WHO Guidelines on Stability Evaluation of Vaccines

Presented by Tim Schofield
Director, US Regulatory Affairs
GSK Biologicals

WHO Guidelines on Stability Evaluation of Vaccines

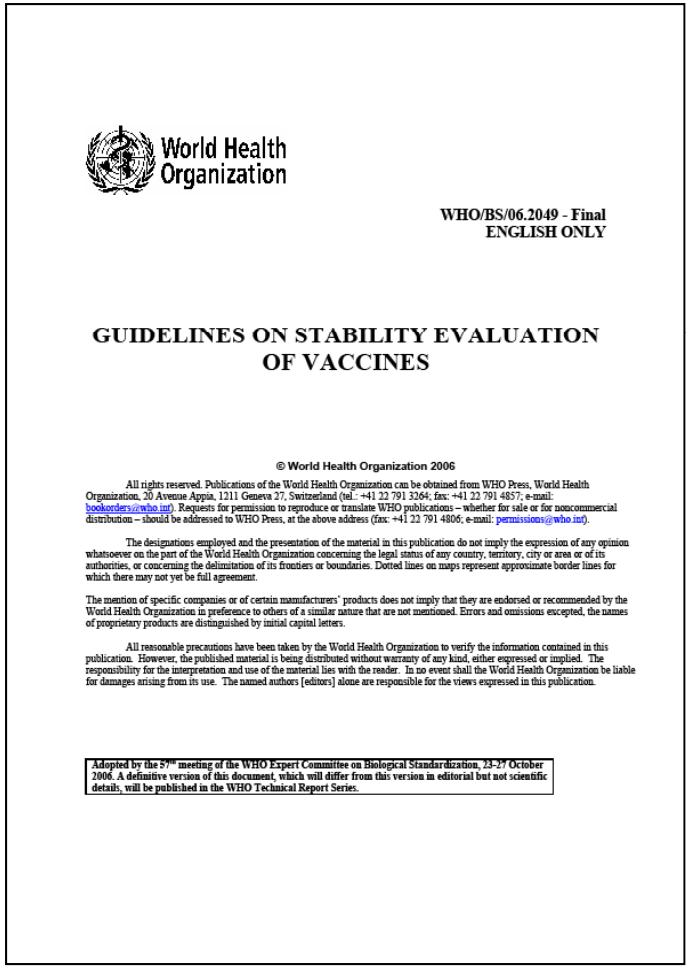
The views and opinions expressed in the following PowerPoint slides are those of the individual presenter and should not be attributed to Drug Information Association, Inc. (“DIA”), its directors, officers, employees, volunteers, members, chapters, councils, Special Interest Area Communities or affiliates, or any organization with which the presenter is employed or affiliated.

Outline

- 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 Standarization, 23-27 October 2006



World Health Organization

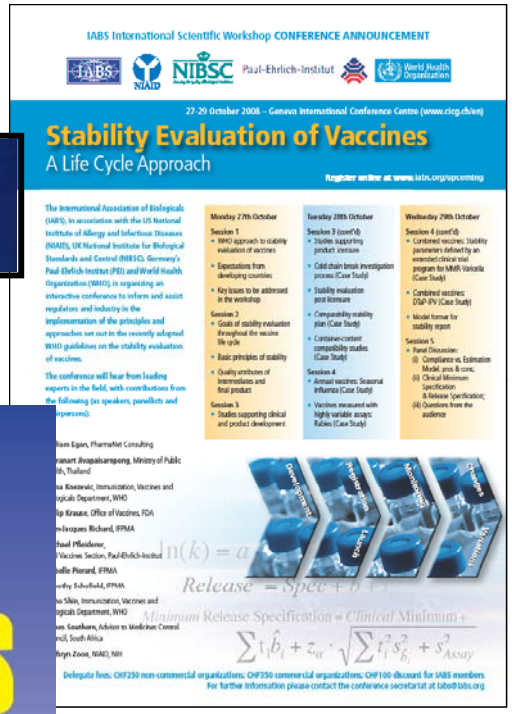
WHO/BS/06.2049 - Final
ENGLISH ONLY

GUIDELINES ON STABILITY EVALUATION OF VACCINES

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)

