Meeting Report

WHO/ Health Canada Drafting Group Meeting on Scientific and Regulatory Considerations on the Stability Evaluation of Vaccines under Controlled Temperature Chain

National Hotel and Suites, Ottawa, Canada

4-6 December 2012

1 Disclaimer: This report contains the collective views of an international group of experts, and does not necessarily represent the decisions or the stated policy of the World Health Organization. The mention of specific companies or of certain manufacturers’ products does not imply that they are endorsed or recommended by the World Health Organization in preference to others of a similar nature that are not mentioned.
Executive summary

Immunization programs in certain regions of the world face severe challenges in maintaining cold chain storage conditions for their vaccines. These challenges could be reduced if a vaccine-specific stability assessment were able to demonstrate that a product could withstand defined periods of exposure to elevated ambient temperatures, i.e., in a controlled temperature chain (CTC), while maintaining the key quality attributes necessary for clinical effectiveness, and the vaccine label would explicitly indicate this potential. With the CTC objective in mind, a consultation was held under the auspices of WHO and Health Canada in Ottawa from 4 to 6 December 2012 in order to identify the issues which will have to be overcome to further develop CTC for vaccines with this potential. The design of stability studies required for this type of assessment, appropriate stability-indicating assays, the statistical methods best used for such evaluations, considerations for vaccines under development versus existing vaccines where some data may already exist, along with when further clinical studies may be required were all discussed.

During the consultation, the participants suggested that the term ‘extended controlled temperature chain’ (ECTC) may be more appropriate than CTC. However, the use of this term would have to be endorsed through the appropriate WHO committee, so CTC is used throughout this report for consistency.

Key conclusions included: 1) it is important to distinguish between approved label information for unplanned product cold chain excursions, potentially useful for all countries, versus label information relating to the planned exposure of vaccine to elevated temperatures suitable for vaccination programs/campaigns in remote regions, the latter of which was the primary focus of this consultation; 2) while not all vaccines would necessarily have the potential for a CTC label, for existing vaccines that did have this potential, additional clinical data may not be needed in most cases; 3) appropriate statistical models are essential for evaluating the effect of the extreme conditions anticipated under a CTC label; 4) validated stability-indicating assays, established by the manufacturer through a product’s licensure under a competent regulatory authority, should provide the basis for any CTC assessment and resultant label change; 5) standardization of an
upper temperature target for a CTC label would permit a clear framework for the design of stability studies and is clearly desirable for both industry and regulatory authorities. However, given the inverse and complex relationship between a specific vaccine’s shelf-life and ambient temperature and the immunization program’s need for the longest hold time at or near a proposed temperature of 40°C to support immunization, a consensus on how to approach this issue requires further discussion; 6) the stability studies undertaken by the manufacturer should consider that the rate of decay may differ at various points over the storage period (e.g. the beginning versus the end of the shelf-life); and 7) at this time CTC stability assessments and label changes should be limited to a single planned excursion from the cold chain for a defined period just prior to use. Allowing the vaccine to be returned to the cold chain would not only require more complex studies on the rate of decay at different time points within the shelf-life, but tracking the history and exposure of individual vials would be difficult to implement in the field. The major recommendation of the meeting participants was that, given the importance of assessing CTC using the best approaches, that stability information to support CTC should be assessed using appropriate mathematical modelling, statistical analysis and rates of decay. Additional guidance on how to perform these studies is required.
Background

2011 - 2020 has been declared ‘A Decade of Vaccines’ with the aim of having a world in which all individuals and communities enjoy lives free from vaccine-preventable diseases. As part of this challenge, a more innovative, evidence-based approach to regulatory considerations of vaccine licensure is required in response to the changing environment. In this context, regulatory agencies from developed countries that have the resources to explore new approaches will have to work together with more resource-challenging regulatory agencies to address these scientific/regulatory issues in coordination with WHO. This includes developing a new consensus on vaccine stability assessment for planned temperature excursions that could support the transport, storage and use of vaccines in remote regions, when there is sufficient vaccine-specific data to support such an excursion.

Vaccines have to be kept under recommended storage conditions that guarantee the maintenance of their quality during production, storage, handling, transportation and use. As a result, extensive measures are put in place to avoid exposure of the product to inappropriate temperatures. Almost all vaccines used in immunization programs today are licensed for storage and distribution within a temperature-controlled supply chain of between 2°C and 8°C. However, keeping vaccines within this range is extremely difficult in countries with limited cold chain and ice pack production capacity. As a result, the increasing cost and/or logistical constraints of vaccine delivery due to these cold chain requirements, significantly hamper vaccine access. Immunization programs therefore would benefit from novel approaches to vaccine stability assessment and management that would permit the use of product at ambient temperatures, in a controlled temperature chain (CTC) for defined periods of time, as appropriate to the stability of the antigen.

