Distribution: General
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Meeting Report

WHO/KFDA Workshop on Stability Evaluation of Vaccines, Seoul, Republic of Korea

23-25 April 2008

Abstract

In April 2008, the World Health Organization and the Korea Food & Drug Administration jointly organized a workshop on evaluating vaccine stability. The main objective of the workshop was to facilitate implementing newly established WHO guidelines. The value of stability studies in understanding vaccine characteristics, establishing shelf-life and release specifications, and monitoring the stability post market was well explained. Optimal designs for goal-based stability studies were proposed and appropriate statistical analyses presented. A statistical model (the term "estimation model" was adopted) based on regression analysis of potency loss over storage time elapsed, was elaborated for describing the stability profile of vaccines. This model was believed to provide a more precise description of the stability characteristics of a vaccine than the current "compliance model". The use of both models was discussed in relation to specific examples and case studies. A document format for assisting standardized stability report was discussed as a possible annex to the WHO stability guidelines adopted in 2006. The participants agreed that a future revision of vaccine stability guidance should highlight the estimation model and that WHO should provide additional training to support NRAs with statistical design and analysis, and to assist their transition from the compliance model towards wider use of the estimation model.

1. Introduction

In 2006, WHO's Expert Committee on Biological Standardization (ECBS) adopted a new guideline for stability evaluation of vaccines to assist national regulatory authorities (NRAs), national control laboratories (NCLs), and manufacturers [1]. This document provides a set of general principles and recommendations for stability studies for all stages of the vaccine life cycle which include clinical development, licensing, post-marketing surveillance, and changes during manufacture. The ECBS recommended that WHO should assist regulators and manufacturers to implement the internationally-agreed principles into regulation and practice. This WHO/KFDA joint workshop was prepared to

fulfill the recommendation of the Committee. In this workshop, there were a total of forty-six participants from all WHO regions who represent NRAs, NCLs, manufacturers associations and nongovernmental organizations. Dr. Southern (Medicines Control Council, South Africa) served as chairperson and Dr. Smith (Health Canada) as rapporteur. Main topics comprised WHO approaches and key issues on stability evaluation of vaccines, goals of stability evaluation, principles of stability, quality attributes, studies supporting licensure/post-licensure, issues on climatic zones and cold chain, annual vaccines (e.g. influenza), highly variable assays (e.g. animal potency test for rabies), combined vaccines, stockpile vaccines, and a model format for stability reporting. This report describes a summary of the presentations and discussions.

2. WHO approach and key issues

2.1 Stability evaluation of vaccines: WHO approach

Dr. Knezevic outlined general WHO strategies to support introducing safe and efficacious vaccines, one of which is to assist regulators and manufacturers for a common understanding in assessing and evaluating the stability profile of vaccines by organizing a series of explanatory and interactive workshops. These series of workshops will help to strengthen regulatory capacity and build a network of regulators and manufacturers for a common understanding of the guidelines.

Activities which assure the quality of existing and new vaccines have served as a basis for vaccine use and have contributed to the WHO's immunization goals. Accordingly, quality assurance of vaccines has been achieved through a program of Biological Standardization which includes setting international written standards such as new guidelines for novel vaccines and revised recommendations (formerly, requirements) for existing vaccines or other guidelines on general matters of regulatory concerns.

Stability is a key facet of vaccine quality. Stability is a cross-cutting quality issue. Stability evaluation must be based on sound scientific principles, standardized test

methods and analysis. Further, monitoring in use as well as during the whole life span of the vaccine product forms an essential part of stability evaluation.

Stability-indicating parameters may include all batch-release specifications, but they mainly focus on safety and potency. New vaccines should be characterized to understand the key parameters that determine stability, including the relationship of an effective potency at the end of shelf-life and a safe potency at releasing the product. The cumulative age of the antigens in the vaccine may be important and at least the age of specific antigens in a batch should be well documented.

2.2 Key issues to be addressed in the workshop

Dr. Pfleiderer introduced his talk to stimulate discussion before going into the main sessions. Since the goal of manufacturers is to release products with an assured shelf-life, the release specification (for potency) will ensure the required potency at the end of shelf-life. Factors influencing stability include, but not limited to, the purity of the antigens, formulation of the vaccine, and storage conditions. The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Q5C addresses standards for stability but is unsuitable for many vaccines. A concept paper by the Committee for Proprietary Medicinal Products (CPMP) of the European Agency for the Evaluation of Medicinal Products (EMEA) on cumulative age of vaccine antigens has proved unworkable. The 2006 WHO guidelines provide an improved understanding of the complexity of vaccines and the need for a case-by-case approach to product specific issues. These product issues may include: (i) how quality attributes change during the shelf-life and which changes will affect clinical efficacy; (ii) how these changes are detectable (relating to the sensitivity of the assays); (iii) how many lots need to be tested (relating to production consistency and the stability of intermediates); and (iv) how these factors need to be investigated during clinical development.

To assign a reasonable release potency specification to a vaccine, it is necessary to know the potency required for acceptable clinical efficacy (end-of-shelf-life potency), and the stability or degradation profile. These data can then be used to estimate a release potency: and then, release potency needs to be clinically safe.

In selecting stability-indicating parameters (including potency), the potential clinical implications of any observed changes should always be considered. Ideally, stability-indicating parameters should be clinically relevant and their acceptance criteria should be defined by clinical trials on a case-by-case basis. In conjugated polysaccharide vaccines, an example would be the level of free saccharides that may result from hydrolysis and deconjugation during storage.

In the discussion, the following issues were raised: (i) differing levels of acceptance criteria for the same parameter, (ii) dual specifications imposed by both potency and thermal stability test for lot release, and (iii) use of stabilizers.

2.2.1 Differing levels of acceptance criteria for the same parameter

The first question from the attendance was on the level of free polysaccharide in a bacterial vaccine: which is the preferred specification, less than 20 % or less than 25 %? An immediate response was that it is important to define this clinically with each product during its development. Acceptance criterion in specifications guidance tends to be defined based on the first approved product, and these may or may not be appropriate for the products subsequently developed. Process validation for each product is critical and this needs to be linked to clinical data for the specific vaccine. An added comment was that it is important to remember that, with certain vaccines, only a portion of the product may be immunologically relevant for protection and that this is different from the case with pharmaceutical products: it is essential, therefore, to define the relevant parameters for a specific product.

2.2.2 Thermal stability test and dual specifications for lot release

There was a brief discussion on questions from a one-pager point of discussion which had been provided before the workshop in which test results were presented as just below but within the limit of the significant figures of an acceptance criterion in thermal stability test for releasing BCG vaccine batches. It could be predictive of a failure in real-time stability testing for the same lot. Or it could be that they had not seen real-time stability failures in the BCG lot for the thermo-stability test, and that, thereof, this may have to be evaluated clinically on a product specific basis. This discussion further stimulated an argument relating to two closely-linked batch release tests: potency and thermal stability.

