of the release specification for the product
 - Moisture of a lyophilized vaccine
 - pH of an adjuvanted vaccine

Basic Principles of Vaccine Stability



- A scientific basis of stability begins with understanding how vaccines degrade
 - First order kinetics
 - The rate of decay is [C] dependent

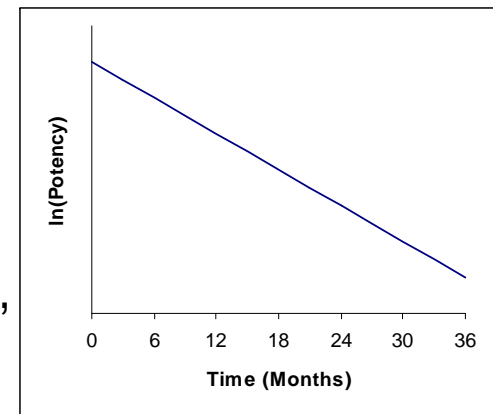
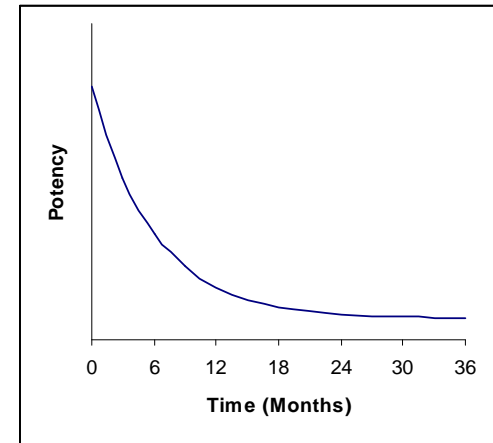
$$\text{Potency} = P_0 \cdot e^{-k \cdot t},$$

where P_0 = initial potency,
 k = degradation rate.

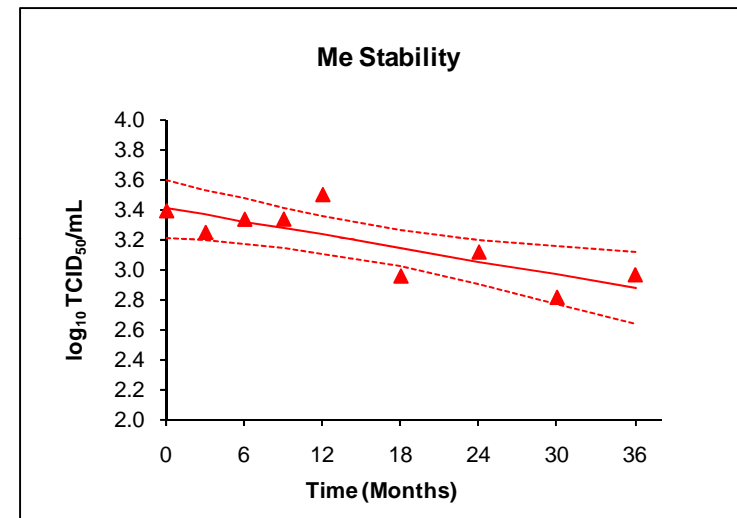
- Linear in log potency

$$\ln(\text{Potency}) = \ln(P_0) - k \cdot t$$

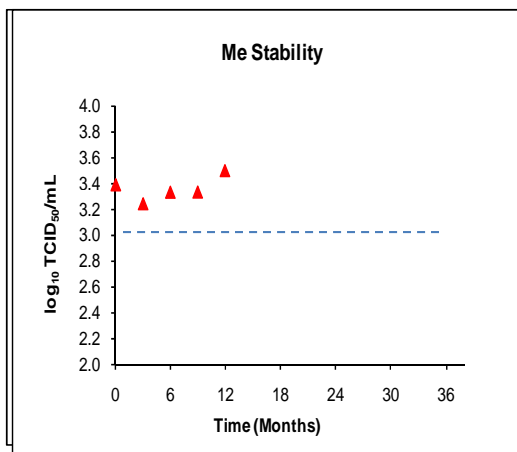
- The log transformation also “normalizes” potency measurements, and “stabilizes” variability across the potency range