Utilizing manufacturer’s product-specific accelerated stability data, CTC quality evaluations have been performed resulting in approved label changes. In addition, field studies have been undertaken using monitors (including vaccine vial monitors, VVMs) to investigate the feasibility of the vaccine use outside of the traditional cold chain, under defined and monitored conditions for limited periods of time. However, at present there is no consensus on how to best perform a
CTC assessment, nor is there guidance available for manufacturers and regulatory authorities. In order to expedite the development of this important yet challenging subject, there is an urgent need for the regulatory community to provide a harmonized approach to the evaluation of the stability of vaccines that have the potential to be stored and transported for defined periods at ambient temperatures. To address this situation, a meeting was convened by WHO to review the scientific and regulatory considerations, as well as the data required to evaluate the stability potential of vaccines stored and used above the 2 - 8°C range for defined periods. The attendees included representatives from national regulatory authorities (NRAs), national control laboratories (NCLs) and industry. This report summarizes the discussions during the consultation. In addition to this report, it was agreed that a paper would be drafted for publication in a peer-reviewed journal that would highlight the discussions and conclusions regarding, key stability indicating parameters, design of stability studies and the statistical considerations required for the evaluation of vaccine shelf-life under CTC conditions. It is important to note that many of the concepts outlined in this meeting report are applicable in general to the evaluation of vaccine stability.

Terminology Development

Controlled Temperature Chain

Generally, vaccines are stored within the 2 - 8°C range, known as the cold chain. However, several vaccines have the potential to be stored safely at higher temperature ranges appropriate to the vaccine’s heat stability profile for at least short periods of time. Previously, the term ‘Controlled Temperature Chain’ was proposed to replace the use of ‘Out of the Cold Chain’ (OCC) which referred to the storage of vaccines outside of the standard 2 - 8°C range (1). While the term OCC was intended to imply that vaccines could be stored out of the cold chain at temperatures above the 2 - 8°C range, but under controlled conditions, the term was not being interpreted as such. In addition, the term OCC seemed to contradict the current training messages and vaccine storage guidelines which stress the importance of storing vaccines in specific controlled temperatures. Following consultations in 2009, it was recommended that the term OCC should be replaced with the term controlled temperature chain (CTC) which was intended
to imply that storage conditions are consistent with labelled requirements, assuring that product will comply with its specification.

During the present consultation, the term controlled temperature chain and its definition were reviewed and it was proposed that either the term "expanded" or "extended" controlled temperature chain (ECTC) may be more appropriate. During the discussions it was generally agreed that the term "extended" should be used for linguistic clarity. However, the term controlled temperature chain (CTC) is used throughout this report because the use of the term “ECTC” will have to be endorsed through the appropriate WHO committees.

The extended controlled temperature chain was defined as temperature conditions encompassing thermal storage, transportation, or use conditions that go beyond those previously defined for a given product.

The working definition of extended controlled temperature chain, which may be dependent on the country in which vaccine is used, allows a specific vaccine to be kept and used at ambient temperatures, up to 40°C:

- For a limited period of time (length of time will vary by antigen and setting) immediately preceding vaccine administration
- Under circumstances where maintaining a 2 - 8°C cold chain is not possible or extremely challenging
- For vaccines meeting a number of pre-determined conditions
- Up until this excursion, the vaccine should continue to be kept in the traditional 2 - 8°C cold chain or other label conditions.

Other definitions relevant to these discussions:
**Extended/accelerated stability data:** The data from studies designed to allow storage or use at an extended temperature range. Accelerated data may comprise a portion of the extended data, ideally when obtained at a temperature equal to or higher than that proposed for storage or use.

**Statistical models of vaccine stability:** The statistical analysis which is used to predict the rate of decay, if any, and the precision of that prediction. This may be performed by linear regression of potency against time or other appropriate techniques. This analysis may be used to predict when the product would fall below specifications, after allowing for confidence limits and variability associated with the model and with the assays, or to set release criteria to assure that the vaccine will retain its potency through its shelf-life when maintained under the labeled conditions.

**The ‘single-point’ stability model:** The model which requires that the product must pass the specification in every assay that is performed until the end of shelf-life.

**Storage conditions:** Conditions under which a product can be stored during the dating period to maintain its specifications. These conditions usually include temperature and time.

**Initiation of use:** Product that is irrevocably committed to use. Use can be initiated by reconstitution, mixing, opening a container, or removal from pre-specified storage conditions.

**Usage period:** Time period after initiation of use during which product can be used.

**Real-time/ real-condition stability studies:** Studies on the physical, chemical, biological, biopharmaceutical and microbiological characteristics of a vaccine, during and up to the expected shelf-life and storage periods of samples under expected handling and storage conditions. The results are used to recommend storage conditions, and to establish the shelf-life and/ or the release specifications. These studies may extend beyond expected storage conditions, particularly in time.
Global views on vaccine stability from the Expanded Programme on Immunization (EPI)