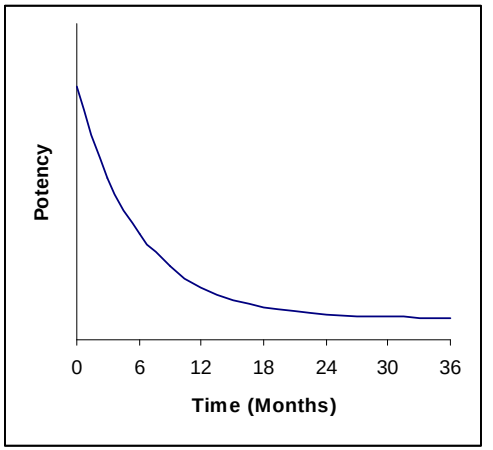
Stability Quality Attributes

- 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

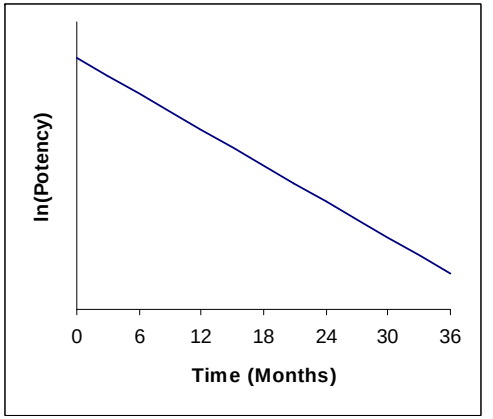
- A scientific basis of stability begins with understanding how vaccines degrade
  - First order kinetics
    - The rate of decay is [C] dependent

$$\text{Potency} = P_0 \cdot e^{-k \cdot t},$$
$$\text{where } P_0 = \text{initial potency},$$
$$k = \text{degradation rate}.$$



    - Linear in log potency

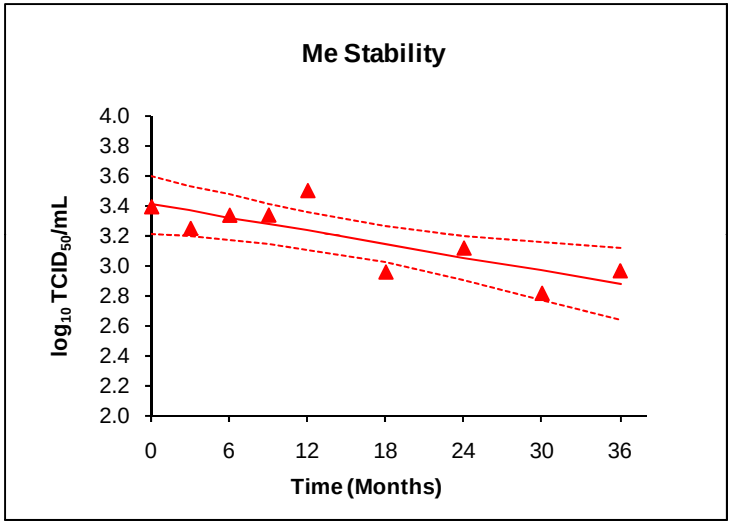
$$\ln(\text{Potency}) = \ln(P_0) - k \cdot t$$



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

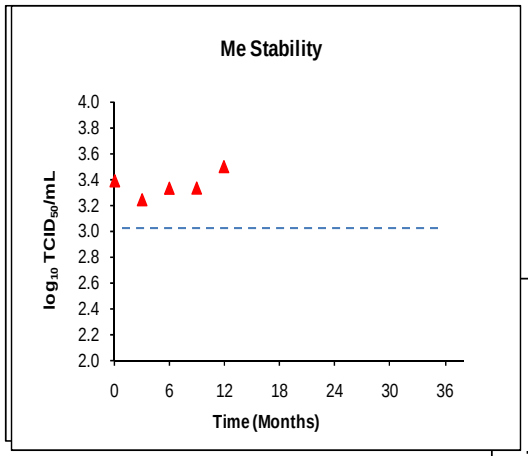
Basic Principles of Vaccine Stability (cont.)