Hepatitis B (Hep B) vaccine, as a typical example, has dual specifications related to potency (i.e. ≥ 20 µg/mL for release and no more than a 10 % loss from its time zero potency when subjected to a thermostability study at 25 ºC). For example, a vaccine lot had a time zero potency of 25 µg/mL and was found to be 21 µg/mL following the thermostability study. Even though both potency values were above the ≥ 20 µg/mL specification, since the 10% limit was exceeded (i.e. 16 %), the lot should be rejected. Additionally, the real time 24 month data at 2-8 ºC for this lot was within specification. A comment was that it is problematic when dual specifications are in place and may not be useful when in fact a vaccine such a HepB vaccine is known to be quite stable. Another comment was that the 10% specification was useful if it was predictive of a lot to meet the end of shelf-life specification; yet NRAs were challenged as to why they would prevent a lot from going to market if a product was generally known to be stable over its shelf-life but the lot was not compliant with the thermo-stability test. This led back to a general discussion on the value of clinical studies with vaccine lots near the end of their shelf-life to understand the clinical relevance with regard to “aged” lots as opposed to low potency lots. A precautionary remark was added that unless clinical studies are done with aged lots at some point in the life cycle of the product, the clinical relevance would not be known.

2.2.3 Use of stabilizers

In general terms, animal- or human-sourced stabilizers such as gelatin and human serum albumin (HSA) are still acceptable, provided these additives are compliant with current guidance. It was also noted that even if natural HSA is changed to a recombinant form, it still has the potential to sensitize recipients to human albumin in other products (i.e. there is always complexity). It was reported that hydrolyzed porcine gelatin is also an acceptable source in many countries. Some vaccines have very different stability profiles when thiomersal is removed but others remain largely unaffected. This again signifies the need for awareness on product specific issues in these considerations and one should be wary of broad generalizations, even with regard to classes of vaccines against the same pathogen.

3. Basic principles and goals of vaccine stability studies

3.1 Goals of stability evaluation throughout the vaccine life cycle

Dr. Krause outlined different goals of stability studies in four different stages of vaccine life cycle, i.e. development, registration/launch, monitoring, and changes/variation. His talk centered on studies for registration/launch which is a critical time in the whole life cycle: pre-registration studies are aimed to obtain supportive information while post-registration studies to assure that the assessments carried out at the time of registration are still correct. The central value of stability studies for registration is potency estimates linked to clinical efficacy (i.e. defining a lower limit), safety (i.e. defining an upper limit) and the need for a potency assay to be predictive of a shelf-life (i.e. not excessively variable). Contrasting compliance versus estimation models, Dr. Krause made the strong case that estimation model is a more accurate assessment of the stability of a product (pre- and post-market) taking into account the variability of point estimates. The value of

forced degradation studies to establish both shelf-life parameters and release potencies was also presented.

The concluding point was that both estimation and compliance models are not compatible with each other and that the US Food and Drug Administration (FDA) does not accept new submissions that use a compliance approach. Manufacturers are encouraged to use the estimation model to develop specifications for their products and this approach is also applied to the post-market stability programs.

After his talk, there were four questions. The first question was on the final slide stating the estimation method will “identify doses below which a mean lot potency is too low to give 95% assurance that that product exceeds the minimum efficacious dose”: does this mean 5 % of the lots would fail? Dr. Krause dissented from the question and explained further: this is merely defining the statistical confidence parameters with regard to exceeding the lower limit; it could be defined at a 99% confidence interval but it was noted that the ICH requires 95%, and an important point to consider is the variability of the potency assay and what this means for the actual potency. Mr. Schofield stressed this consideration in his talk later by adding that the 95% interval relates to lots released at the minimum specification, when in practice, manufacturers typically target to over-formulate to account for assay and production variabilities, which provides an additional safety margin; this underlines the importance of clearly defining the target potency relating to the minimum potency in the context of the assay and other variabilities.

The second question was of the number of lots to be tested relating to estimation model. Dr. Krause elaborated further. It is important to understand the intention of a stability program. The intention should be to characterize the product and not a specific lot. Therefore, the number of lots that needs be tested depends on how variable the product is. In general, the more variable the product (or assay), the more lots should be on test. Improving the assay to reduce variability can also be considered, as can the time points tested. For a post-market stability program that is intended to confirm the stability of the product, time points at the beginning and near the end of shelf-life are more statistically

important. Time 0, end of shelf-life and one point beyond shelf-life provide a better estimate than the typical full time course and also reduce the number of tests.

Dr. Krause answered the question of ways to approach to clinical trial potency specifications. There should not be potency specifications for clinical trials but there should be reliable estimates of potency for a batch. Low potency lots will assist in defining the lower limit, as high potency lots will help define the upper safety limits.

Dr. Krause consented to the point raised by the last question - should there be studies using final products produced from old and younger bulks to look at the effect of cumulative age? - as it was recommended by the current WHO guidelines [1], the stability of the characteristics of a final product should be guaranteed during the whole shelf-life, irrespective of the age of the intermediates at the time they are used in the production process. In addition, forced degradation studies on final products with different age of bulks may provide more information in a more manageable time frame.

3.2 Basic principles of stability

Mr. Schofield, on behalf of all the other representatives from the International Federation of Pharmaceutical Manufacturers & Associations in the workshop, opened his talk with a comment about the question from the previous presentation concerning the 95% confidence interval for the minimum potency specification at lot release. He also mentioned the implications of using a compliance model to evaluate the stability of a product versus the application of the estimation model which is more observational. The former may lead to controlled studies with a selection of lots based on certain parameters. Whereas, the latter tends to promote a more random selection of lots, potentially with more focused testing on more lots for the same cost, and provides a better estimate of the performance of the product (rather than the performance of a specific lot). His presentation focused on (i) understanding mathematical formulas that model how vaccines degrade over time (e.g. linear/nonlinear kinetics and Arrhenius equation); (ii)

statistical considerations in characterizing uncertainty and study design; (iii) understanding the relationship between stability and specifications; and (iv) appreciating the variability of potency assays in characterizing stability. From a statistical standpoint, stability variability is managed through increasing the number of the potency assay and through strategic selection of time points. Repetitions within run will have less benefit than repetitions on different days. Other ways of reducing variability include (i) calibration to a standard; (ii) reference to an unincubated sample (e.g. -70 °C); and (iii) group testing.

Another issue was on replicates with values both above and below the specification. It was noted that this was acceptable provided the mean was above the specification. This is particularly important with highly variable assays. Another point was that there should be a distinction between replicates for a lot versus testing with multiple lots at the same time point. Lots tested consistently below specification should not be lost track of in an averaging process. There was no objection to this point.

Mr. Schofield stressed that, for post-approval stability studies, there is greater statistical value in obtaining data for time points at the beginning and end of shelf-life with at least one time point beyond the end of shelf-life, then obtaining full time points (including 3, 6, 9 months) between time zero and the end of self-life. This was further exemplified by the matrix testing example in which a fourth lot was added to a stability program. The testing design excluded most intermediate time points, reduced the number of tests by 25 %, provided an equally robust estimate of the product's stability performance, and widened the scope of the study with a fourth lot.