Ms S. Zipursky (Optimize) described the challenges of delivering vaccines in developing countries including the practical problems encountered in the field in maintaining cold chain where there are no roads or electricity. Since it is not possible to dispense with the cold chain requirements for vaccines at this time, it is important to consider new technologies, the logistics of the supply chain as well as any untapped thermal stability, that some vaccines may have, to reduce the dependency on cold chain. The example of immunization campaigns in the 1960s and 70s with the relatively thermal stable lyophilised smallpox vaccines in use at that time was described. These, relatively thermal stable 1st generation smallpox vaccines, gave countries flexibility in delivering vaccination programmes into remote regions, often in the absence of cold chain. Recent campaigns using modern vaccines in Chad and Benin have emphasised the value for the flexibility provided if cold chain is not required during the last phase of an immunization campaign (e.g. from district store to health centre or health centre to vaccination). The freezer packs/ice required to maintain cold chain add weight and cost during transport and local storage and the ice generation capacity is frequently limited. In addition, some vaccines may also freeze when carried against frozen icepacks and the vial labels occasionally come off if the vials become wet, illustrating the additional challenges with the maintenance of cold chain in these regions. Campaigns cause a surge in the amount of vaccine to be stored and this is becoming worse with the widespread use of single dose vaccines. The lack of capacity in cold rooms is a challenge in large campaigns and temporary cold chains have to be established, requiring transporting freezers just to make icepacks. Multi-dose vials also must be kept in a cold chain once reconstituted, adding to the strain on resources.

The use of CTC would expand options for immunization strategies and ease the burden of delivering vaccines to the right groups at the right time. This approach also reduces or eliminates the risk of freezing vaccines. CTC would also promote the integration of supply chains for vaccines and drugs and reduce the costs/constraints that ice pack requirements impose on transport and the need for specialized equipment. The more cold chain requirements for vaccines
can be reduced, the easier facility integration with other supply chains such as anti-malaria drugs becomes.

The objective of this CTC project is to have on-label use of vaccines outside of the normal cold chain requirements for as long as possible, provided there is no impact on the vaccine quality that would affect clinical outcomes. This can only be achieved by the collaboration of manufacturers, discussions with and between regulators, the availability of guidelines to support these CTC evaluations, new technologies to aid implementation and support for field studies to assess these programs and their impact. It is hoped that additional regulatory pathways can be defined to allow vaccines to be licensed to reflect any additional stability potential and identify and develop technologies to enable the implementation of CTC, such as a VVM with an integrated peak temperature indicator. Work is ongoing to assess and develop appropriate threshold indicators and “time out of fridge” technologies. Collaborations to document existing CTC practices and develop and field test guidelines have been undertaken with AFRO and WPRO regional offices. Conditions specific for individual vaccines are reflected in label changes for several vaccines and training materials have been developed and trialed. In order to facilitate this program, the portfolio of current International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) and WHO prequalified vaccines have been reviewed as part of Gates CEO round-table initiative. Priority was given to products where IFPMA manufacturers are a main supplier to UNICEF markets and where the public health benefit from CTC was felt to be most significant in the short term (i.e. the next 3-5 years).

Transportation of vaccines throughout the cold chain: International perspective

Mr D. Maire (WHO) summarized the data required to support international shipping, packaging, and distribution of vaccines so that vaccines are kept in the cold chain throughout storage at the manufacturer, transport to and storage at intermediate points and finally transport to and storage at the health facility. He outlined the guidelines available from WHO for international shipment (2, 3, 4) and national storage and transport (5, 6). The minimum assigned shelf-life for vaccines supplied to UN Agencies is 18 months. Most vaccines have to be stored at 2 - 8° C. The times at which they may be stored at each stage of the cold chain are:
• Primary vaccine store - Up to 6 months
• Intermediate vaccine store
  – Region- up to 3 months
  – District- up to one month
• Health centre -Up to one month
• Health post - Up to one month

WHO has a classification for temperature criteria for international shipment of vaccines (for at least 48 hours) and shipping containers are tested to ensure compliance and fitness for purpose. Manufacturers have to validate the route of shipment and temperature profiles encountered at different times of the year. There is a wide range of temperature monitoring devices and alarm settings for international shipments, depending on the type of vaccine. There are also temperature checks at the point of arrival and if there is a breach of these conditions, the delivery is rejected. Data from UNICEF indicated that of approximately 2000 shipments per year, with shipment duration of approximately 48 hours, the rate of shipment failures is quite small: 0.8% in 2010; 0.7% in 2011 and 0.4% in 2012.

VVMs are used on all vaccines supplied to UN Agencies, although they are not used in the PAHO region. There are 4 types of VVM according to the time to their stability endpoint at a given temperature (see Table 1 below) and each vaccine has a VVM assigned on the basis of its stability profile. Stability of vaccines for VVM assignment is established from 3 different lots, each of which is tested at three temperatures (i.e., 37°C, 25°C and 5°C) to determine its failure point.

Table 1  Description of types of VVM

<table>
<thead>
<tr>
<th>Category (Vaccines)</th>
<th>Number of days to endpoint at +37°C</th>
<th>Number of days to endpoint at +25°C</th>
<th>Time to endpoint at +5°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>VVM 30 high stability</td>
<td>30</td>
<td>193</td>
<td>&gt;4 years</td>
</tr>
<tr>
<td>VVM 14 medium stability</td>
<td>14</td>
<td>90</td>
<td>&gt;3 years</td>
</tr>
<tr>
<td>VVM 7 moderate stability</td>
<td>7</td>
<td>45</td>
<td>&gt;2 years</td>
</tr>
</tbody>
</table>
Based on this approach, vaccines have met these criteria as follows:

- Hepatitis B (VVM 30) can be stored for 6 months at 20 to 25°C; or 1 month at 37°C;
- MMR (VVM 7) can be stored for 1.5 months at 20 to 25°C; or 1 week at 37°C;
- OPV (VVM 2) can be stored for 2 days at 37°C; note that storage between 20 to 25°C is not determined using this methodology.
- The VVM assigned to combination vaccines is based on the least stable component.