- A first order kinetics equation (log of potency) is fit to vaccine stability data using least squares regression
- Like all statistical estimates, the least squares regression equation is associated with variability
 - This can be expressed as a confidence interval on the regression line
 - Forms the basis for ICH shelf-life determination

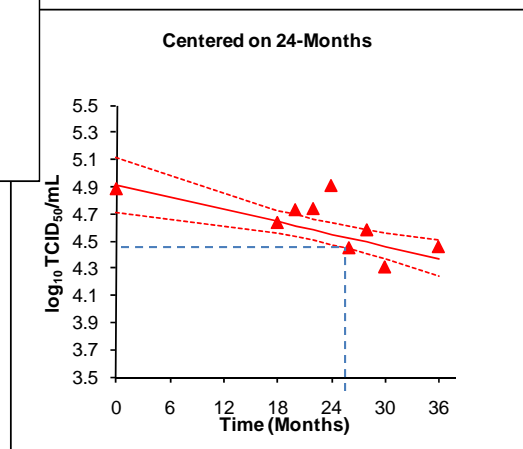


- Study design should acknowledge the goal of the stability study
 - ICH intervals are designed to provide sufficient data at time of filing
 - Statistical design can be used to minimize uncertainty



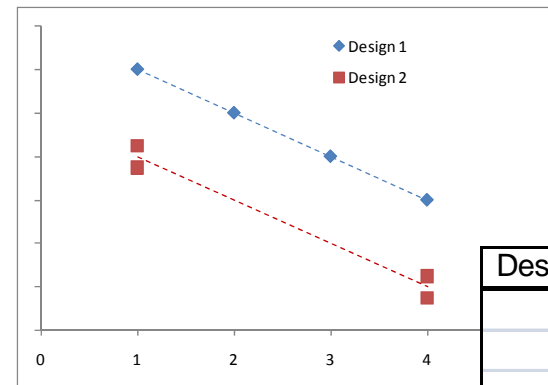
– Shelf-life Determination

- Data clustered at the desired shelf-life will minimize impact of uncertainty on SL determination