In the ensuing discussion, an immediate question was how the estimation model deals with a test failure with a lot in a post-market situation. Mr. Schofield answered that no single post-market test result should be the basis of a decision and that this is the essence of the estimation model (as opposed to the compliance model); however, even in the estimation model, a failed test should trigger an investigation by the manufacturer and testing of retained samples would provide insight to the situation. Dr. Krause commented

that the manufacture needs to place the result in the context of the statistical model established for the product; there needs to be a consistency of approach and an NRA should not mix up both models for the same product, e.g. the estimation model in premarket evaluation and the compliance model for the post market stability; NRAs need to use their own testing programs to establish confidence in a manufacturer's testing rather than to focus too much on each test result; out-of-specification (OOS) results still need to be investigated but understood in the larger context, and sound statistical modeling (i.e. in an estimation model) can best provide that context. Dr. Smith added that there can be a convergence between the two models while transition is made to the estimation model. With an older product established under a compliance model, in the event of a failed test in a post-market stability program, repeat testing and/or testing at later time points should be undertaken to determine how representative the initial failed test was of the lot. If the lot continues to fail in testing (i.e. the line representing the lot remains below specification), under either model this would be the basis of an expanded investigation to determine how representative the lot was for the product in general. Modeling the data in the estimate approach is just the evolution of our regulatory process and still respects specifications.

Mr. Schofield further pointed out that a key to success in the estimation model was that the selection of lots for stability programs should be as random as possible to provide the best estimate of the overall product stability performance. This led to a more general discussion of the design of stability testing programs and the best intervals for testing. To summarize, it is important to have a clearly defined goal in mind in designing a stability program. The intervals that one would select would be quite different if one were conducting an initial characterization of a product in a pre-market versus undertaking a study to confirm that a product was conforming to defined specifications of a product in a post-market. A pre-approval stability characterization program would potentially involve more frequent test intervals, but a confirmatory post-market study may only require a simplified testing scheme, as discussed previously. Exchange of views proceeded to issues on the testing of intermediates versus final products. Mr. Schofield suggested that, from a manufacturer's prospective, the stability of bulks is a business decision for a

company and should not be an issue for NRAs. There was no consensus on this point, but stability of intermediates and cumulative stability were covered in later presentations. Mr. Schofield was asked to provide participants with a table comparing compliance and estimation models to help further discussions (Table 1).

3.3 Quality attributes of intermediates and final products for which stability evaluation is useful

Dr. Pfleiderer introduced his talk by saying that initially there were theoretically based concerns about the cumulative age of antigens and a concept paper was developed. However, in practice few issues were presented in the field and tracing of antigen history is now the focus. Additionally, there is generally a rapid turnover of most antigens due to supply management, which means that in the clinic most antigens in use are not that old. Therefore, further steps for developing specific guidance have no longer been taken.

There are many quality attributes relevant to stability studies for vaccine intermediates and products. Many of these attributes can be defined by technical means (e.g. quantity, identity, integrity, and others - that can be defined by in vitro techniques), some are biological (e.g. immunogenicity - can be defined by in vivo studies), and others are clinical (e.g. efficacy and safety). Technical stability parameters are acceptable where tests correlate with efficacy or safety in humans, but these are questionable where bridging from technical to clinical parameters is not possible. In this regard, one should carefully consider the following points in searching for and detecting changes in the stability profile of a product or its intermediates: (i) is a comparability exercise needed? (ii) is test methodology suitable and sensitive? (iii) is there a need for extended stability testing? (iv) how to interpret changes? (v) are there limits in technical procedures?; and (vi) when to turn to clinical investigations?

The recombinant Hep B vaccine case was presented as a practical example of potential consequences from undetected quality changes, that highlighted the discrepancy between the enzyme-linked immunosorbent assay (ELISA)-based test results for potency (stable)

and the clinical experience (unstable). The ELISA was a consistent test but was not measuring immunogenicity which is a key surrogate marker for the vaccine's efficacy. This is a warning when considering appropriate potency testing. In conclusion, one needs to define where a change in a product attribute will have consequences in the clinic. This requires that manufacturers and NRAs work closely together.

At the end of his talk, Dr. Pfleiderer was asked how stability testing can be applied for the long term storage of intermediates in some vaccines. He replied that this has in general been abandoned due to its complexity and the fact that there has not been a problem with most vaccines in the clinic. The next question was how tests which are not useful or predictive of stability can be eliminated, given that not all tests for various quality attributes in stability programs listed may be clinically relevant.

Dr. Pfleiderer indicated that small phase III clinical trials (e.g. 25 to 50 subjects) with products near the end of shelf-life might help identify tests that might not be related to the safety or efficacy of the vaccine. Technology that identifies changes in products over time but which are not relevant to clinical outcomes, only confuses the picture and these can be eliminated. The next question was how long-term storage is defined. Intermediates which are stored for longer periods are typically frozen, and liquid intermediates are usually not stored for more than hours to days. In either case, data must be provided to support the storage period and conditions. Mrs. Jivapaisarnpong commented that short-term storage of up to a week was often not supported by data but rather through a lot release testing. There was no specific discussion of this point but the practice of not requiring data to support the storage of intermediates may vary between jurisdictions and the licensing history of a product could also be relevant (e.g. it may be more common with older vaccines).

4. Stability evaluation throughout the vaccine life cycle

4.1 Studies supporting clinical development and product development

Dr. Krause listed the main issues of stability in vaccine development: (i) potency assays, (ii) forced degradation studies, (iii) stability study design to optimize stability estimates, and (iv) key information to obtain in clinical studies. The focus was on potency assays as central to understanding and evaluating a product in development and its stability profile. His talk defined necessary attributes for potency assays as (i) predictability of clinical benefit, (ii) amenability to validation, (iii) stability-indicating, and (iv) precision adequate to ensure that dose is safe and effective throughout the dating period for use in stability studies and for use in the bridge between marketed and clinical trial materials. Each progressive phase of development is based on an ability to relate their respective measure of potency. As clinical development progresses, the measure or measurement of potency may change. Knowledge on in–vivo and in–vitro potency assay characteristics will evolve during the course of clinical development. Sometimes it may take more than one assay to fulfill all the purposes of potency assays. Additionally there is a need to understand the performance of assays over time and through clinical development. For this purpose it is needed to maintain stable reference preparations against which potency results may be standardized. There is also considerable value in retaining samples of material used during the clinical development in order to bridge between clinical studies, for example if the retesting of potency in updated assays becomes necessary.

