Vaccine stability evaluation concepts

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Nature of Biological Products

- **Easily degrade at high temperature, therefore, cold chain storage until the end of shelf life is needed.**
- **Mostly filled in closed containers.**
- **Biological/biochemical/chemical/physiological characteristics are related to efficacy & safety of the products.**
- **Some environmental factors (such as light, pressure, pH) can also effect some product stability**

Stability of Vaccines & Therapeutic Biological Products

- **No change in product characteristics that related to changes in product safety and efficacy**
- **Stable product is the one that complies with the specifications of the initial license throughout life cycle (non-clinical & clinical studies & lot release)**
- **Specific to each product characteristics: difference in degradation rate → big differences on parameters and frequency of the testing selected**

Stability of Vaccines & Therapeutic Biological Products

- **For complex protein molecule products (ex.vaccines); There are difficulties in application of the pharmaceutical accelerated stability testing program and the mathematical models used in data analysis**
- **Real time – real condition stability study is required for establishment of shelf-life**

Factors Having a Strong Impact on the Stability of Biological Products

- **Purity**
- **Formulation**
  - **Stabilizers such as gelatin, thimerosal, AlOH, etc.**
  - **Other components such as pertussis toxoid, tetanus toxoid**
- **Presentation**
  - **Lyophylized VS liquid**
- **Storage condition**
  - **Frozen VS cold temperature**

ICH Guidelines: Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products (Q5C)

- **Applies to well-characterised proteins and polypeptides, their derivatives and products of which they are components, and which are isolated from tissues, body fluids, cell cultures or produced using rDNA technologies.**
- **May apply to conventional vaccines, after consultation with the appropriate regulatory authorities.**
- **Does not cover antibiotics, allergenic extracts, heparin, vitamins, whole blood, or cellular blood components.**

WHO GUIDELINES ON STABILITY EVALUATION OF VACCINES

- **Applies to all vaccines against infectious diseases**
- **Focus on how to evaluate vaccine stability, not to provide guidance on how to stabilize a vaccine.**
- **Genetic stability is not considered in the GLs.**

General consideration of the GLs

- **Temperature is the only one environmental factor that affects characteristics of all vaccines over time. Other environmental factors (e.g. light) might be considered in the development of new vaccines.**
- **Photostability is not considered as a mandatory test in vaccine stability studies.**
- **The impact of humidity is not relevant for the vast majority of vaccines.**

General consideration of the GLs

- **Real- time/real-condition stability study is mandatory requirement for establishment of shelf life of vaccine.**
- **Temperatures higher than the storage condition (Accelerated stability studies) is not a mandatory required in vaccine stability studies. It can be used to establish the stability profile of the vaccine.**

Types of stability study

- **Real time / real condition stability studies**
- **Accelerated (degradation) studies**
- **Stress Testing**
- **Thermal stability testing**
- **Supporting stability study**
- **Stability studies for utilization period**
- **Impact of container and closure system**
- **Stability of a vaccine in the case of known "short time excursions" outside the labeled storage conditions**
- **Stability study to support selection of VVM**

Real time / real condition stability studies

Studies on the physical, chemical, biological, biopharmaceutical and microbiological characteristics of a vaccine, during and up to the expected shelf-life and storage periods of samples under expected handling and storage conditions.

In general at 2-8^{o} C.

Accelerated stability studies

Studies designed to determine the rate of change of vaccine properties over time as a consequence of the expose to temperatures higher than those recommended for storage. Those studies may provide useful support data for establishing the shelf- life or release specifications but should not be used to forecast real time real condition stability of a vaccine. They could also provide preliminary information on vaccine stability at early developmental stages and assist in assessing stability profile of a vaccine after manufacturing changes.

In general at 25, 37, 40^{o} C for weeks or months

Stress Testing

Studies performed to determine the impact of extreme environmental factors such as light and extreme temperature (may include oxidizing agents, freeze thaw, pH). These studies are not usually performed as part of a stability program, but are used instead to establish protective packaging and container conditions, and to support exclusionary labeling.

Thermal stability testing

Stability of a vaccine after exposure to a temperature, higher than those recommended for storage, for a specified period of time, often expressed in terms of change in potency.

Example:

OPV: potency shall not be reduced more than 0.5 log CCID50

Thermal stability testing for lot release

- **Thermal stability should be considered as a vaccine characteristic that provides an indicator of consistency of production in the context of lot release.**
- **Thermal stability test is not designed to provide a predictive value of real time stability but to test a conformation with defined specification for a tested vaccine.**

Stability studies for utilization period

Stability studies done to determine time period during which a liquid or a reconstituted preparation of the final vaccine in an opened container can be used.

