

## Q & A for Stability Guideline on Vaccine

**Introduction:** In principle, ASEAN has adopted the WHO guidelines on stability evaluation for vaccines as endorsed at the 21st PPWG Meeting in June 2014. This Q&A document serves to provide clarification in the ASEAN context.

**Q&A No. 1:** It is stated in ICH Q5 C Stability Testing of Biotechnological /Biological Products, for vaccines consisting of well-characterized proteins or polypeptides, the expiration dating should be based on real-time/real-temperature data submitted in support of the application. Can NRA accept the pure estimation model in the application submission? If not, what is the minimal data acceptable?

**Answer:**

For vaccines, pure estimation model is not acceptable. In accordance with WHO Guideline on Stability Evaluation of Vaccine, stability of a vaccine, and therefore the proposed shelf-life, expiry date and storage conditions should be determined on the basis of the results of real time stability studies. Stability studies should be performed on material representative of the final manufacturing process and final formulation.

When a shelf-life of more than 6 months is proposed, and change in a stability parameter is linear, 6 months' real time, real storage condition data should be submitted as a minimum. Modelling of the minimum release specification with less than 12 months of data is highly unreliable.

In addition, the conclusion of any linear trend in the stability parameter should be based on a minimum of 12 months' data from pilot and commercial batches.

Pilot scale data may be acceptable provided that comparability is demonstrated between the pilot and manufacturing scale batches to support product registration and commitment to conduct stability study on manufacturing scale batches following approval is provided.

Accelerated degradation testing should be provided as a support to real time real conditions studies and not as their replacement

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**Q&A No.2:** For multi-dose vaccines (e.g., 10 dose vials), what are the requirements for in-use stability testing? In the absence, can the default in-use shelf life be based on CPMP/QWP/2934/99 - Note for Guidance on In-use Stability Testing of Human Medicinal Products and CPMP/QWP/159/96 corr - Note for Guidance on Maximum Shelf-life for Sterile Products for Human Use After First Opening or Following Reconstitution?

**Answer:**

In order to establish the in-use shelf life, the principles of existing stability testing guidelines for pharmaceutical/biologicals should be applied. If information on the in-use period is indicated in the package insert, stability data is required to support the in-use period claimed. For multi-dose

vaccines, WHO recommends using the vaccines as soon as possible within six hours after opening or discarding all opened vials at the end of the immunization session, whichever comes

first. In addition to WHO guideline, for particular in-use stability, the two CPMP guidelines (CPMP/QWP/2934/99 - Note for Guidance on In-use Stability Testing of Human Medicinal Products and CPMP/QWP/159/96 corr - Note for Guidance on Maximum Shelf-life for Sterile Products for Human Use After First Opening or Following Reconstitution) can be used as references.

**Reference:**

- 1) WHO Policy Statement: Multi-dose Vial Policy (MDVP) Revision 2014
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**Q&A No. 3:** How many stability batches are required for the submission of post-approval variations for vaccines?

**Answer:**

Generally, real-time stability data from 3 batches are required to support a manufacturing change for vaccines. Use of accelerated data solely to support such a change may be acceptable if appropriately justified.

As shown in WHO, TRS 993, 2015: Guidelines on procedures and data requirements for changes to approved vaccines, the number of batches and data required are dependent on the type and condition of variations. This Guideline should be considered and applied as appropriate for supporting each variation/change. The smaller scale and bracketing stability study may be acceptable, when justified.

**Reference:**

- 1) WHO TRS. No. 962, 2011. Annex 3: Guidelines on stability evaluation of vaccines
  - 2) WHO TRS. No. 993, 2015. Annex 4: Guidelines on procedures and data requirements for changes to approved vaccines.
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**Q&A No. 4:** Is thermal stability testing for lot release mandatory just for live-attenuated vaccines? Other type of vaccine will be justified on a case-by-case basis depending on the link with immunogenicity at elevated temperature?