- 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

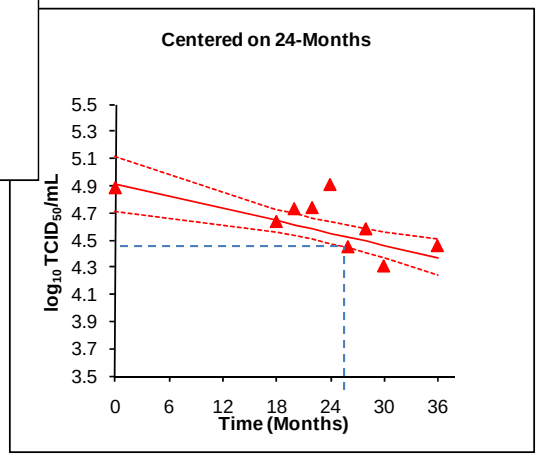


Basic Principles of Vaccine Stability (cont.)

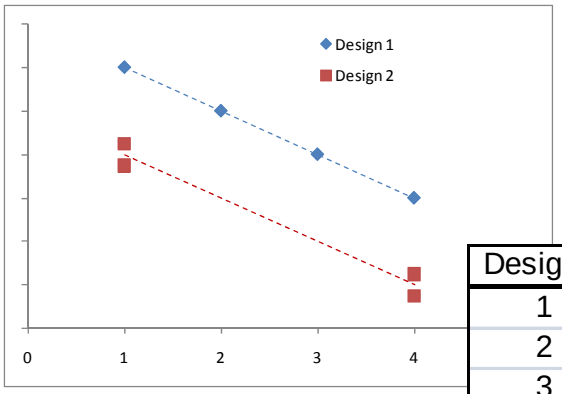
- Study design should acknowledge the goal of the stability study
  - ICH intervals are designed to provide sufficient data at time of filing
  - Statistical design can be used to minimize uncertainty



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



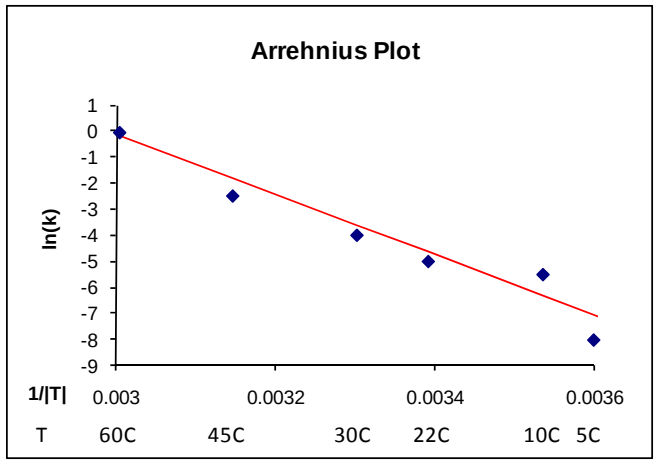
- Determination of loss rate
  - Testing at beginning and end will reduce uncertainty on the loss rate