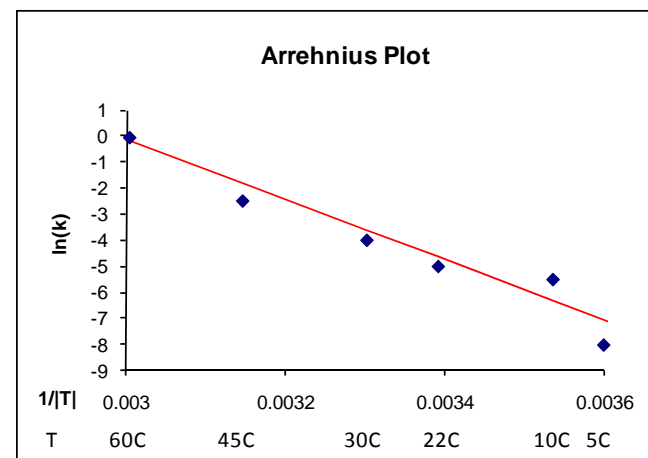
– Determination of loss rate

- Testing at beginning and end will reduce uncertainty on the loss rate



Design 1	Design 2
1	1
2	1
3	4
4	4
$s_b=0.45$	$s_b=0.33$
Reduction=25%	

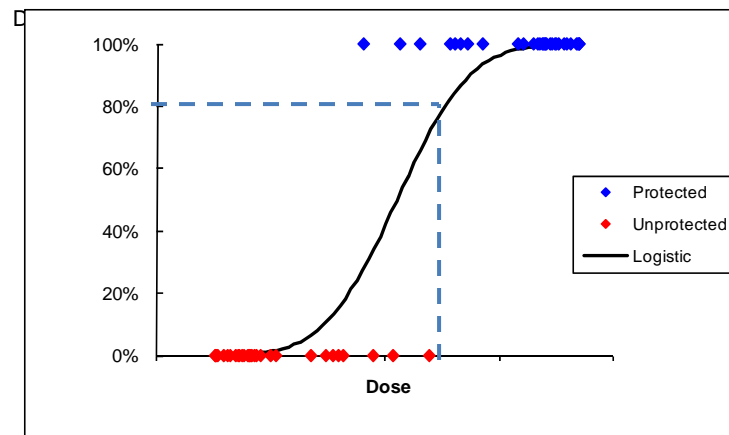
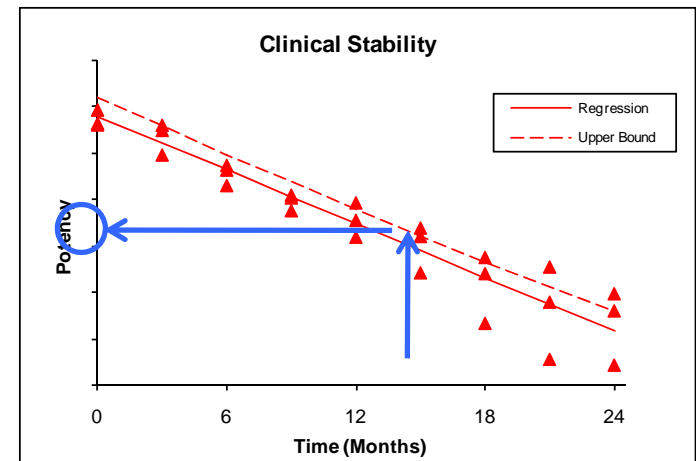
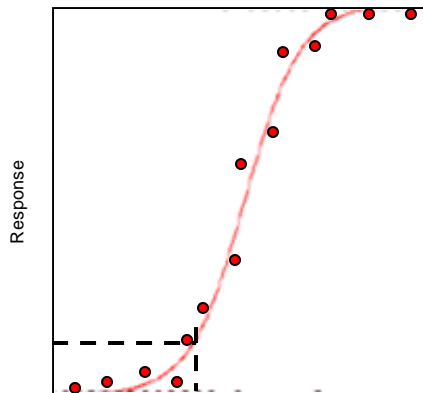
- Strategic use of accelerated stability data
 - Understanding vaccine stability
 - Mechanism of degradation
 - Kinetics model
 - Formulation development
 - Impact of bulk stability on final product stability
 - in lieu of sequential stability
 - Benchmark for vaccine changes
 - Process change
 - Facility change



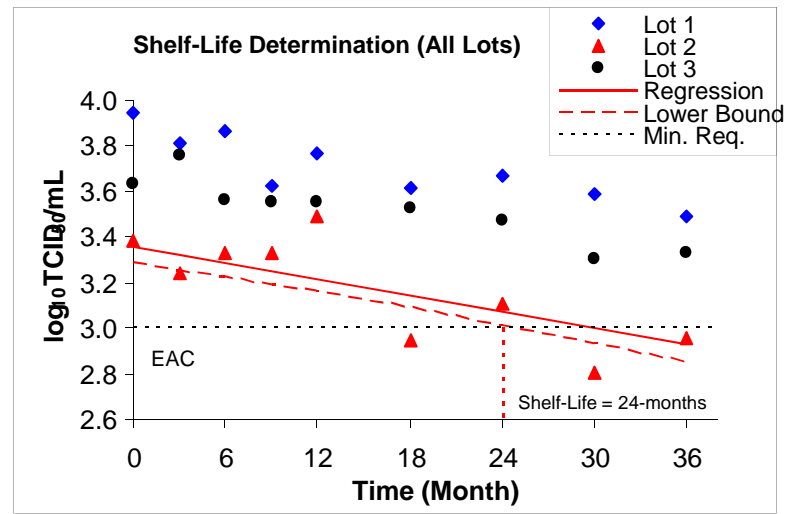
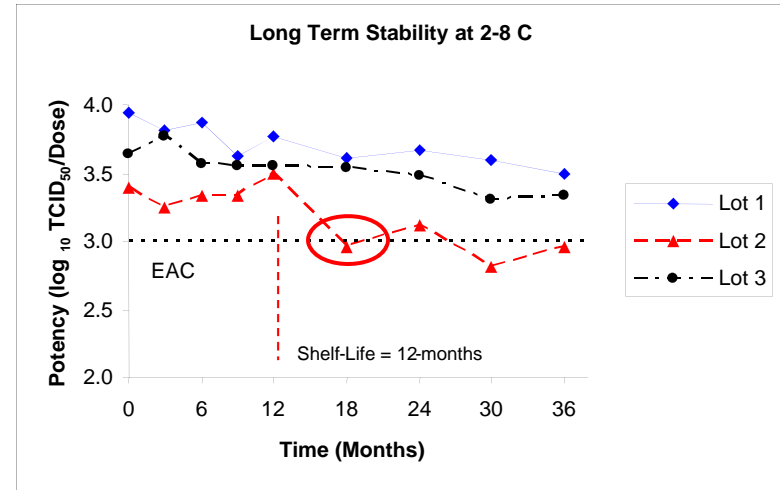
Stability During Development (cont.)