**Answer:**

Normally thermal stability testing for lot release is required for live-attenuated vaccines, however, this test is also required for inactivated JE vaccine. Therefore, appropriateness of thermal stability test for lot release of other vaccines should be carefully considered and the need for it is justified.

In principle, if the rate of change has no relevance for the safety and efficacy of a particular vaccine, it would be difficult to justify a thermal stability test at lot release other than as an indication of lot-to-lot consistency. For example, decrease of the antigen content could be detected after exposure of the vaccine to elevated temperature, but may or may not be directly linked with immunogenicity and subsequent efficacy of the vaccine. Therefore, the appropriateness of such an assay should be carefully considered on a case-by-case basis. It should not be required for lot release assay if there is no added value. WHO TRS for specific vaccines on the need of thermal stability testing for lot release can be used as references.

**Reference:**

- 1) WHO TRS. No. 962, 2011. Annex 3: Guidelines on stability evaluation of vaccines
- 2) WHO TRS. No. 963, 2011. Annex 1: Recommendations for Japanese encephalitis vaccine (inactivated) for human use (Revised 2007)

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**Q&A No. 5:** How does one define thermal stability for their product? How much difference in temperature is considered and at what time frame? Is potency the only parameter that is critical in thermal stability, or does it depend on the type of vaccine?

**Answer:**

Thermal stability is stability of a vaccine after exposure to a temperature higher than that recommended for storage, for a specified period of time, often expressed in terms of change in potency. It is a part of lot release specifications.

The appropriateness of thermal stability testing as part of lot release should be explored during the vaccine development stage. Scientific rationale should be based on the assessment of the actual value of the test in the overall understanding of vaccine quality and the effect of production variables. In general, temperature at 37° C is used for thermal stability assay and the time frame of incubation period depends on type of vaccine. For example, the incubation period of existing liquid vaccines e.g., OPV is 2 days and JE (inactivated) vaccine is 1 week while for lyophilized vaccines e.g., JE live, Measles, MMR and Dengue (live-attenuated) vaccine is 7 days, BCG vaccine is 4 weeks and Yellow fever vaccine is 2 weeks.

Reference:

- 1) WHO TRS. No. 962, 2011. Annex 3: Guidelines on stability evaluation of vaccines.

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**Q&A No.6:** Intermediates, (especially final bulk) are essentially the final finished product without filling into the final container closure system. However, stability testing on the final finished product sometimes only includes potency, sterility, endotoxin, pH. Will manufacturers be expected to submit the same amount of stability dataset for the intermediates (as for the final finished product) and post-approval stability protocol be extended to intermediates?

**Answer:**

The stability indicating parameters and storage period should be identified and justified for intermediates of all stages of production and adequately supported by stability results. The parameter of study should be defined, taking into account a potential link between biological activity (e.g., toxicity or potency) and safety and efficacy demonstrated in clinical trials. Parameters that might change over time but have no correlation with efficacy and safety in clinical terms may in some cases be used to help to demonstrate consistency of production. Manufacturers should define the stability profile and propose stability-indicating parameters for the vaccine in question. This provides assurance that changes in product characteristics, including potency, will be detected by appropriate physicochemical and biological assays.

For live-attenuated vaccines, the titer is an obvious stability-indicating parameter that can be directly studied on the intermediate and/or final lot. Parameters other than potency-indicating ones should also be considered since they indicate changes in vaccine quality with unknown effects on efficacy and safety. Such parameters may include, in addition to in vivo and in vitro potency, antigen content, appearance, pH, general safety, specific toxicity, antimicrobial agent content, and completeness of adsorption, sterility, adjuvant (adsorbent) content and changes in physicochemical properties. For non-live vaccines, it may not be possible or relevant to test the potency directly on an intermediate and this will have to be studied on formulated (e.g., adsorbed) vaccines. Time points as well as stability-indicating parameters should be discussed with the national regulatory authority in the context of study design and data analysis.