Most uncertainties in transport are in the middle of the cold chain from national to provincial storage centres or from district store to the health facility. National transport containers are also stress tested. Temperature excursions before vaccines reach health facilities have been documented in many studies but most problems are as a result of freezing, not exposure to high temperature. In reality, there is a low risk of high temperature exposure during international UNICEF shipment and tools are available to detect failures should they occur. Nevertheless it is important to strengthen temperature monitoring at all levels with ongoing reliance on VVM and threshold indicators.

**Regulator’s perspective**

Dr B. L. Moraes Moreira (ANVISA) summarised the laws in Brazil relating to quality control and regulation of vaccines including the requirements for stability studies and thermal cycling excursion studies. Operational qualification of vaccine shipments, includes repeated testing in a controlled environment with limited variable inputs and must challenge worst case situations, based on a number of factors. Performance qualification (PQ) of a shipment system consists of consecutive, replicate field transportation tests to demonstrate that the process is effective and reproducible. Temperature excursions outside of their respective labelled storage conditions may be acceptable, if the company provides stability data and scientific/technical justification demonstrating that product quality was not affected. Stability data to support temperature excursions can also now involve thermal cycling excursion studies. A guideline to establish the
operational qualification and PQ requirements of containers is being developed and it is anticipated that it will be published by October 2013. There is a need to have a global guideline to guide health authorities on how to develop stability data to support temperature deviations during deliveries and also to harmonize the stability data evaluation by regulators.

Mrs T. Jivapaisarnpong (Thai NCL) described some examples of issues that have arisen in Thailand. In a vaccine and cold chain system survey in 2004, measles (lyophilized) and hepatitis B vaccines (liquid) were transported between each link in the distribution chain (i.e. central, store, regional, provincial, district and health center) using a vehicle with a cold room and ice box. A data logger and freeze indicator were used to monitor temperature. When an elevated temperature excursion was observed the potency test for measles vaccine was performed, and when freezing temperatures were observed the shake test for hepatitis B vaccine was performed. From 43 routes of routine transportation: 74.4% experienced sub-zero temperatures, 100% experienced temperatures above 8°C, 11.6% above 22°C and the temperature excursion period was more than 1 hour. The potency of all measles vaccine (108 samples) passed the requirements but hepatitis B vaccines only passed the shake test 26/32 times when the freeze indicators were positive (i.e. temperature < 0°C). The points considered when temperature excursions occurred included the type of vaccine, heat or freezing sensitivity, the temperature and time of an excursion, the amount of vaccine stored and its expiry date. When evaluating excursions, a potency test would be conducted if the replacement cost of the vaccine (considering the remaining shelf-life etc.) exceeded the cost of the test. If a potency assay was conducted, the result was compared with the potency at release. Even with a satisfactory result, it was recommended that vaccine be used as soon as possible. If a potency assay was not conducted, vaccine was discarded or, if the excursion was considered minor, it was recommended that the vaccine be used as soon as possible and this was to be within 1 month.

Points to consider related to a planned CTC excursion:

- the stability profile of vaccine, which depends on the type of antigen, the production process, formulation and excipients;
- whether the excursion would occurred shortly after production or towards the end of shelf-life;
• the calibration of the cold storage.

Dr K.-T. NAM (KFDA) described the regulation and management system of vaccine storage and transportation in Korea (Rep.). The transport of vaccines is well controlled and temperature excursions are reportedly extremely rare. In summer, when temperatures are high, vaccine is transported at night. Various acts of parliament provide the legislative basis for regulation and there is a requirement for notifications and guidance for industry. The storage temperature at the point of sale has to be maintained at all times at approved storage condition, using dedicated refrigerators or freezers equipped with automatic temperature monitoring devices. There are regulations covering all aspects of transportation and all suppliers are inspected. Some vaccines produced in Korea are prequalified, so these may have to be considered for CTC label changes, if they were to be exported to countries where this would be relevant.

General considerations

Dr M. Baca-Estrada (Health Canada) summarized the proposed scope of the guidance document which will be developed and the need to support the evaluation of vaccine stability under CTC, since several vaccines are stable outside of 2 - 8°C for a period of time. The scope of such a document would be limited to the scientific and regulatory considerations to evaluate vaccine stability under CTC, where the regulatory decisions will be reflected in the vaccine label and product insert. A proposed CTC specific document should not address quality evaluations to support label changes to deal with unplanned temperature excursions but should focus on planned excursions in the context of immunization programs in cold chain challenged regions. The examples of recent approvals illustrated below, represent label changes to support unplanned excursions and changes to permit a period out of cold chain at the point of vaccine use during immunizations campaigns in Africa respectively.

For example, Health Canada has approved a label change for Prevnar which now includes the statement:
‘Prevnar 13 has been shown to be stable at temperatures of up to 25°C\(^1\) for 4 days. Cumulative multiple temperature excursions between 8°C and 25°C are permitted, as long as the total time does not exceed 4 days (96 hours). These data are not recommendations for shipping and storage but may guide decisions for use in case of temporary temperature excursions.’