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

Stability During Development

- 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

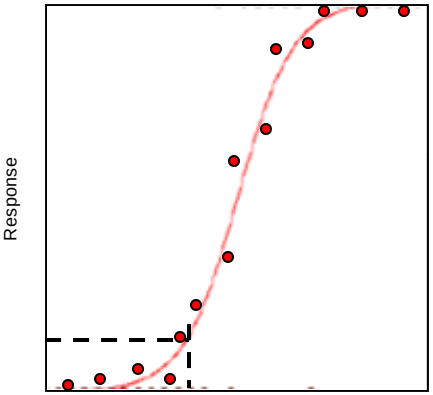


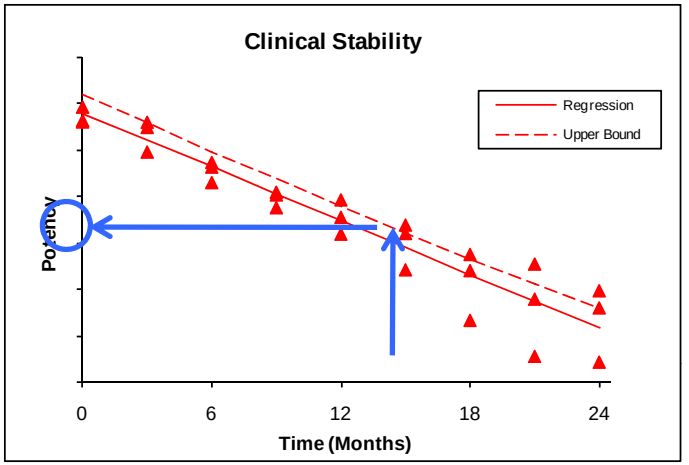
Stability During Development (cont.)

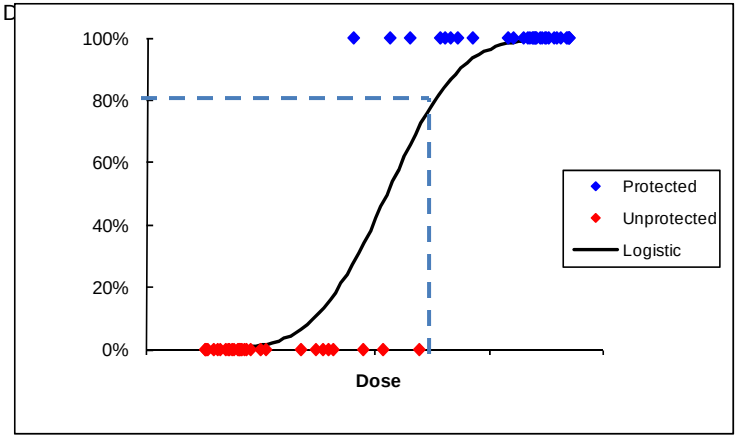
- Use clinical stability to define what the subject received, and thereby specifications
  - Using immunogenicity as the endpoint,