Forced degradation studies, defined as studies under extreme conditions, are critical to understanding decay kinetics (e.g. linear or non-linear degradation model), degradation products, stability-influencing parameters (e.g. pH, moisture), and stability estimates at temperatures other than those intended for use. Viral (or bacterial) aggregation may have an effect on non-linear degradation of a live product. Forced degradation studies may reveal these non-linear relationships associated with viral aggregation. A single plaque forming unit (PFU) may be either a viral particle or an aggregate of particles (live and dead) and these have differing potential to infect and induce protection. This relationship is important to understand for live vaccines since changes in manufacturing may affect aggregate size and potentially the protection associated with the potency estimate. Forced

degradation studies can also be applied to determine that degradation rates at one stage of production do not affect degradation rates at subsequent stages.

Important stability parameters to estimate during product development include prediction of % loss in potency over the dating period at key temperatures (e.g. labeling, shipping, and storage) and the level of certainty associated with those predictions. These should be real-time data. In order to predict outcome after excursions, enough data should be collected under accelerated conditions to know where an Arrhenius model can be extrapolated. By using an estimation model, we have prospective information that better satisfies the goals of thermal stability studies.

Optimization of stability estimates depends on decay kinetics. For instance, if degradation is known to be linear, points at the beginning and the end of study will give the most accurate slope. Intermediate time points can be used in determining whether decay is linear or not. Key information to obtain in clinical studies include the highest dose believed to be safe and the lowest dose believed to have sufficient efficacy. During the talk, there was discussion on the implications of aggregation versus PFU and its clinical significance. The main conclusion was that forced degradation studies are useful to identify non-linear degradation. If linear degradation is evident, the clinical significance can then be considered and evaluated. Forced degradation studies in the context of the estimation model allows one to “assemble” a stability profile in much shorter time frame than cumulative age studies permit (the latter may take well over a decade in some cases). This modeling provides more confidence about the stability profile for a product as it is marketed.

In the discussion, Dr. Krause indicated that artificially aged lots have been used in clinical studies to support the end of shelf-life during the development of a product. The advantage is that it provides more control over the process and is timelier.

4.2 Studies supporting product licensure

The talk was divided into five subtopics: (i) long term stability of bulk intermediate, (ii) long term stability of final container product, (iii) accelerated stability at conditions of handling and use, (iv) release and manufacturing models, and (v) investigation process for cold chain break. Mr. Schofield described the first four subtopics and Dr. Laschi covered the last.

Mr. Schofield first defined study goals and quality criteria for long-term stability of bulk intermediate and of final container product. While bulk is tested for establishing storage conditions and time to ensure its suitability for filling into final container, the final product is tested to establish a shelf-life and to develop a release model to be sure of satisfactory potency through shelf-life. He suggested that cumulative age can be assessed as part of ongoing monitoring of vaccine stability or can be assessed by accelerated stability studies comparing artificially aged lots.

The essence of this presentation was to illustrate the application of generally accepted statistical principles for determining shelf-life and minimum release potency. These analysis methods have been in use for pharmaceuticals for over 30 years and have also been accepted by the ICH. The estimation model uses these principles to best describe the stability profile of a product that takes into account the variability of a single point estimate. Specific examples were provided in which specifications are established for the end of shelf-life, which highlighted the difference between the compliance model and the estimation model. In one example, the compliance model would inappropriately truncate the shelf-life for a vaccine at 12 months due to a single marginally low estimate at 18 months for one of three lots. In this example, each of the other 17 potency estimates for all three lots was above the minimum threshold until 24 months, including the last potency estimate for a lot with a marginally low result at 18 months. Using the same data, the estimation model sets a shelf-life of 24 months, and the modeling provides the statistical rigor required within our current regulatory framework. As was noted during

the presentation, the application of these methods “is not cheating” but in fact represents the best description of the data using well established statistical protocols.

A similar approach is used to develop a composite model for product release. This release model starts with a clinically supportable minimal level of potency and results in a minimum release potency calculated from decay rate estimates for varying excursion conditions as well as for shelf-life period at labeled storage. This model also includes release assay variability estimates. Forced degradation stability data are also a key component to this model in that decay rate estimates for differing excursion conditions need to be extrapolated.

Dr. Laschi then described an investigation process for a cold-chain break. For a product stored at 5 ± 3 °C, the impact of cold-chain break during shipping and storage is evaluated based on stability data at elevated temperature and structural changes data for low temperature. The investigation process involves the evaluation of internal excursions (filling, inspection, packaging) and external excursions (shipping, distribution, outside storage), and this evaluation is based on the temperature and exposure time of a product. The tolerance limit for internal excursion is defined based on accelerated stability studies and it is product-specific. The tolerance limit for external excursion is based on a ratio formula or a reference graph which associates time and temperature. The investigation for the impact of low temperature involves liquid vaccines and freeze-dried vaccines. Diluents are also subject to the investigation if the composition is chemically defined (e.g. NaCl solvent or thiomersal solvent).

In the discussion, an immediate question was raised to manufacturers (other than Merck) whether they are using the estimation model in vaccine development. Dr. Pierard answered that similar approaches were being employed by GSK in their vaccine development programs.

There was a brief discussion between participants and Dr. Laschi. On the question how freeze-thaw studies are conducted (i.e. from frozen to 37 °C), Dr. Laschi explained that

some defined conditions are used but these are not comprehensive and may not mirror reality. She also indicated that the reference curve of temperature versus time is not necessary if a Vaccine Vial Monitor (VVM) is used. She affirmed that a visual inspection of the product will also be conducted with each excursion and her company will undertake an investigation if the excursion occurs while the product is outside the control. She indicated that temperature excursion data are now included in a product submission but were not in the past.

4.3 Stability evaluation post licensure

The topic outlined post-licensure stability evaluation comprising (i) a monitoring plan and (ii) a comparability stability plan. Mr. Schofield introduced a monitoring plan; Dr. Pierard - examples of facility/process comparability studies; and Dr. Laschi - container-content comparability studies.

4.3.1 Post-licensure stability monitoring plan

Some NRAs consider requiring post-licensure annual stability studies. In the estimation model, these studies are valuable to: (i) confirm and update shelf-life and release specifications; (ii) monitor shifts or trends over the manufacturing history; (iii) enable the study of the influence of other parameters on stability; (iv) provide evidence of process validation; and (v) provide a basis for comparison after a process change. However, there is a risk to the manufacturer in that an individual OOS result, which may not accurately reflect the product's stability, could lead to NRA actions that are economically damaging if a questionable result is misinterpreted. It was noted that a manufacturer estimates that there is a 30 % chance of an OOS based on the frequency of the testing, independent of the stability of the product (i.e. the higher the frequency of testing the more likely a false negative will result). The acceptance of the estimation model for stability monitoring (where the variability of the assay and the individual results are incorporated into the

overall analysis) will reduce the likelihood of this and provide the NRA with more confidence in the overall results.

In the discussion, the following points were noted. One question was "at what point would a process change require a clinical study?". Dr. Knezevic pointed out that this should be dealt with on a case-by-case basis. Mr. Schofield added that the use of accelerated or forced degradation comparability studies would allow us to compare lots produced before and after the process change. This could then be informative to the decision regarding the need for clinical study. The next question was if one needs to do a comparability study for all changes. Mr. Schofield's response was that, if there are any reasonable grounds to believe that there could be a change in the product, then a comparability study should be undertaken. Dr. Krause commented that, even if a manufacturer changed a stabilizer and all the specifications were met, accelerated and real time stability data would still be required. Another question was: what if the situation in which the purification was changed but the new lots were well characterized and found to be the same? Mr. Schofield replied that one should still conduct accelerated and real time stability and that the accelerated data would be much faster to obtain.