- Use clinical stability to define what the subject received, and thereby specifications
 - Using immunogenicity as the endpoint, interpolate the potency associated with a clinical correlate of efficacy
 - Using efficacy as the endpoint, perform a logistic analysis and interpolate the dose corresponding to a desired efficacy claim



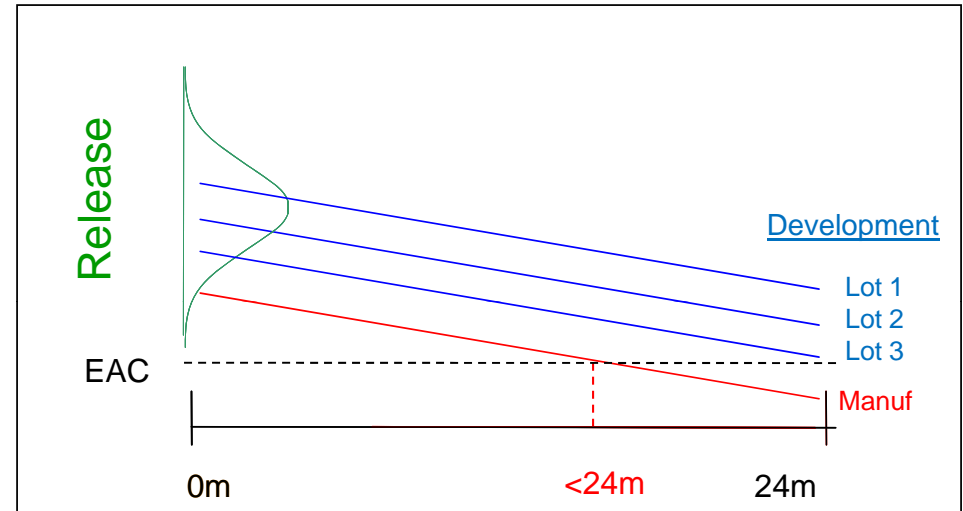
- Shelf-life determination – measles example
 - Is shelf-life 12-months due to a stability measurement at 18-months for lot 2 which falls below the expiry acceptance criteria (EAC)?
 - “Compliance Model”
 - ICH Q1E defines shelf-life as the time where the lower bound on the confidence interval intersects the EAC
 - “Estimation Model”
 - Risk based approach



Stability Supporting Licensure (cont.)



- Note: Shelf-life determination does not account for variability in release potencies of future manufactured lots
 - A manufactured lot released below the stability lots will have EAC before end of shelf-life
- A minimum release limit assures EAC by end of shelf-life
 - Calculated from combination of accumulated losses over shelf-life, together with statistical uncertainties