    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

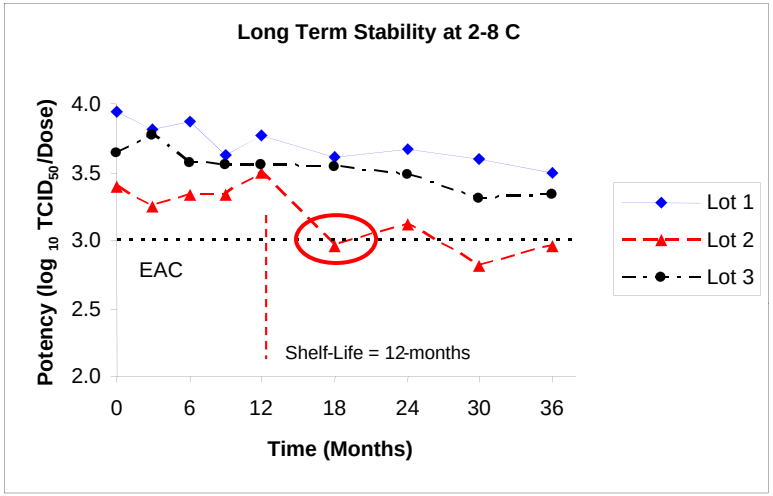


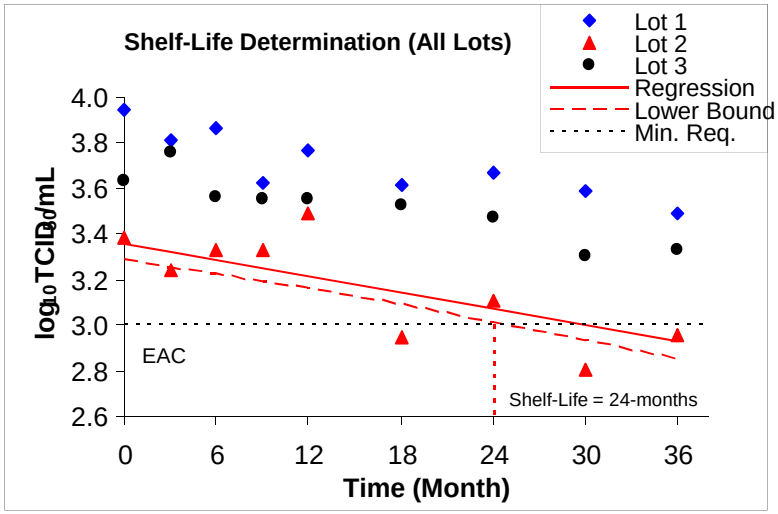




Stability Supporting Licensure

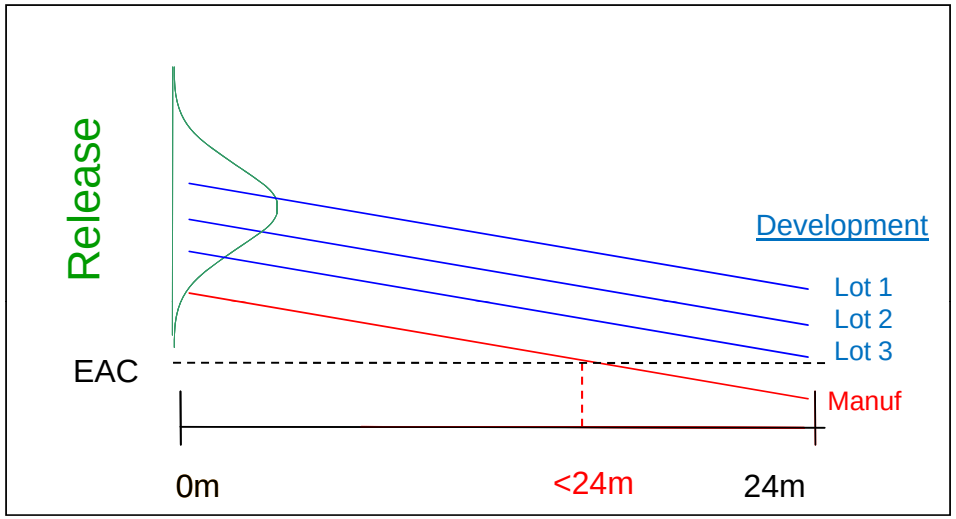
- Shelf-life determination – measles example
  - Is shelf-life 12-months due to a stability measurement at 18-months for lot 2 which falls below the expiry acceptance criteria (EAC)?
    - "Compliance Model"
  - ICH Q1E defines shelf-life as the time where the lower bound on the confidence interval intersects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



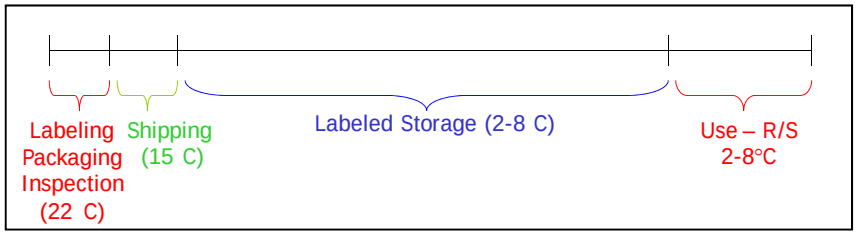


Stability Supporting Licensure (cont.)