Whereas, for a vaccination campaign in Benin, the label approved by the Indian NRA (DCGI) supported by a stability evaluation performed at Health Canada stated that:

‘MenAfriVac to be stored at 40°C for not more than 4 days immediately prior to administration provided that the vaccine has not reached its expiry date and the vaccine vial monitor is still valid.’

Both of these situations followed the similar principles but specifics of each analysis were different.

Dr T. Wu (Health Canada) described the stability studies required to be undertaken by manufacturers throughout product life-cycle including product development, licensure and post-licensure. The goals of stability studies are to establish product stability characteristics which support the proposed shelf-life for licensure and support post-licensure manufacturing changes. In these stability studies, adequate characterization is required noting that vaccine decay rates may change over shelf-life. Some products may have a greater loss of potency at the beginning of shelf-life, whereas, the loss observed for other products of the same vaccine type may be greater at the end of shelf-life. There are no perfect potency tests or perfect stability data sets and analysis and decision making should be based on scientific principles and a robust risk/benefit analysis. The specifics of the stability assay(s) being used in the evaluation must be considered carefully, since all tests have limitations. The data analysis must determine the rate of product decay using appropriate statistical methods and not simply consider whether the test sample met

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\(^1\) At the time of the workshop, the approved label indicated a higher temperature (40°C). However, based on an expanded data set subsequently provided by the manufacturer, the excursion temperature on the label was amended to 25°C with a provision for multiple excursions between 8°C and 25°C.
or failed the specifications. The most important stability-indicating parameter for vaccines is potency, although safety assays such as those for residual toxin/reversibility of toxoid and toxicity of degradation products are also important to consider. Additional critical parameters include the moisture content for lyophilized vaccines, pH where this is known to affect stability and adsorption rate. Various types of tests are used in the measurement of potency: counts of live virus or bacteria, physicochemical tests (total and free polysaccharide and carrier protein, molecular size etc.), in vivo immunogenicity and in vitro antigen content using immunoassays.

Although in vivo assays are potentially capable of detecting changes in antigen integrity, especially if it is a challenge test or measures functional antibodies, they are highly variable with a high invalidity rate. In vivo assays are also time consuming, costly to perform and are not compliant with reduction in animal usage (i.e. the 3R approach). In vitro assays are less variable, rapid and 3R compliant. However, stability indicating in vitro assays are not always available or they may not be sensitive enough to detect conformation changes of antigen adequately. Some tests (in vitro and in vivo) are more predictive of clinical effectiveness, whereas, others are only a measure of consistency of manufacturing. Ideally a battery of tests should be performed, including in vivo and in vitro assays, to establish antigenicity and stability characteristics of the vaccine, clinical relevance for each test and to verify the suitability of in vitro tests for lot release and stability monitoring.

A critical point identified was that in vivo immunogenicity assays are only relevant if they are designed properly. These assays must be demonstrated to have an adequate dose–response range, with multiple lots that represent the commercial product and the assay should be capable of detecting sub-potent or degraded lots. Health Canada has encountered several situations where immunogenicity assays developed as potency tests employ booster injections for each antigen dose in order to reduce assay viability. However, the use of multiple injections per dose can also produce a shallow dose–response curve with little resolving power. Potentially, such tests can be incapable of detecting differences between vaccine lots with differing antigen content. In general, an immunization schedule using one injection per antigen dose is preferred and additional injections per dose can only be justified if the immune response in the selected animal model is inadequate after a single injection.
The specifications of potency tests should be considered as product specific and must be based on potency characteristics of vaccine lots demonstrated to be efficacious or immunogenic in clinical studies. With products that decline in potency over a product’s shelf-life, different potency specifications at release and end of shelf-life should be established. Release specifications should be set to ensure that vaccine quality (safety and efficacy) will be adequate throughout product’s dating period as defined by the products stability profile. Ideally the upper limit for the potency should have been demonstrated to be safe in clinical trials. Specifications at end of shelf-life should be linked to the minimum potency demonstrated to be efficacious in clinical trials. These requirements are detailed in ICH document Q6B (7). In order to perform potency tests effectively, reference standards are required to ensure comparable potency throughout the life cycle of a vaccine. The reference standard can be used to set test validity criteria, to ensure that test performance is consistent over time and the stability of the standard itself must also be appropriately monitored. The stability data required for licensure and to support shelf-life is product-specific real time data generated from a minimum of three lots using manufacturing process similar to that used for clinical and commercial lots. Appropriate statistical methods as described in WHO guidelines on stability evaluation of vaccines (8) should be used to determine the rate of product decay and the precision of that determination. Accelerated stability data, which is commonly generated during product development and characterization for licensure, can form the basis of a CTC stability assessment and label change, provided the target temperature for the CTC application has been included in the studies (e.g. 40°C). In such a case the accelerated data at the CTC target temperature would be considered the “real time” data for the period at elevated temperature and would be evaluated along with the real time data at the more traditional 2 - 8°C condition. It should be noted that using this approach, it is possible to consider previously developed accelerated stability data for a CTC label change, provided that data is relevant for the current manufacturing process. With new products that are still in development and being considered for a CTC application, stability studies for pre and post-licensure can designed with this in mind. Routine post-licensure stability studies are undertaken to monitor the stability of commercial production and also to support major manufacturing changes, once the changes have been assessed and approved. When considering a post-licensure manufacturing change which has the potential to impact stability, a comparative pre and post-change forced degradation stability study, with commercial batches at
the relevant production step, is the most useful and cost effective data to generate in support of the maintenance of the approved shelf-life. As mentioned above, real time data available through the routine stability monitoring program would still be required but, with the use of forced degradation data, the regulatory approval of the change will not have to be delayed while real time data accumulates.