4.3.2 Comparability stability plan

The goal of a comparability stability plan is to compare lots produced by a new process with those from a current process and to demonstrate equivalence in the stability profile. Accelerated stability studies can be used to support the process change as an alternative to the classical stability design (3 lots, every 3 or 6 months). Three examples of comparability studies under one or more accelerated conditions were presented and include: (i) validating an additional secondary manufacturing site (Example 1); (ii) validating an alternative method for the stopper preparation (Example 2); and (iii) qualifying monovalent oral polio vaccine (Example 3). Such studies allow for rapid evaluation of the impact of the change (facility or process) on the stability profile.

In the discussion, Dr. Pierard indicated that the data for validating a second manufacturing site (i.e. lots from each site were held at 37 ºC for 21 days) were filed as a variation (or change). She also explained the reason why only one temperature was used in Example 1 and 2, but three temperatures were used in Example 3. In the first two examples, it had previously been shown that there were no changes with these products over the time interval at temperatures below 35 ºC. In Example 3, the three temperatures were a requirement of the study. Dr. Pierard pointed out that pre-approval criterion has been established and that the tests were discussed with the NRA for two of the three studies presented. When questioned if one can use historical data for the pre-change lots, she cautioned there would be an additional risk of increased variability if direct comparisons are not performed.

4.3.3 Container-content compatibility studies

The container-closure system should be evaluated at the latest for a registration file because it has the potential to affect the product as a result of interactions between the container/closure and the content. The mechanism of the interaction may include (i) content-to-container migration (adsorption, absorption, permeation-out) and (ii) container-to-content migration (leaching-in and permeation-in). The consequences of these interactions may include decrease in the activity of the product and changes in pH, appearance and/or safety. A container-content compatibility stability study can be planned depending on the knowledge of the container material and the product. This stability study will allow detecting changes through the tests for pH, appearance and potency. The evaluation for the potential impact of container-to-content migration include: (i) supplier data evaluation; (ii) toxicological evaluation; (iii) extraction (extractables) studies; and (iv) migration (leachables) studies.

The NRA will require information on any new container-closure system that includes: (i) composition and properties of the new materials; (ii) analysis of extractables and their influence on the product; and (iii) comparable stability of the product over time – this could be accelerated as described above.

5. Special consideration in vaccine stability evaluation

5.1 Considerations for various climatic zones and cold chain in developing countries

There were two talks under this topic. Dr. Southern focused on issues of potential damage caused by freezing of vaccines during transport or storage. Dr. Chen introduced Project Optimize, a PATH-WHO joint collaboration intended to improve immunization systems and technologies, and raised questions on regulatory issues of product labeling requirements.

Many vaccines contain aluminum based gel adjuvants. These adjuvants are denatured and flocculate after freeze-thawing of the vaccine. This is usually detected by the WHO "shake test". Freeze damage may cause loss of vaccine efficacy or local adverse events (e.g. abscesses), which can result in significant losses of vaccines for public health use. Freeze damage is typically common in poorer community clinics where domestic refrigerators are used for vaccine storage. This instability is not related to the thermal degradation models of vaccine stability discussed in the WHO Guidelines [1]. Some newer formulations of adjuvanted vaccines do not readily flocculate when frozen and thawed, making the WHO "shake test" of no value. The development of vaccines that do not require refrigeration and/or vaccines that are not damaged by freezing will make more vaccine available for use in some countries.

Project Optimize examines the feasibility of improving the thermo- and freeze-stability of current vaccines and searches for the use of additives in formulation which results in either stable vaccines that do not require refrigeration or protects vaccines from the effect of freezing. This has been shown possible for a limited range of vaccines thus far. The advent of thermostable vaccines may require a review of the current WHO Guidelines [1] to ensure that these special circumstances do not affect the principles of vaccine stability

testing. Challenging questions on labelling requirements for such vaccines were raised and discussed as described below.

Logistics and cold chain systems are the backbone of health services in lower and middle income countries. These systems are being challenged by (i) new vaccines in the pipeline; (ii) little spare capacity of cold chains; (iii) slow uptake of system and technology innovations; and (iv) lack of products specifically suited for these markets. There is a need for a guiding vision of how logistic systems should look in the future. The primary objective of the Optimize Project is to develop a shared vision of future support systems for health services that will address the challenges of management, storage, transport, and use of vaccines through more cost-effective and well-managed systems and by advising / influencing product characteristics.

Widening storage temperature requirements for vaccines may be benefited by (i) relieving the cold chain constraints, (ii) reaching hard-to-reach populations, and (iii) maximizing the values of the vaccine stability and technological innovations. Here are two examples with suggestions for label changes.

Human papillomavirus (HPV) vaccine was given as an example of an already existing stable vaccine. HPV vaccine will likely be used for outreach to schools and may be suitable for ambient temperature storage. The vaccine is currently labeled for storage at 2-8 °C. The shelf-life at this storage condition is 3 years. A study predicts that the vaccine has a half-life of 130 months at 25 °C or 18 months at 37 °C [2]. The following theoretical label claims for storage conditions were projected for discussion:

- “Store at 2-25 °C. 3-year shelf-life.”
- “Store at 2-8 °C. Excursions up to 37°C allowed for 1 year. 3-year shelf-life.”

Hep B vaccine was mentioned as another example of improved stability by changing formulation. The existing Hep B vaccine is stable for 1 month at 37 °C, has a 3-year shelf-life at 2-8 °C, and is freeze-sensitive. PATH has developed a new Hep B vaccine

formulation. The research data suggest that the new formulation will be stable for over 12 months at 25 °C, or over 6 months at 37 °C, and is not freeze-sensitive. The following theoretical label claims for storage conditions were projected for discussion:

- "Store at 2-8 °C. Excursions from -10 °C to +25 °C allowed for 12 months. 3 year shelf-life."
- "Store at 2-8 °C. Excursions from -10 °C to + 37 °C allowed for 6 months. 3 year shelf-life."

