



***STABILITY STUDY
OF
BIOLOGICALS***

Stability of vaccines: key definitions

Stability is the ability of a vaccine to retain its chemical, physical, microbiological and biological properties within specified limits throughout its shelf-life.

- Real-time/ real condition stability studies: physico-chemical, biological & other vaccine characteristics during & up to the expected shelf-life and storage periods under expected handling and storage conditions

What is a Stable Vaccine?

- A vaccine with a very long shelf life
A vaccine lot that complies with release specifications throughout shelf life
- Technical specifications
Vaccine that complies with the principles of the initial license through out life cycle
Technical, non-clinical and clinical specifications

Factors Having a Strong Impact on Stability of Vaccines

- Purity
- Formulation
- Stabilizers
 - Human Serum Albumin (HAS), recombinant human Albumin (rHA), Gelatine, Sugars, Sorbitol
 - Thiomersal
 - AIOH, AIPO
 - Ions (Buffer systems)
- Pharmaceutical form
 - Lyophilized versus liquid
- Storage
 - Frozen versus refrigerator

Guidelines on Stability of Vaccines

- ICH HARMONISED TRIPARTITE GUIDELINE QUALITY OF BIOTECHNOLOGICAL PRODUCTS:
- STABILITY TESTING OF BIOTECHNOLOGICAL/BIOLOGICAL PRODUCTS, Q5C, dated 30 November 1995
- Development of a CPMP Points to Consider on Stability and Traceability Requirements for Vaccine Intermediates, dated 2000
- WHO guideline on stability evaluation of vaccines, dated 2006
- Other regional guidance

All these guidance documents provide rather general instructions.

Product specific cases must be considered case by case.

Product Specific Issues

- To what extent may critical quality attributes change during shelf life without affecting safety and efficacy?
- Are all potential changes detectable by technical means?
- How many stability lots are needed to address the impact on stability due to variances inherent to the manufacturing process
 - Wide specifications
 - Number and age of intermediates
 - How can these uncertainties best be investigated during clinical development and post-marketing monitoring

Stability evaluation: guiding principles

- Vital part of quality and safety assessment of a vaccine
- Temperature sensitivity
- Specific biological activity: potency assay
- Design of stability studies - depends of the objectives of
- stability studies:
 - 1) Determine shelf-life, storage conditions and to support licensing
 - 2) monitor vaccine stability in the post-licensure period
 - 3) Support manufacturing changes: comparability

- Defining acceptance criteria for
- stability parameters by clinical trials

The vaccine life cycle

- Registration/launch is the critical time:
 - studies prior to that point are aimed at obtaining information to support registration.
- Subsequent studies are aimed at assuring that the assessments at the time of registration are still correct

Using stability data and specifications to set shelf life

- Goal: Throughout its shelf life, product must be comparable to batches shown to be safe and effective in clinical studies
 - Stability data are used to make predictions that can be extrapolated to future batches of product
 - The most accurate predictions are based on mathematical modeling of biologically relevant stability-indicating parameters

Potency Definition

Specific ability or capacity of the product, as indicated by appropriate laboratory tests or by adequately controlled clinical data obtained through the administration of the product in the manner intended, to effect a given result

Why do we do a potency assay?

- • In development, to:
 - Assure that safe potencies are not exceeded in clinical trials
 - Obtain information that will support licensure-including correlation of potency with clinical response
- After licensure, to assure that lots behave similarly to those tested in the clinical trials that supported licensure
- The potency should not be below the lowest potency believed to be efficacious
 - The potency should not exceed the highest potency believed to be safe
- The potency assay thus provides a “bridge” between licensed material and the clinical trials

What does a potency assay tell us?

- The assay estimates the mean potency value for a lot
- There are two sources of variability in the measured potency of an individual vial from the same vaccine lot– manufacturing variability and assay uncertainty
- Thus, we can never know the actual potency in an individual vial that was used in a clinical trial
- We can know the characteristics of the lot of vaccine from which that vial came (we routinely estimate the mean potency)

Variability in potency assay results

- The standard error of the mean potency of a lot provides information about the accuracy with which we can estimate the mean potency, and thus provides information about both of these sources of variability, combined
- The SEM provides information about our level of certainty that we know the mean potency of the lot; just as the mean potency does not provide information about individual vials (which is impossible to obtain, when assays are variable), the SEM provides information about that estimate
- The standard deviation of the mean potency provides information about the distribution of potency test values, but does not tell us about the underlying actual values
- Conformance to GMP and assuring consistency of manufacture provides assurance that the manufacturing variability remains constant over time

Clinically relevant parameters

- L.L.: the lowest dose at which we are comfortable, based on the clinical data, that the vaccine is going to be effective. This is normally a specification.
- U.L.: The highest dose at which we are comfortable, based on the clinical data, that the vaccine is going to be safe. This is normally a specification.