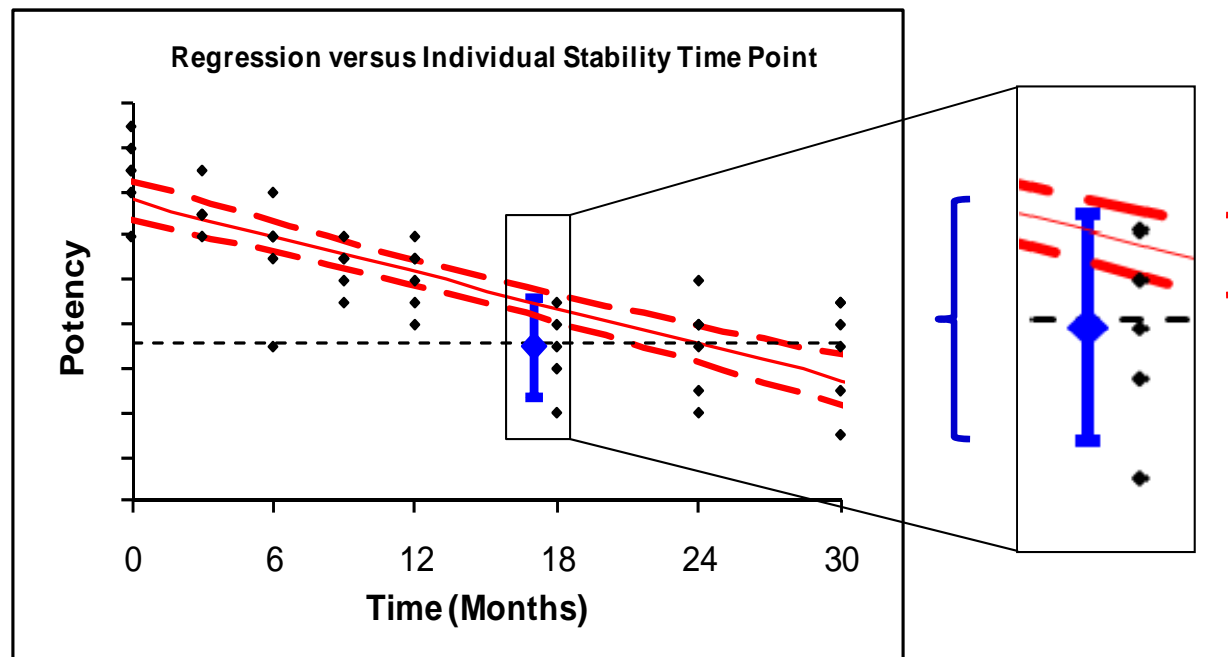


$$\text{Minimum Release} = \text{EAC} + \sum t_i b_i + t_{df} \sqrt{\sum t_i^2 s_{b_i}^2 + s_{\text{Assay}}^2}$$

Post Licensure Stability Evaluation



- Similar to shelf-life determination, stability modeling should be utilized to estimate product quality during stability monitoring
 - Highly variable measurements yield sporadic stability OOS results
 - The stability model yields a more precise estimate of vaccine quality

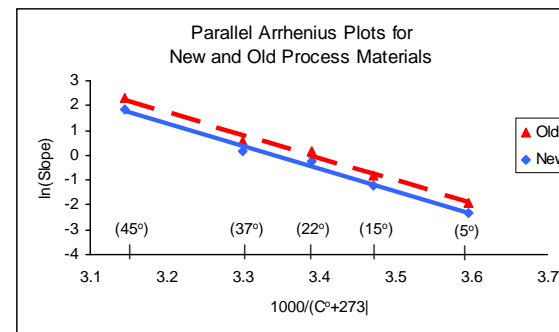
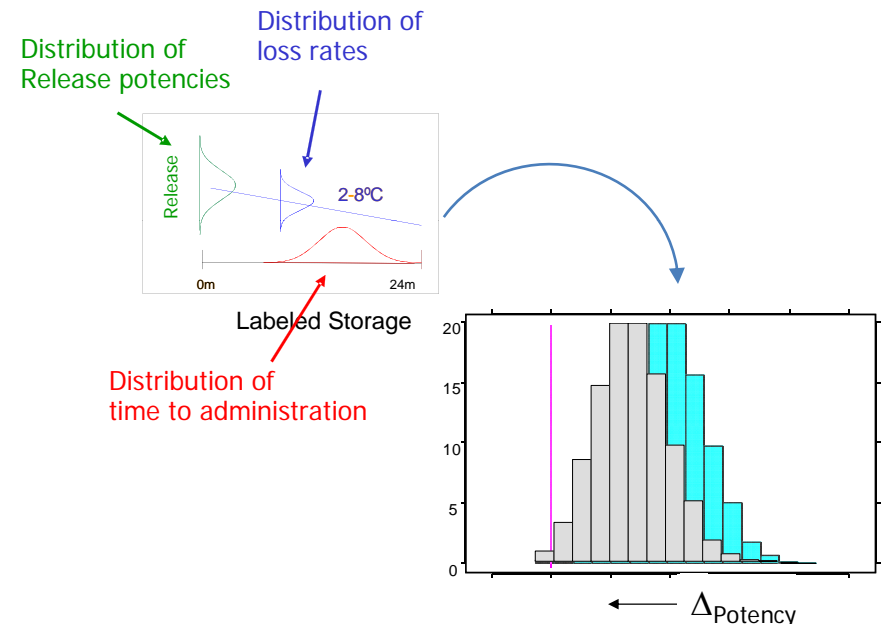


Post Licensure Stability Evaluation (cont.)