Post-approval stability study of the intermediates is not necessary if the stability data of intermediate has been already conducted in practice.

Post licensure stability studies monitoring the vaccine stability are required on final container lots.

Reference:

**1) WHO TRS. No. 962, 2011. Annex 3: Guidelines on stability evaluation of vaccines.**

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**Q&A No.7A:** Not all post-approval changes require the need to conduct a stability study. Therefore, clarity in section 7.6 should be provided to highlight the type of major post-approval changes that require stability study, e.g., separating changes to the antigen/drug substance from changes to the vaccines, because as stated, it could cover both, and could continue to make some users think that all changes may require stability data of subsequent material (i.e., changes of DS would also require DP stability).

**Answer:** Some major changes in DS may require additional stability studies of both DS and DP. The stability studies of DP can be done by the annual stability program. This is considered on a case by case basis; the examples are shown in WHO Guidelines for procedures and data requirements for changes to approved vaccines.

**Reference:**

- 1) WHO TRS. No. 962, 2011. Annex 3: Guidelines on stability evaluation of vaccines.
  - 2) WHO TRS. No. 993, 2015. Annex 4: Guidelines on procedures and data requirements for changes to approved vaccines.
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**Q&A No.7B:** Please also clarify the amount of stability data required for post-approval changes.

**Answer:**

In principle, limited real-time stability data is acceptable to support post-approval variation as real-time/RT stability data in conjunction with accelerated, thermal cycling and in-use stability studies as provided at registration.

Based on the product knowledge established at registration, post-approval changes under the circumstance that does not impact product quality, limited stability data is acceptable with commitment to carry out the study. Some examples of stability data required for post-approval changes are presented in WHO TRS. No. 993, 2015. Annex 4: Guidelines on procedures and data requirements for changes to approved vaccines.

**Reference:**

- 1) WHO TRS. No. 962, 2011. Annex 3: Guidelines on stability evaluation of vaccines.
  - 2) WHO TRS. No. 993, 2015. Annex 4: Guidelines on procedures and data requirements for changes to approved vaccines.
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**Q&A No.8:** What are the requirements for post-licensure stability monitoring?

**Answer:**

Post-licensure stability monitoring is a tool for detecting any signal of changes that may affect the product characteristics and/or quality. In practice, at least one final container lot produced per year is recommended for real-time, real-condition stability studies.

Moreover, annual stability monitoring is a requirement for GMP assurance, and should therefore be conducted, unless no product batch is manufactured that year.

The submission of annual stability data to the NRA will be in accordance with the NRA's requirements.

**Reference:**

- 1) WHO TRS. No. 962, 2011. Annex 3: Guidelines on stability evaluation of vaccines.
  - 2) WHO TRS No. 986, 2014. Annex 2: WHO good manufacturing practices for pharmaceutical products: main principles.
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**Q&A No.9:** Can reduced design (i.e., matrixing & bracketing) be used when performing stability study on vaccine products with varying container closure size?

**Answer:**

For reduced design by bracketing, the smallest and largest container size are generally considered representative of all proposed container sizes on the assumption that the stability of the other container sizes is represented by the data generated at the extreme container sizes.

Other than container size, other characteristics of the container, such as container wall thickness, closure geometry, surface area to volume ratio, headspace to volume ratio, water vapour permeation rate or oxygen permeation rate should also be considered when selecting the representative container sizes to be placed on stability studies.

For reduced design by matrixing, a statistical design is used to ensure that tested samples are representative of all samples and worst-case scenario.

**Reference:**

- 1) WHO TRS. No. 962, 2011. Annex 3: Guidelines on stability evaluation of vaccines.
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**Q&A No.10:** “What data should be provided in case of known “short-time temperature excursions” outside the labelled storage conditions?”

