WHO Guidelines on Stability Evaluation of Vaccines

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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 Standardization, 23-27 October 2006
Overview of WHO Guidelines (cont.)

- Supported by implementation workshops
  - Seoul, Korea (Apr 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
      \[
      \text{Potency} = P_0 \cdot e^{-k \cdot t},
      \]
      where $P_0 =$ 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

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• 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
• 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

![Long Term Stability at 2-8 C](image)

![Shelf-Life Determination (All Lots)](image)
• 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

Minimum Release = EAC + \sum t_i b_i + t_{df} \sqrt{\sum t_i^2 s_{b_i}^2 + s_{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
• 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
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.

\[
\log \text{Potency} = a_1 \cdot e^{b_1 \cdot t} + a_2 \cdot e^{b_2 \cdot t}
\]

\[
= 3.43 \cdot e^{-0.0840 \cdot t} + 1.72 \cdot e^{-0.0033 \cdot t}
\]
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

![Graph showing stability analysis and probability of OOS]

\[ \text{Probability of OOS} = 1 - (0.95 \times 0.91 \times 0.82) = 29\% \]
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.