- 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



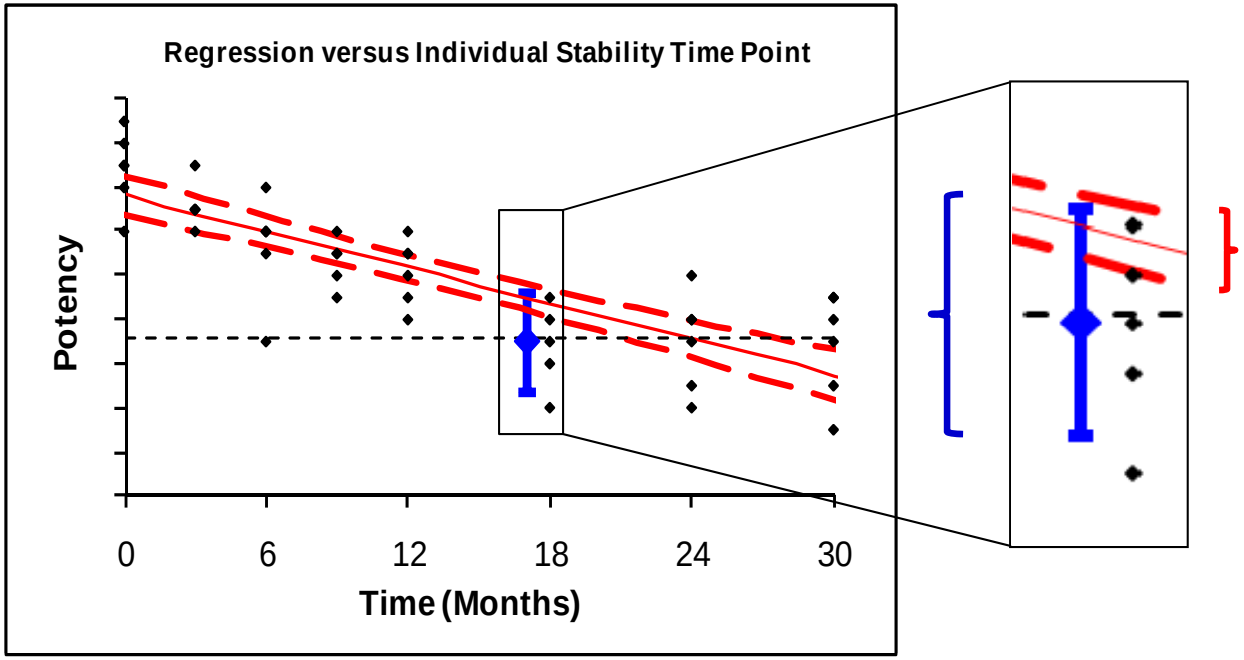
- A minimum release limit assures EAC by end of shelf-life
  - Calculated from combination of accumulated losses over shelf-life, together with statistical uncertainties