The following points discussed are worth noting. The participants received well the rationale and challenging issues raised by Dr. Chen. Regarding the HPV proposal case, Mr. Schofield, as one of co-investigators for its thermal stability, agreed that the vaccine was very stable and was technically able to withstand higher temperatures than it was currently licensed for. There was a question from the participants about the definition and clinical relevance of a half-life in terms of stability-indicating parameter and method. Mr. Schofield further explained that the HPV stability study measured antigenicity with an in vitro method. Due to some logistic issues, an in vivo study was not possible. In response to a question on how to get the suggested change of storage temperature approved for HPV, Dr. Krause replied that if data are available and one had the support of the sponsor, one would simply file a submission to the FDA. Regarding the Hep B case, Dr. Knezevic mentioned that if vaccines were suitable for room temperature storage, then a WHO option could be to consider cool rooms to house vaccines in developing countries. Mr. Schofield cautioned that one would have to ensure that a vaccine was tolerant of worst case high temperature excursions. Dr. Knezevic added that VVM for 1 to 2 temperatures might be required in such a case. A major challenging question was how to measure the cumulative heat/freeze exposure. A point was also made that every vaccine has an expiry date on the label with defined storage conditions instead of shelf-life period. One suggestion was to make a specific label for a targeted country. Another suggestion was that a feasible method would be proposing labels with single expiry date with defined storage conditions. Data to support label changes must be clear. In the case of excursions

that are beyond the label, the manufacture would be contacted for clarification. The predefined storage conditions on the label must be supported by data.

There were diverging opinions in the feasibility of scientific studies to support the proposed examples of the theoretical label claims. Apart from this, there seems to be another issue on market demand. The discussion indicated that economic forces, e.g. guaranteeing purchase would be an important factor which will motivate the manufacturer to develop more stable products with wider temperature range. The case of pandemic influenza vaccine development was taken as an example, which was driven by government sponsored demand for the product.

5.2 Annual vaccines: breakout session with a seasonal influenza vaccine case study

Following annual strain change of seasonal influenza vaccines, the NRA expects that the manufacturer will present information establishing the stability of the new vaccine for the 12-month shelf-life. Real-time studies are not practical in these circumstances of shortly available lead-time for manufacture before the flu-season use. In practice, retrospective data from the vaccines of previous seasons are presented. Although this gives confidence in the process, it would not identify a sub-standard current vaccine. Consideration should be given to the use of accelerated stability studies comparing current and previous vaccines. This proposal requires substantial investment in research to discover suitable parameters for such a study. This would be of value in evaluating new pandemic flu vaccines.

A case study material that had been prepared by Mrs. Jivapaisarnpong was used as points for discussion. To summarize the discussions, while the various breakout groups did not come to a consensus on the questions posed within the case study, the exercise did serve to crystallize the concepts in estimation model for many of the participants and was, therefore, a success as a learning tool for the workshop. The most contentious area was

the use of accelerated stability as part of the annual registration process. Again, since this brought new focuses and ideas to an old problem, the exercise was very useful.

5.3 Vaccines measured with highly variable assays: breakout session with a rabies vaccine case study

The potency of inactivated rabies vaccine is determined by a live virus challenge test in mice, known as "NIH test". As with many animal tests, there is often considerable variability in the results of NIH test. The data sets in the case study reflected this, with test values above or below the minimum threshold of 2.5 IU – International Unit - per dose for some vaccine lots in the model stability program.

Again a case study material prepared by Mrs. Jivapaisarnpong was used as points for discussion. Here is the summary of the discussion. As in the flu vaccine case study, there was not complete agreement on all questions between discussion groups among participants. However, a better understanding of principles of the estimation model was gained. In particular, the use of the slope ratio to determine the comparability of data sets was highlighted, as was a potential of accelerated stability studies, and a matrix design to these studies to provide insight into a product's stability profile. Overall, the breakout session was an excellent hands-on learning activity that drove the discussion forward and a similar approach is recommended for future workshops.

5.4 Combined vaccines

5.4.1 MMR-Varicella

Dr. Pfleiderer began his talk by saying that in a specific MMRV – Measles, Mumps, Rubella, Varicella - vaccine, the mumps and varicella components compete for immuno-

dominance. Higher titres of the mumps component were required to achieve the acceptable seroconversion rates seen with the mumps component in the MMR alone. This minimum mumps titre threshold in MMRV was sharply defined between lots and only evident in a lot-by-lot comparison but not in the pooled data. It was reported that reductions in potency between lots as small as 0.3-0.6 logs at the time of immunization resulted in reduced seroconversion rates by 4 to 7 % for both 1st and 2nd immunizations between the lots. Given the decline in the potency over self-file for the mumps component, clinical studies with lots near the end of shelf-life defined the minimum titre required at the end of shelf-life and the elevated titres needed at release to achieve the end of shelf-life minimum titre.

Ensuing questions included: what is the titer of the mumps component in MMRV compared to titer required for MMR alone and what should the maximum titer for the mumps virus be given potential risks with elevated titers? Dr. Pfleiderer replied that the release titer must be high enough at release to maintain sufficient potency at the end of shelf-life and the elevated titers needed to compensate for the presence of varicella in MMRV, did not result in safety problems. Dr. Knezevic commented that, since the MMRV issue presented was product specific, the mumps component titer would have to be defined for each product specifically and take into consideration the stability of the mumps component in each product. Dr. Pfleiderer reminded participants of the main point which was that the required potency at the end of shelf-life was sharply defined for the mumps component in MMRV versus MMR. This had to be evaluated clinically, paying attention to the results with specific lots and the respective potencies for the mumps component.

There was discussion with regard to the difficulty in linking the small differences in potency for the mumps component and the seroconversion rates in the example due to the variability in the potency assay (noted at 0.4 logs in the data presented and known to be in the range of a log between labs). Dr. Pfleiderer responded that the difficulty in drawing conclusions from this one data set was acknowledged but the example presented was supported by other similar data sets and the general pattern was more evident from that

perspective. A higher potency specification was established for the mumps component in this MMRV vaccine as a result of this analysis. Overall, while there was not enough time to reach a consensus on the data presented, this was an interesting example of the need to balance lot specific information versus analyses of pooled data and the potential complexity if such analysis for multi-component vaccines.

5.4.2 - DTaP-IPV

Key points during the presentation of Mrs. Jivapaisarnpong covered the numerous hold times for the various components and their intermediates of a combined diphtheria, tetanus, acellular pertussis, and inactivated polio vaccine (DTaP-IPV). This is a complex issue and perhaps the stability results for the final product is a reasonable approach at this time to support the hold times of the intermediates.

The point of discussion worthy of note was the question "have final lots actually been in use with components that had been stored long term and is this an issue?" Dr. Pfleiderer answered that the complexity of studies required to evaluate this issue caused the abandonment of interest in pursuing this approach, and that the alternative was to use pharmacovigilance data to identify potential problems and to date, no problems have been identified. Mr. Schofield, Dr. Utami and Dr. Pfleiderer all agreed that, while the cumulative age of antigens is an issue to be aware of in a general sense, there were no data to suggest that this has been a problem and final product stability data tends to support this. Dr. Knezevic pointed out that the focus should be on the traceability of antigens by manufactures and NRAs. If issues are noted through pharmacovigilance, data must be available and evaluated if the age of a component was a factor. Another element of this is to identify less stable components and potentially have manufacturers indicate the age of components within a vaccine. Dr. Morgeaux agreed with the focus on the more fragile components and cited an example of a toxoid as one such case. Dr. Krause added that forced degradation studies can be very useful to identify the less stable components of products and identify issues to focus on.