**Stability indicating parameters**

Dr C. Conrad (PEI) considered the parameters of vaccine stability that would need to be evaluated by regulators to support the storage/use of a vaccine under a defined temperature range above the original 2 - 8°C labeled storage conditions. In line with previous presentations, the focus of this effort would be to facilitate distribution of vaccine during the final stages of the delivery chain, such as from storage at the health centre to the remote field site for vaccine administration, assuming that unused vaccine would not be returned to the cold chain following this planned excursion. Unplanned excursions was not the focus of these discussions and it was understood that a 2 - 8°C cold chain would be maintained just prior to the defined CTC period. The use of vaccine under these conditions would have to be carefully planned to avoid wastage of stock as unused vaccine would have to be discarded at the end of the defined CTC period, even if the VVM still indicated that the vaccine could be used. Any vaccines which are re-labelled to facilitate this change would have to meet a number of pre-determined conditions. Options such as shortening a products shelf-life to allow for a portion of a vaccine’s “stability budget” to be used at a higher temperature for a shorter period of time were discussed. One consequence of such an approach would be that there would be at least two versions of a vaccine; one with a shelf-life defined under a typical 2 - 8°C cold chain condition and a second version under a CTC label with a shorter shelf-life, which would also include a provision for an extended temperature range over a defined period at the time of vaccine administration.

As noted in the previous talk, there is no single stability-indicating assay or parameter that profiles the stability characteristics of a biological product. Changes in the identity, purity and potency etc., should be determined with the appropriate approved methods. Assay validation would have to include evaluation of the CTC conditions. The integrity of container/closure
systems at the elevated temperatures and different humidity should also be considered. Ideally, regulatory decisions would be made on studies that predict clinical behaviour of the vaccine and any decision as to the need to generate clinical data should only be made after the assessment of stability data. It was noted that the evaluation of the quality, non-clinical and clinical data for a CTC application would be more challenging where there is no direct quality parameter or potency test that correlates with clinical safety and efficacy. Additionally, for complex vaccines such as MMR-varicella, where interference between components is known to occur, the relative levels of components should be considered. Where surrogate markers are available the lowest potency below which a vaccine will not result in sero-protection, needs to be understood or defined to support a CTC evaluation. Surveillance data may give supportive information but when this is not done with the involvement of the manufacturer, it should not be considered alone and potentially as supportive information. Any label changes to allow CTC distribution must be product specific and, where possible, should be considered during product development. Going forward, opportunities and data requirements for a CTC label should be communicated to manufacturers. Exposure to 45°C rather than 40°C may affect protein denaturation and some potency assays may not detect this degradation resulting from these elevated temperature conditions. Safety issues also need to be considered if there is degradation. At present, three batches of similar potency are generally included in clinical trials but it may be more appropriate to include batches of different potency in clinical trials to explore these scenarios, in addition to demonstrating sufficient consistency in clinical response to commercial batches. In order to define stability and comparability criteria to evaluate CTC suitability, as with licensure studies, several types of stability data should be considered including: product specific typical real-time 2 - 8°C data, forced degradation and accelerated data, which may help elucidate the degradation profile/kinetics of degradation as well as the degradation products. As noted before, accelerated data obtained under a maximum CTC temperature (e.g. 40°C) would be considered “real time” stability data for the extended temperature condition. Several types of tests may need to be considered in order to determine the best stability-indicating assays of adequate test sensitivity. Ideally the suitability of such tests should have been established during clinical trials and specifications should be link to expected clinical outcomes. The use of different specifications for release and expiration should be supported by sufficient data to demonstrate that clinical performance is not affected.
The properties of different types of vaccines have to be considered separately and these families of products include: Protein based vaccines (e.g. Hepatitis B, HPV), Life attenuated products (e.g. MMRV, Yellow fever, OPV), Whole virus-inactivated vaccines (e.g. Rabies, IPV, HepA), Polysaccharide conjugate vaccines (e.g. Hib, pneumococcal and meningococcal products) and Toxoid based vaccines (e.g. D,T and Combination products). Control of each of these families of products is complex. For example, in spite of extensive experience with regard to the manufacturing and control of hepatitis B vaccine, small manufacturing changes over time, with a specific product, were later revealed in clinical studies to have had an adverse impact on clinical performance of the vaccine. Antigenicity and immunogenicity are generally assessed with in vitro assays or in vivo (mice) respectively but, even with the antigenic characteristic of HBsAg, using either monoclonal or polyclonal antibodies will give different levels of information. Additionally, the degree of adsorption to Alum/MPL is also important, as is the degree of aggregation or structural stability of the particles. For live viral vaccines, assays of importance include virus concentration by immunofocus or plaque assay, pH and residual moisture for lyophilized products. For polysaccharide conjugate vaccines, the saccharide that is covalently bound to the carrier protein is immunologically critical for clinical protection and measures of conjugate integrity (e.g. free polysaccharide) are an important index of vaccine potency, as is the sialic acid content for certain conjugates. Combination toxoid vaccines are highly complex and because suitable in vitro assays are underdeveloped at present in vivo potency tests are generally used.