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

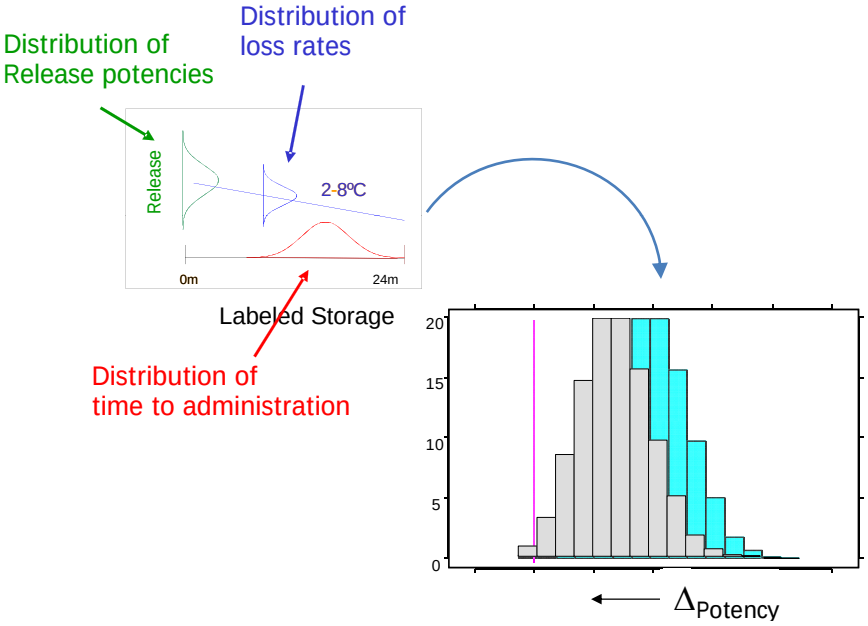
Post Licensure Stability Evaluation

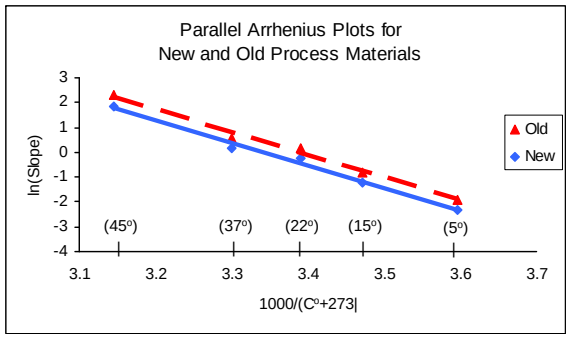
- Similar to shelf-life determination, stability modeling should be utilized to estimate product quality during stability monitoring
  - Highly variable measurements yield sporadic stability OOS results
  - The stability model yields a more precise estimate of vaccine quality



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



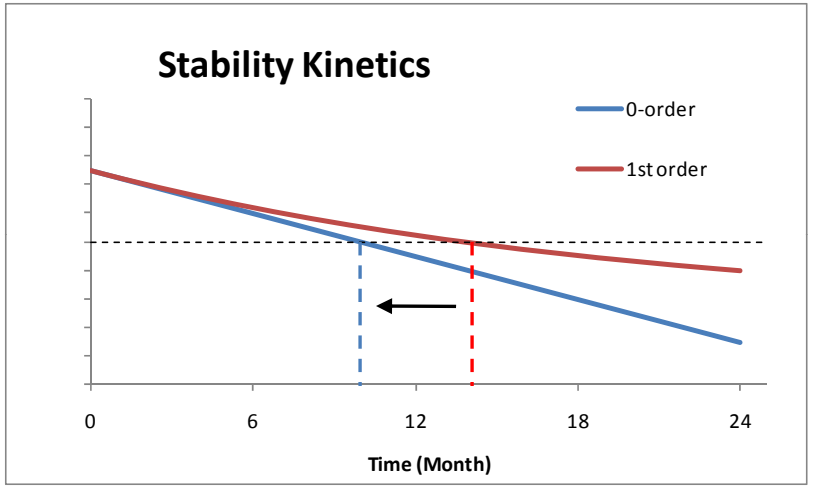


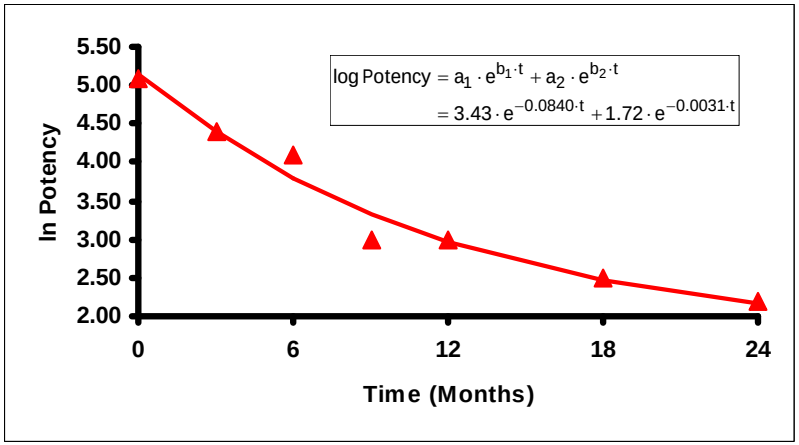
Challenges to Implementation

- 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.)