5.5 Stockpile vaccines

Dr. Morgeaux described stability issues relating to stockpile vaccines. This is a particular problem that has been previously encountered with stockpiles of Smallpox vaccine set up in the 1980s after eradication was confirmed. The approach has been to retest the stock at about 5 year intervals and "assume" that the vaccine would be potent in the interim if emergency use was required. This needs to be considered for Polio vaccines (monovalent) and for Pandemic Influenza vaccines. It is important that each country that intends to establish a vaccine stockpile considers some key issues (e.g., the roles of the Government, NRA and manufacturers).

In a proposal to develop a National Vaccine Stockpile Policy, the responsibility for the product must be established since the manufacturer may cease to operate during the vaccine storage period. A retest policy must be established, and a policy for emergency use in the intervals between retests considered. A policy for stockpile replacement should be considered, and the criteria for requiring this established.

The use of accelerated stability studies, providing a more accurate estimate of the stability characteristics of the various vaccines during real-time storage would be of value. This could be part of the Product Licence at the time of establishing the stockpile.

In the discussion, it was noted that each country had its own approach to stockpiled vaccines and that not all products were licensed or even stored as finial products (e.g. OPV is to be held as both a bulk and monovalent final product). The idea of coordinating these activities between NRAs was viewed positively and it was suggested that one tool would be to list issues that distinguished stockpile vaccines, as a means of focusing on the key issues. A few NRAs confronted and involved in quality assessment and stability studies of vaccine stockpiles were in favor and agreed that a common reflection would be useful to draft recommendations, advice and/or guidance for assuring the quality and safety of stockpiles in view of having the same approach for the extension of self-life all along the long extended period of stockpiles storage. A specific workshop organized

under the auspices of both WHO and the European Directorate for the Quality of Medicines & HealthCare (EDQM) for this reflection and for drafting advice and/or guidance would be useful.

5.6 Model format for stability report

Dr. Shin described a brief background, scoping questions, and further work of developing a model report format for stability studies. It has been proposed that WHO develop a model format for reporting the overall program of vaccine stability testing. This has been complicated by the variety of different product types and the requirements of different NRAs. The proposal that was tabled at the time of 2006 ECBS meeting was considered too complex, and duplicating much of the information required in the format of the Batch Summary Protocol. However, it was considered that the model showed the value of such an approach and it was suggested that the model should be reconsidered as a stability summary format that cross-references to data in other parts of the Product Summary File or equivalent document. This document is considered a priority for inclusion in further workshops and a working group was formed. From the various session discussions it was apparent that a variety of stability tests and test protocols are required during product development, release specifications (including national lot release), annual stability monitoring, and in-use monitoring and evaluation of temperature excursions.

6. Conclusions and next steps

From the workshop, it was clear that the estimation model provides a more meaningful measure of vaccine stability than any one single assay value. Thus a product may be characterized by a scientifically estimated rate of potency decay with time at defined temperature(s). This stability characterization should be the basis for establishing end-of-expiry potency, shelf-life and release specifications for potency explicitly linked to clinical efficacy and safety.

However, the value of the estimation model is dependent on several factors apart from the true stability that are difficult to measure; and particularly dependent on assay variability and lot-to-lot consistency. The compliance model remains important for point estimates, such as compliance with Release specifications at lot release. However, potency data collected from field-samples and during annual stability tests should be interpreted in light of the Stability model that is established during product development.

It was generally agreed that although the stability of many characteristics and properties of a vaccine may be measured during the life of a single lot, or the life-cycle of a particular product, the measure of potency and its relationship to clinical efficacy is the key parameter.

Biological assays are accepted as the most meaningful measures of vaccine potency – as linked to clinical efficacy. These are expensive in terms of time and resources.

The inherent variability of the assays used for vaccine potency is the most important hurdle in establishing the stability of a vaccine. This can lead to out-of-specification values due to the natural scatter of results.

A program of experiments can be designed to estimate the stability of vaccine potency at one or more temperatures. The statistical analysis from multiple measurements of vaccine potency, sampled over time – as described at this meeting – can be used to provide a model of vaccine stability and a measure of the confidence in applying the model. The Estimation model is a tool to assess the relevance of a point value.

Statistical models can give a meaningful measure of the vaccine stability characteristics, and from this model calculations can establish a release specification and shelf-life, and can guide actions following temperature excursions during use.

The estimation model can also be used to compare the quality of different lots of a vaccine prepared by modified processes. This comparison can be conducted at increased temperatures – leading the accelerated acquisition of results – an accelerated stability test.

It was recommended that future revisions of vaccine stability guidance highlight the advantages of the estimation model and that efforts be made to provide additional training for the development of in-house statistical support for NRAs, to assist their transition towards implementation of this model.

Special consideration should be given to the assessment of stability in combination vaccines, and the potential for interference between new vaccine components should be considered. It is not possible to extrapolate the stability of the combination vaccine from the known stability of the components.

The cumulative stability of stored intermediates should be considered, but it appears that this is a complex and theoretical problem. No incidents of concern have been attributable to age of intermediates at this time. This is perhaps best managed as a commercial risk of the manufacturers – to reduce lot failures. It is considered that NRAs should require defined storage conditions and time limits for intermediates and the age of antigens should be tracked more closely.

A working group on model stability report format was organized and additional coordination for vaccine stock-piles was identified.

The value of the development of thermostable and freeze-stable vaccines is acknowledged. It is possible that these developments may require a review of the WHO guidelines on stability of vaccines when these products become available.

The information gathered at this and further workshops will be collated and distributed to the participants – and more widely, ensuring that the issues raised and considered will

become part of the network consciousness and will help inform policies and decisions of manufacturers and regulators.

7. Reference

[1] WHO Expert Committee on Biological Standardization. Guidelines on stability evaluation of vaccines. Adopted 2006. http://www.who.int/biologicals/publications/trs/areas/vaccines/stability/en/

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Table 1. Comparison of methods

	Compliance	Estimation
Ease of use	simple, requires only comparison to minimum requirement	requires knowledge of modeling tools such as regression
Control of risk	lack of control of risk; more data generate excess producer risk; less data generates excess consumer risk	simultaneous control of risks; more data control both producer and consumer risk
Understanding of kinetics	no fundamental knowledge of kinetics except conformance to minimum requirement	model of kinetics provides understanding of vaccine properties, and can be used as a tool for experimentation
Predictability	no ability to forecast throughout shelf-life	can predict (interpolate and extrapolate) with associated uncertainty
Maintenance	excess effort in investigating assay variability	assay variability “modeled” into estimation of stability profile
Conformance with other standards of practice	inspectors/laboratories expect to be able to test product to show it complies with minimum requirements	independent of other standards of practice; goal is to study stability, not compliance to minimum requirements

ANNEX 1

Assessment of Questionnaire Responses

WHO/KFDA Joint Workshop on Stability Evaluation of Vaccines, Seoul, Korea, 23-25 April 2008

The objectives of the questionnaire were:

- To identify current gaps in implementing the WHO Guidelines on stability evaluation of vaccines (adopted in 2006)
- To identify further needs for WHO workshops on the same topic and ways of improving future workshops

Here is the summary of responses on the WHO Guidelines on Stability Evaluation of Vaccines.