The consistency approach (9) using in vitro assays to replace the more variable in vivo assays is an alternative approach for lot release testing and has been applied to support 3R objectives. The approach is based on the principle that the quality of vaccines is a consequence of a quality system (GMP and QA). Through a quality system, consistent production of lots with similar characteristics to those lots that have been shown to be safe and effective in the clinic can be maintained. Consistency builds on product development (including clinical testing) and routine production using suitable analytical tools and the continuous evaluation of data generated over time (trend analysis). Release specifications are established based on the characteristics and critical parameters of the clinical consistency lots, as assessed with appropriate test
methodologies and robust statistical analysis. The need for some in vivo consistency tests, at least until in vitro methods are in place, will continue and may also be required for product characterization following manufacturing changes, if the alternate in vitro assays are not sufficiently qualitative in terms of the vaccine’s characterization. Although release specifications are essential tools to maintain the consistency of manufacturing, other in-process characteristics and parameters measured on the intermediates and the final product also contribute to the assessment of consistency. The application of any assay (in vitro or in vivo) for the regulatory approval of CTC, would require that the test be validated to perform over the extended temperature range to ensure continued clinical effectiveness.

Design of stability studies and statistical considerations

Dr P. Krause (CBER, FDA) reviewed the design of stability studies and statistical considerations applicable to temperature excursions. A central concept presented was that for all stability evaluations including those for CTC applications, release potency and shelf-life are optimally evaluated using relevant statistical models of product stability under predicted conditions of storage. This provides both the most accurate results and an indicator of the level of confidence in those results. The consensus developed through two previous WHO vaccine stability guidance implementation workshops on the advantages of statistical modeling was mentioned and participants at the CTC workshop were referred to the 2009 Special Issue No. 6 of Biologicals that summarized those discussions. Included in that issue of Biologicals was a more detailed development of the general vaccine stability assessment principles presented by Dr. Krause at the CTC workshop and participants were also referred to that specific paper (10).

Stability-indicating assays should identify degradation that is relevant to vaccine effectiveness and the assays must be amenable to validation. The more precise the assay the better and it was noted that animal assays pose particular challenges because of their high variability. The lowest potency that is considered to be effective can be determined through clinical trials (or by other means) and is defined as the potency lower limit (LL). Similarly the highest potency that does not give rise to safety concerns can be determined through clinical trials (or other means) and is defined as the potency upper limit (UL). The actual potency of a product must be between the

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UL and LL (also known as the clinical window) such that marketed product is comparable to batches shown to be safe and effective in clinical studies throughout its shelf-life. Assay variability (or precision) must be considered when establishing shelf-life and a release model.

Even when different lot release models are used, information about assay variability and statistically valid stability evaluations can be used to predict the likelihood that a product will have potency at any given level at end-expiry, and can be used to calculate the mean end-expiry potency level that any given release model actually assures. Therefore, regardless of whether or not the release model is based on this approach, these statistical methods have substantial utility in evaluating the robustness of the release model, especially in the context of additional thermal stresses.

Lot release specifications, which are based on assessment of stability data from commercial batches studied during development, must account for and thus intrinsically predict the stability of future batches. The most reliable predictions to support the dating period are based on mathematical modeling of test data derived from clinically relevant vaccine stability-indicating parameters. Over time a vaccine will lose potency, aggregate or form potentially toxic degradants, concerns that must be addressed by the stability program. Supportive data to study product degradation can often be obtained in accelerated or forced degradation studies. There may also be alterations of the container (including leaching, degradation of stopper material) that data from real time, accelerated or forced degradation studies can help to address. Product stability is influenced by the formulation, which often includes specific buffers or surfactants, or the product could be lyophilized. Stability can also be influenced by the container and closure system and of course the storage conditions (e.g. temperature/protection from light). There are numerous opportunities for product degradation during shipping, storage at clinic and after reconstitution. Stability related quality attributes differ between products, which may include pH for liquid presentations or moisture for lyophilized products. These parameters need to be assessed to determine their influence on the rate of change in quality for any specific vaccine.

The minimum release potency specification is typically calculated to ensure that the release potency is sufficiently high to allow for expected stability losses, and should encompass all
anticipated conditions throughout storage and shipping. These anticipated losses in potency throughout the dating period should be considered in determining the minimum release potency (or lower release limit, LRL) in order to address these potential potency losses over time. An error term (factor) that encompasses assay variability and the precision associated with potency loss estimates must also be considered in establishing the LRL; this error term includes the assessment of statistical confidence in the results. The error term used in the calculation of upper release potency specification is usually based on assay precision only (URL) (10). The range between lower and upper potency release limits (LRL-URL) is called the release potency window. When assay precision is high and manufacturing variability is low, it is easier to construct a release model due to improved understanding of release potencies and better estimate of stability.