- Stability comparison after a process or facility change

- Stability is a product quality attribute
- Distribution modeling can be used to determine an acceptable change in stability rate
 - Using distributions of release, slope, and time to administration
 - Can determine the distribution of expiry potencies; a shift in the distribution of expiry potency can be used to derive a limit on the change in degradation rate
- Accelerated stability can be used to facilitate an early evaluation of a change in stability



Challenges to Implementation

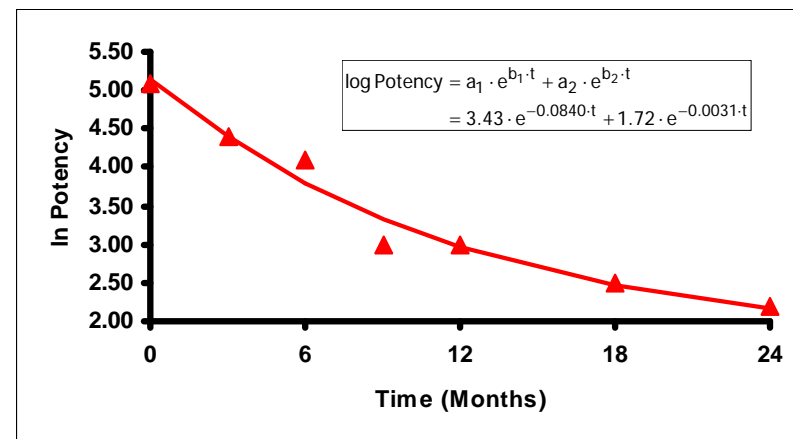
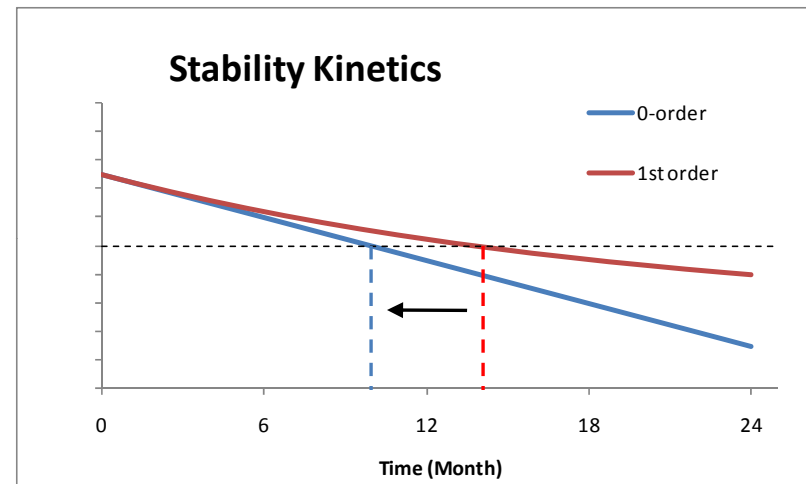


- Statistical thinking and modeling
 - Appreciation of variability and risk
 - Growing awareness of the need for skilled statisticians in nonclinical development
 - Statistical approaches to bioassay development, validation, and maintenance
 - Application of design of experiments to support quality by design
 - Statistical process control
 - Stability modeling and comparability strategies
 - Statistical training of industry and regulatory scientists
 - User friendly software solutions

Challenges to Implementation (cont.)