**Answer:**

Shipment validation report should be submitted. If there is a high risk of “short-time excursions” outside the validated cold-chain during handling and transportation, stability studies under conditions that mimic, as far as possible, those of the foreseeable exposures should be performed.

Such studies should involve exposure to suitable temperatures higher than those recommended for storage, for a defined period. The temperature data recorded by using temperature data logger or

other temperature recorder during transportation of each shipment can be used and may be submitted for the vaccine lot release process.

**Reference:**

1) WHO TRS. No. 962, 2011. Annex 3: Guidelines on stability evaluation of vaccines.

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**Q&A No.11:** Do we need to conduct in-use stability study for reconstituted vaccine products?

**Answer:**

Yes, the expiry time for use of reconstituted product should be established and supported by appropriate stability and compatibility studies. The stability studies shall be approved by the NRA.

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**Q&A No.12:** What are the considerations for data extrapolation of stability data for vaccines?

**Answer:**

The extrapolation of stability data should be considered on a case by case basis, using quantitative data from stability-indicating parameters.

For data extrapolation within the same product, extensive testing during the development of a vaccine should provide the information on stability-indicating parameters.

Moreover, it could also help to establish some predictive values of the parameters that could potentially serve for the extrapolation of the data at the later stage. These predictions can be based on biologically relevant mathematical modelling of stability-indicating parameters.

The prerequisites for the extrapolation of the data are consistency of manufacturing, quantitative results of the assays performed on clinically relevant parameters, the use of appropriate design of the study and analysis of the data. Further considerations on the design of the studies to support licensing and the analysis of the data are discussed in sections 7 and 8 of TRS 962 Annex 3.”

Data extrapolation between different vaccine products is generally not acceptable.

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**Q&A No.13:** Can extrapolation of stability data for individual strains be considered to establish the shelf life of the combined vaccine in accordance with the shortest shelf life of individual strains?

**Answer:**

It is stated in WHO TRS No. 962 Annex 3 Section 9 that each vaccine component (after combination) should be tested to support initial licensure of combined vaccines.

Determination of the shelf-life of a combined vaccine should be based on the shortest shelf-life component. Data generated on monovalent vaccines should support the stability of a combined vaccine.

However, stability of a combined vaccine should not be based on extrapolation of the stability data of the individual components alone because the stability profile of each monovalent vaccine after combination, may be changed due to the manufacturing process or interference from other antigens and formulation ingredients.

**Reference:**

- 1) WHO TRS. No. 962, 2011. Annex 3: Guidelines on stability evaluation of vaccines.

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**Q&A No.14:** What is the approach for the selection of time-points for stability monitoring?

**Answer:**

In general, the current approach recommended for the testing frequency is at 0, 3, 6, 9, 12 months on the first year, every 6 months on the second year and every year thereafter is recommended.

However, appropriate time-points for testing should be chosen based on the characteristics and stability profile of the vaccine in question, e.g., rate of change of the measured parameter, purpose of testing, study design and subsequent data analysis.

**Reference:**

- 1) WHO TRS. No. 962, 2011. Annex 3: Guidelines on stability evaluation of vaccines.

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**Q&A No.15:** Is the cumulative study required for vaccine stability?

**Answer:**

According to WHO TRS No. 962 Annex 3 Section 5.2-5.3, the cumulative stability study is used to ensure that the stability of the final drug product is guaranteed during the whole shelf-life, irrespective of the age of the intermediates (within their respective shelf-life) at the time they are used in the production process.

Stability data on the final product should include the data generated on the intermediates of different ages used in the final formulation. The storage conditions and periods for the intermediates should be specified until sufficient evidence has become available to demonstrate that the age of intermediates has no impact on the quality, safety and efficacy of the drug product.

At present, a cumulative study is not mandatory for MA, however, national regulatory authorities are encouraged to request and assess the data.

**Reference:**

- 1) WHO TRS. No. 962, 2011. Annex 3: Guidelines on stability evaluation of vaccines.