- 33/45 participants returned the questionnaire (73%).
- 12/33 responders (36%) indicated that their country has already adopted the WHO guidelines as national guidelines.
- 9/23 responders (39%) indicated that their country was planning to implement the WHO guidelines as national guidelines.
- 14/20 responders (70%) indicated that the WHO guidelines should be implemented as national guidelines.
- 28/33 responders (86%) agreed that the WHO guidelines provide necessary information or recommendations (9% disagreed)
- 22/33 responders (67%) agreed that the WHO guidelines are clearly understood and provide necessary details (18% disagreed)

- 18/33 responders (54%) agreed that the WHO guidelines provide necessary examples (27% disagreed)

Here is the suggestion for improving WHO Guidelines on Stability Evaluation of Vaccines.

- What to improve?
  - Provide statistical models and calculations
  - Provide examples for process change
  - Provide more practical guidance with current regulatory views
  - Clarify direction to estimation model and role of potency testing
  - Clarify cumulative stability
  - Elaborate recommendations given as "case-by-case basis"
  - Elaborate how to evaluate data statistically

- How to improve?
  - By adding further detailed guidance as annex
  - By revising

Table 1. Questions and responses on implementing WHO guidelines

Questions	No. of responders				
	Yes	No	Don't know	No answer	Sum
1. My country has already adopted the WHO Guidelines as national guidelines	12	13	3	5	33
2. My country is planning to implement the WHO Guidelines as national guidelines	9	3	9	2	23
3. The WHO Guidelines should be implemented as national guidelines	14	2	3	1	20

Table 2. Questions and responses on current gaps of WHO guidelines

Questions	No. of responders (N=33)					
	Strongly agree	Agree	Don't know	Disagree	Strongly disagree	No answer
4. The WHO Guidelines provide necessary information or recommendations	6 18%	22 67%	0 0%	3 9%	0 0%	2 6%
5. The WHO Guidelines are clearly understood and provide necessary details	3 9%	19 58%	2 6%	6 18%	0 0%	3 9%
6. The WHO Guidelines provide necessary examples	3 9%	15 45%	2 6%	9 27%	0 0%	4 12%

Here is the summary of responses about the workshop.

- Most responders (>80%) agreed that (i) they were well informed about the workshop objectives; (ii) the workshop met their expectations, (iii) the content was relevant and applicable to their job; (iv) the workshop objectives were clear; (v) the workshop activities stimulated their learning; (vi) the activities gave them sufficient practice and feedback; (vii) they accomplished the objectives of the workshop; (viii) they would be able to use what they learned; (ix) they would recommend the workshop to their

colleagues; and (x) they would be interested in attending more advanced workshop on this same subject.

- 27/33 (82%) responders considered that the workshop was the right length.
- 17/33 (52%) responders considered that the workshop was intermediate level, while 13 responders (39%) as advanced level and 1 responder (3%) as introductory level.
- Responders favored the following points for improving the workshop:
  - Better information before the workshop (16)
  - Clarity of workshop objectives (12)
  - More time for the workshop (9)
  - Up-to-date content (8)
  - More stimulating activities (8)
  - Improved instructional methods (7)
- More case studies and practical examples were suggested for improving the workshop.
- Responders valued interdisciplinary network and dialogue between manufacturers, regulators, and statisticians, stability study evaluation and exchange of information, statistical aspect for decision making, case studies and regulatory experience and others.

Here are the suggestions for improving the workshop.

For workshop content:

- Provide more case studies
- Include more technical aspects in QC/QA
- Include practical examples to reach a determined objective (like deciding which model is better)
- Describe estimation model more broadly

For workshop flow:

- Provide daily or subject-wise conclusion
- Allot more time for free discussion/case studies
- Allot more frequent breaks with shorter time to increase attention

- Circulate final results of the workshop

Additional written comments or suggestions were:

- Provide more learning opportunities
- Organize workshop by Region
- Organize workshop each year in different countries
- Include topics for stability study & shelf-life extension for stockpile vaccines
- Is there any value to include batch info in the stability report? Batch info such as age of starting material, bulk and intermediate, date of manufacture, site of production, batch size
- Practical methods specific for different kinds of vaccines should be covered or discussed
- Periodical updates & information to be shared to get better on the long run
- Excellent workshop
- Thank KFDA for supporting this workshop
- No immediate improvements necessary
- Periodic updating & sharing of information to get better on the long run

In conclusion, the current WHO guidelines need more information and various examples detailing principles for better consideration and implementation by Regulatory Authorities and Industry. Further workshops will help Regulatory Authorities and Industry to better understand and consider/implement the WHO guidelines. Better info-sharing, more analytical examples/case studies and more time for group discussion may improve the future workshops.

Table 3. Questions and responses on evaluating the workshop

Questions	No. of responders (N=33)					
	Strongly Agree	Agree	Don't Know	Dis-agree	Strongly Dis-agree	No Answer
I was well informed about the objectives of this workshop	20 61%	10 30%	1 3%	1 3%	0	1 3%
This workshop met my expectations	15 45%	16 48%	0	0	0	2 6%
The content is relevant and applicable to my job	21 64%	10 30%	0	0	0	2 6%
The workshop objectives were clear to me	19 58%	12 36%	0	0	0	2 6%
The workshop activities stimulated my learning	22 67%	9 27%	1 3%	0	0	1 3%
The activities in this workshop gave me sufficient practice and feedback	12 36%	17 52%	2 6%	0	0	2 6%
I accomplished the objectives of this workshop	13 39%	15 45%	2 6%	0	0	3 9%
I will be able to use what I learned in this workshop	17 52%	15 45%	0	0	0	1 3%
I will recommend this workshop to my colleagues	24 73%	6 18%	2 6%	0	0	0
I would be interested in attending more advanced workshop on this same subject	19 58%	9 27%	3 9%	0	0	1 3%

This workshop was	Too short	Right length	Too long	No answer
	5	27	0	1
	15%	82%		3%
The level of this workshop	Introductory	Intermediate	Advanced	No answer
was	1	17	13	2
	3%	52%	39%	6%

How would you improve this workshop?	Ticked	Blank
___Provide better information before the workshop	16	17
___Clarify the workshop objectives	12	21
___Reduce the content covered in the workshop	1	32
___Increase the content covered in the workshop	4	29
___Update the content covered in the workshop	8	25
___Improve the instructional methods	7	26
___Make workshop activities more stimulating	8	25
___Improve workshop organization	2	31
___Make the workshop less difficult	4	29
___Make the workshop more difficult	0	33
___Slow down the pace of the workshop	3	30
___Speed up the pace of the workshop	1	32
___Allot more time for the workshop	9	24
___Shorten the time for the workshop	0	33