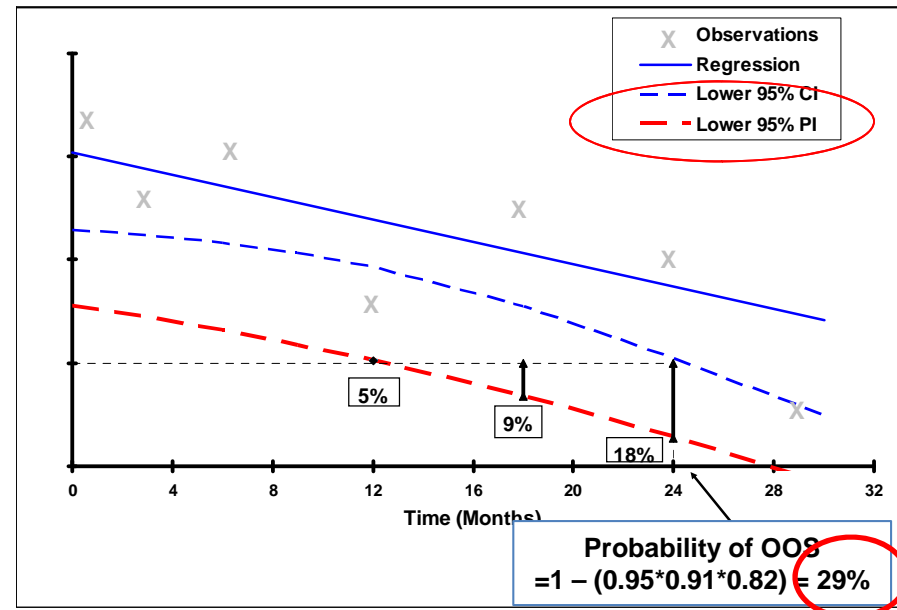
- Inaccurate stability modeling can lead to poor estimates of vaccine shelf-life
 - The default model for stability of vaccines is a 1st order kinetics model
 - Modeling by 0-order kinetics can lead to underestimation of shelf-life, and limitations on vaccine supply
 - Some vaccines degrade by higher order kinetics, leading to complex stability modeling



Challenges to Implementation (cont.)



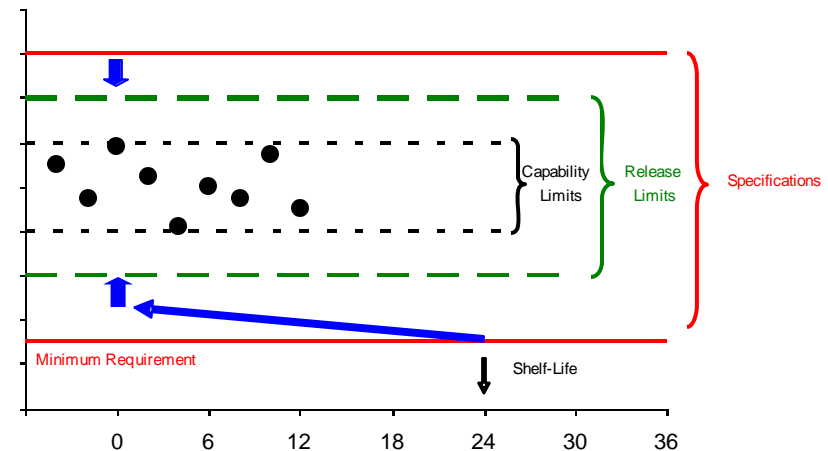
- Harmonization of stability modeling and stability monitoring
 - ICH shelf-life determination uses a model of the mean product stability profile
 - . . . however, stability OOS results are cited during post licensure studies
 - Ex., a batch which yields a 24-month shelf-life pre-licensure would have a ~30% chance of yielding a stability OOS if tested post licensure
 - Post licensure data should be statistically modeled to reduce risk of failing a good lot



Challenges to Implementation (cont.)



- Application to legacy products which are controlled to target
 - Legacy vaccine specifications are typically established to assure **consistency** at release
 - No provision for product stability
 - Release and EAC are the same
 - The WHO Guidelines should be applied to vaccines which have been developed with a vision towards supporting release and expiry requirements



- The WHO Guidelines on Stability Evaluation of Vaccines provides a scientific framework for assuring vaccine quality throughout shelf-life
- Appropriate statistical design and analysis reduces the uncertainty in vaccine stability evaluation, and thereby risk
- Implementation of the guidelines has both statistical and practical challenges which must be addressed to help assure adequate supply of quality vaccines to the world