Dose

- Stability profile
- Analytical assay variability
- Confidence limits

Two models

- Compliance model
 - Substantially all potency measurements should exceed some predefined quantity
- Often, the mean potency from clinical trials is used to set this minimum specification
- This is very difficult (perhaps impossible) to reliably implement in original clinical tests were performed based on an understanding of mean potency, not on an understanding of “all potency measurements”
- Estimation model
 - The mean potency of substantially all vaccine lots should be at a level that is not less than the mean potency of vaccine lots shown to be effective in clinical trials

Compliance model

- Shelf life is set arbitrarily depending on the luck associated with each individual assay at each time point, and based on the starting potencies of lots on test
- Release potency must be high enough to prevent test results that fall below L.L. due to assay variability, from requiring an unacceptably short shelf life, or from subsequently failing stability monitoring studies

Estimation method

- Statistical methods (when appropriate, a regression line) also can be used to estimate lower bounds on the mean potency estimate at end-expiry for any given release potency, thus allowing estimation of shelf life

Development-what do we need to know about stability?

- What are the kinetics of decay?
- What are the degradation products?
- Are there stability-influencing factors that should also be controlled?
- Do we have sufficient knowledge of the stability of intermediates?
- Are the assays adequate?
 - Are potency assays stability-indicating?
 - Are potency assays precise enough to support product development?
- Do we have a sufficient understanding of material tested in clinical trials?
- Do we have a sufficient understanding of product performance at potency ranges likely to be encountered post-licensure?

TYPES OF STABILITY

- **Real Time Stability**: Long term stability under recommended storage conditions for the **shelf life** proposed for the product.
- **Accelerated Testing**: Studies under exaggerated storage conditions.
- **Stress studies**: More severe conditions than those used for accelerated studies.

TEMPERATURES

- **Real Time:** Storage Temperature of the product e.g. 2-8°C for Tetanus Vaccine
- **Accelerated:** $15 \pm 2^\circ\text{C}$ higher than the maximum temperature of storage at real time storage of the product e.g. $25 \pm 2^\circ\text{C}$
- **Stress:** $+10^\circ\text{C} \pm 2^\circ\text{C}$ than the accelerated temperature e.g. $35 \pm 2^\circ\text{C}$

SAMPLE

- **DRUG SUBSTANCES:**
INTERMEDIATE PRODUCT: ACTIVE
RAW MATERIAL
FORMULATED BULK: FINAL BULK
- **DRUG PRODUCT:**
FINISHED PRODUCT: FINAL LOT

S.No.	Criteria	No. of batch	Type of study
1	Introduction of new product	3	Long term and accelerated
2.	Change in method of production	3	Long term and accelerated
3.	Change in formulation	3	Long term and accelerated
4.	Change in container	3	Long term and accelerated
5.	Change in manufacturing equipment	1	Long term and accelerated
6.	Change in location	3	Long term and accelerated

DESIGN

Bracketing: Extremes of certain design factors e.g.

Strength: **10 ug**, 25ug, **100 ug**

Package size: **1 dose**, 5 dose, **10 dose**

Matrixing: A **selected subset** of the the total number of the possible samples for all factors is tested **at specified time** and at a **subsequent time another subset** of samples for all factors is tested.

Stability indicating parameters

- Choice of parameters to be tested: depends of the
 - product characteristics
 - Link between vaccine quality and efficacy or safety as
 - demonstrated in clinical trials – ideal case
 - Potency, antigen content, appearance, pH,
 - completeness of adsorption, adjuvant content; physicochemical
 - properties etc
 - New vaccines: parameters to be identified during the product development

- **Real Time** 2-8°C for 4 years

(for 3 years expiry)

0,3M,6M,9M,12M,18M,24M,36M & 48
M

Accelerated Temperature 20-25°C
for 6 months

0,1M,2M,3M & 6 Months

Stress Study: 35°C for 1-2 months

0,1,2,3,4,5,6,7& 8 weeks

ACCEPTANCE CRITERIA

- In general, significant change is defined as:
- 5% change in assay from the initial value or failure to meet the acceptance criteria by biological or immunological parameters or as applicable for the specification of the product.
- Any degradation product (impurity) exceeding its acceptance criteria

ACCEPTANCE CRITERIA

- Failure to meet the acceptance criteria for physical and chemical parameters
- Failure to meet the acceptance criteria for dissolution for stipulated dosages.

Cumulative age of an antigen in the final Product

- Reported as a major issue in practice
- Final product should be stable during the whole period of shelf-life irrespective of the age of its intermediate products
- Data should be collected on an ongoing basis – usually not available before approval of storage periods and shelf-life
- Accelerated stability studies - to demonstrate that an aged intermediate did not affect stability of the final product

Thermal stability testing – lot release

- An indicator of consistency of production
- Not designed to provide a predictive value of real time
- TS is a shelf-life specification in current WHO vaccine
- specific recommendations
- Live attenuated vaccines – OPV, MMR, YF
- For other vaccines: consider relevance of the rate of
- change for safety and efficacy

Stability of combined vaccines

- Determination of the shelf-life should be based on the shortest shelf-life component
- Data obtained for monovalent vaccines should support stability of combined vaccine
- Stability of combined vaccines should not be based on the extrapolation of the stability data of the individual components alone

Labelling

- Recommended storage conditions and expiry date
- – Sensitivity of vaccines to environmental factors (eg light, freezing) and preventive measures
- If VVMs are to be used, adequate stability data should be generated to support selection of appropriate VVM for the vaccine in question