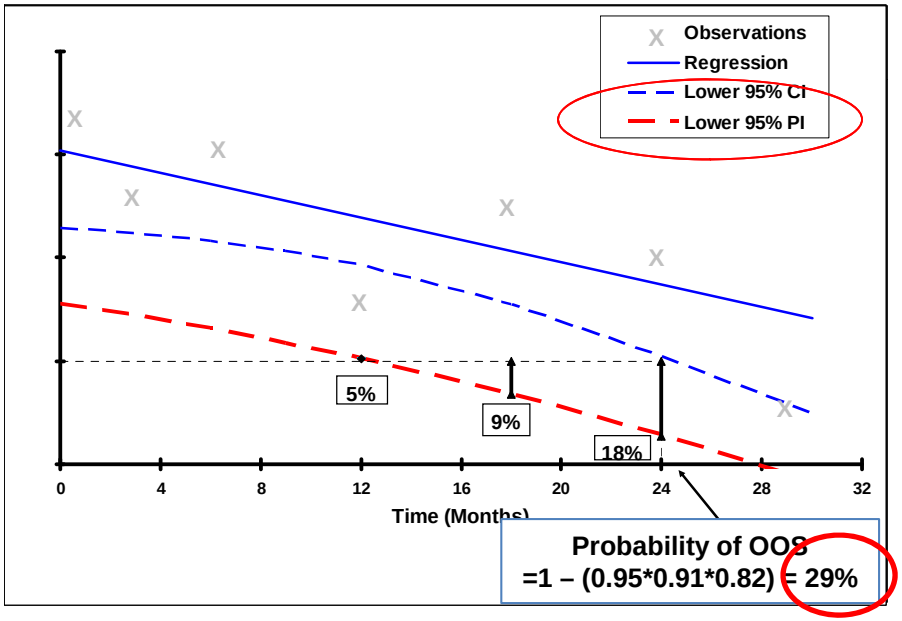
- Inaccurate stability modeling can lead to poor estimates of vaccine shelf-life
  - The default model for stability of vaccines is a 1st order kinetics model
  - Modeling by 0-order kinetics can lead to underestimation of shelf-life, and limitations on vaccine supply
  - Some vaccines degrade by higher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





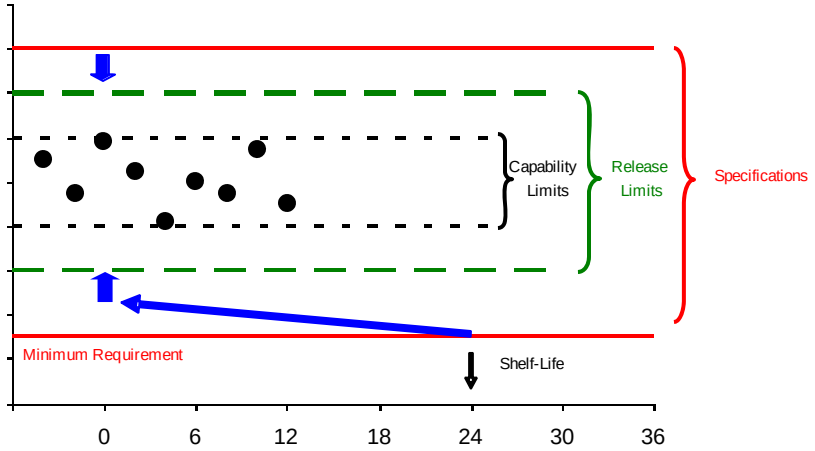
Challenges to Implementation (cont.)

- 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



Summary

- 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