Example: after reconstitution and kept at room temp/2-8^{o} C

Impact of container and closure system

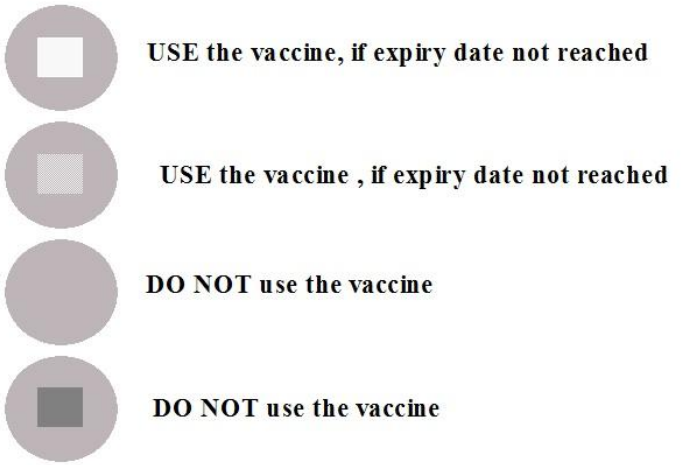
- **For liquid form products.**
- **This should be tested by exposing and maintaining samples into different positions during a certain period of time. (upright; horizontal or inverted position).**
- **These positions should mimic possible situations that may occur during the transport and storage and that provide contact between vaccine and the closure system**

Stability of a vaccine in the case of known "short time excursions" outside the labeled storage conditions

- **Possibility of temperature excursion during transportation**
- **Take the samples out of cold chain (2-8^{o}C) and put them at 25^{o}C for a short period such as 1 day or 8 hrs and then return them back to the normal cold chain condition.**
- **Samples can be taken out of the cold chain at the first period and/or the middle period and/or the last period of shelf life after released.**
- **The release specification may be calculated by adding the correction factor from this stability study.**

Stability study to support selection of VVM

- A vaccine vial monitor, or VVM, is a circular indicator, printed directly on the vaccine vial label or affixed to the top of the vial or ampoule. The inner square of the VVM is made of heat-sensitive material that is initially light in colour and becomes darker when exposed to heat over time.



Stability study to support selection of VVM

- **Stability study is to determine the change rate of potency that is related to change of VVM indicator colour at different temperatures and time exposure**
- **The rate of potency change which related to VVM color change is a product specific characteristic.**
- **Four categories of VVMs are needed because of the different temperature and time sensitivities of EPI vaccines including**
  - **VVM2 for the least stable vaccines (2 days to end point at +37^{o}C)**
  - **VVM7 for moderate stability vaccines (7 days to end point at +37^{o}C)**
  - **VVM14 for medium stability vaccines (14 days to end point at +37^{o}C)**
  - **VVM30 for high stability vaccines (30 days to end point at +37^{o}C)**

Stability study protocol

- **Minimum three lots.**
- **Where the same strength and container is used for three or more fill contents so the smallest and the largest container size are considered as representative of all.**
- **Pilot scale data may be acceptable providing that manufacturing scale batches are tested following approval and comparability demonstrated.**

Stability study protocol: Points to be discussed with NRA

- **Stability indicating parameters are defined on case by case basis, mostly include potency/ antigen content, appearance, pH, general safety, specific toxicity, antimicrobial agent content, completeness of adsorption, sterility, adjuvant (adsorbent) content, and changes in physico- chemical properties.**
- **Quantitative assay is required to detect the rate of change**

Stability study protocol : Points to be discussed with NRA

- **Testing frequency (3, 6, 9, 12, 18 and every 6 months afterwards) described for pharmaceuticals does not apply to all vaccines. The appropriate time points for testing should be set up based on characteristics of the vaccine, the rate of change of the parameter measured, the purpose of testing, study design and subsequent data analysis.**

Stability of Intermediates & Cumulative age

- **The stability study of intermediate is required if the intermediate is not used in the next step of production immediately.**
- **Total age of all components at the end of shelf-life is considered as cumulative age. stability data of the final product should include the data generated on the intermediates of different ages used in the final formulation.**

Stability data analysis

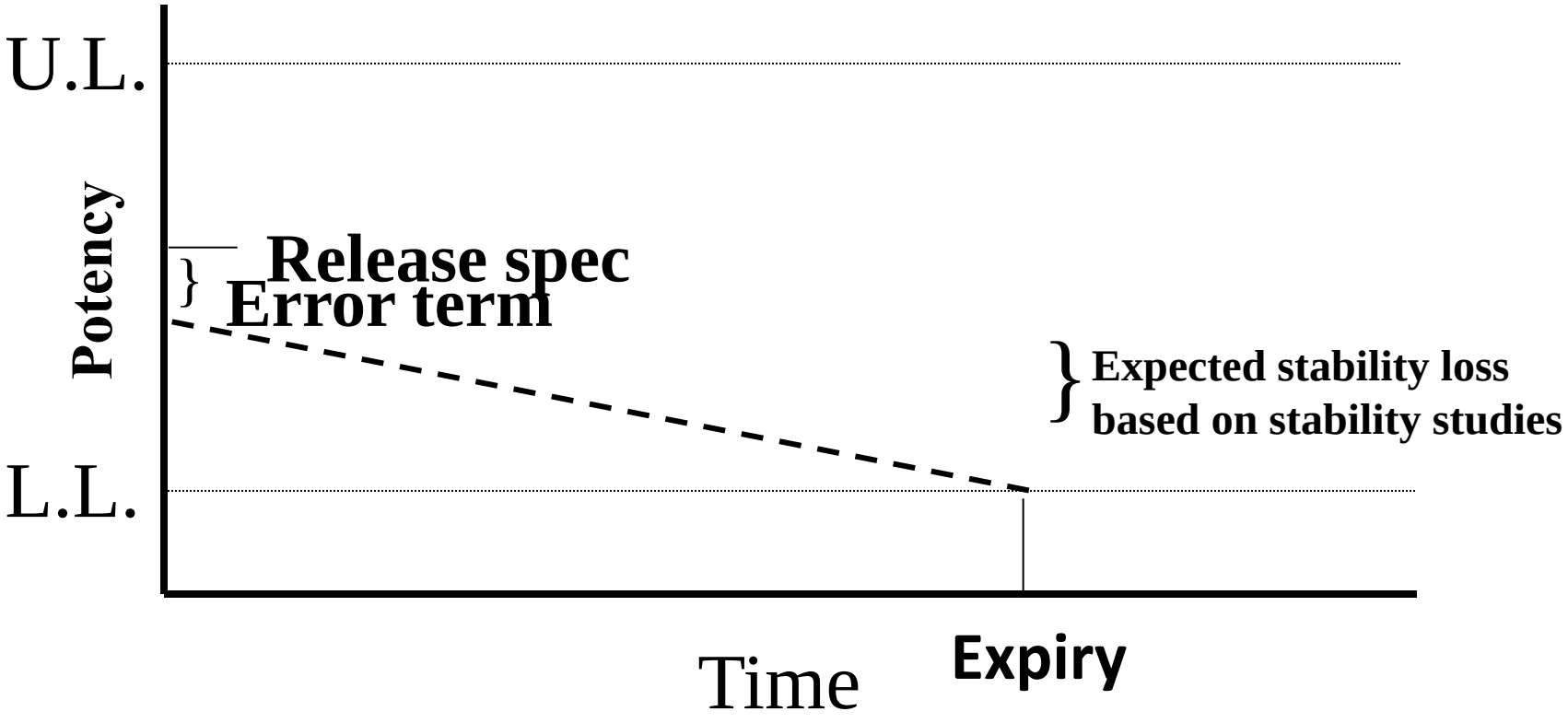
- **Comparing stability study measurements to an acceptance criterion. (Compliance Model)**
- **Statistical modeling such as regression analysis may be used to analyze data from stability studies. Modeling can be performed after three or more stability time points have been obtained.(Estimation model)**

Vaccine stability evaluation for use in a controlled temperature chain (CTC)

Possibilities which vaccines are out of cold chain

- **Unintended excursion**
  - **Shipment during production period**
  - **Labelling process**
  - **Shipment during field distribution**

Calculation of minimum release potency



ECTC

- **Use of the vaccine in out of cold chain condition.**
  - **Off-labeled use**
  - **Stability data is approved by regulator for ECTC use. (Specific labeling required)**

Extended controlled temperature conditions (ECTC)

Approved short-term temperature conditions, above those defined for long-term storage, transportation and use, for a given product immediately prior to administration. Any temperatures above the approved long-term storage temperatures in the cold chain could be considered for ECTC application.

CTC: planned & defined temperature excursion

- **Vaccine decay rates may change over the shelf-life of the product and is product specific.**
- **Stability studies for the purpose of ECTC use should be carried out on each individual product. Worst case scenarios should be included in the study design.**

ECTC: planned & defined temperature excursion

- **The stability studies for ECTC should focus on a single planned excursion from the cold chain .**
- **The stability studies on multiple planned excursions (cycling) is quite complicated.**
- **To implement ECTC, a peak threshold indicator has been developed to measure the peak temperature exposure in order to ensure that the maximum defined temperature (such as 40°C) is not exceeded.**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