Current models for product release and shelf-life determination do not routinely allow for excursions. Allowing for excursions would require a demonstration that the vaccine, as filled, contained a potency reserve that could be used to allow storage of a product at higher temperatures for specific periods of time. With sufficient data, models can indicate whether the product is truly excursion resilient, and if not how such a potency reserve could be created, for example, by shortening the shelf-life of products that will be subjected to planned excursions or considering ways to tighten release specifications to enhance the excursion-resilience of a product. The impact of excursions may be predicted from the expected decay (slope for products following first-order decay kinetics) during the excursion, which may be experimentally determined or estimated by Arrhenius kinetics when a vaccine is shown to follow the Arrhenius model. The precision of that estimate can be determined and considered in the “error term”. For many products, it seems likely that potency loss due to an excursion may not be highly dependent on when that excursion occurs during the dating period but this would need to be established for each product. Allowing for an excursion at the end of shelf-life could compress the release window and shorten the expiry date. If the minimum release specification were raised, more safety data could be required if this also led to a need to release product at potencies at levels above the upper release limit. Enhanced thermostability could be achieved by overfilling or by setting the end-expiry date earlier than it otherwise needed to be. Given that current end-expiry specifications are set based on rigorous clinical trials and the product licensure process,
unless expiration dates were changed, excursions at higher temperatures could not generally be undertaken without a significant risk of reducing potency below the current end-expiry specification. For vaccines with substantial shelf-life, the potency loss allowed during a reduced 2 - 8°C storage period could be diverted to permit the planned excursions under a CTC label. However, changing vaccine expiration dates raises logistical and regulatory issues, since keeping track of different expiration dates for the same product would be complex and it is difficult (and in some countries illegal) to routinely and accurately re-label vials. For products in development, additional stability could be built into the vaccine through higher release potencies within the URL to cover a planned CTC excursion or the expiry date could be shortened. Improving the precision of potency tests could improve stability estimates. Although manufacturers may not want to explore assay precision improvements with current products, due to additional validation costs, this could potentially be achieved by increasing the replicates in an assay. Reducing the time that vaccines are out of the recommended temperature during manufacturing (e.g. by more rapid labeling) or shipping under colder conditions (where possible) with resultant lower loss rates, may provide additional potency reserve that could be used during planned CTC excursions.

If comprehensive statistical models are not used for the stability assessment and the traditional “single-point model” (10) is used instead, there are several disadvantages in evaluating planned CTC excursions. This is because in setting release specifications or establishing shelf-life, the single-point model does not provide statistically robust estimates, discards most of the data and confidence in the values assigned cannot be determined. This is particularly problematic if a product is released near the lower potency limit. Nevertheless, a single-point model can provide acceptable results when assays have very high precision or there is a very wide therapeutic index and filling is at levels that substantially exceed the minimum required potency. Because these situations are rare for vaccines, use of the single-point model is strongly discouraged for CTC applications.

**The evaluation of controlled temperature chain conditions and vaccine shelf-life**
Dr H. Meyer (PEI) described the issues relating to vaccine quality, safety and efficacy under CTC and emphasized the need for rigorous data assessment before label storage conditions could be changed. The presentation considered whether quality and stability data (including animal data) were sufficient to predict clinical performance for CTC applications or whether additional clinical data would be required. It was noted that while vaccine characteristics, such as the identification of critical quality attributes and stability at different temperatures, are established during product development, the clinical studies that must consider vaccine performance throughout the product’s shelf-life are generally performed with recently manufactured material that has been stored at 2 - 8°C. This presentation also considered the use of aged lots for dose finding studies to determine the lowest antigen content that elicits a protective immune response and establish shelf-life through clinical trials.

During the clinical development of new vaccines intended for CTC applications, in principle different temperature ranges and time periods outside the standard storage conditions to simulate the planned CTC conditions could be evaluated and could also include the use of multi-dose containers, repeated withdrawal of vaccine from the container and stability after reconstitution. The stability testing could be undertaken using a panel of in vitro and/or in vivo assays (animal studies), optimally on aged lots and perhaps even with lots having experienced the desired controlled temperature excursions. However, this is not always feasible or practical, especially when no accepted correlate of protection exists or no surrogate markers are established and considering the time required to conduct some of these studies.

For approved vaccines, the existing stability data package includes long-term stability studies, annual studies, accelerated stability studies and thermostability studies. The evaluation of controlled temperature excursions may be undertaken through extended stability studies using relevant assays at different time points throughout the shelf-life, where the temperature exposure used in study should be similar to what realistically would be expected; preferably worse. Clinical evaluation of CTC may be required for complex multivalent vaccines (pentavalent, hexavalent etc.), new adjuvants and delivery systems and should consider the study population. The assessment of the data might be different in different regions depending on the epidemiological situation (e.g. against polio in EU where routine immunization is still
undertaken). A CTC label can only be established for a specific vaccine and cannot be established for a class of vaccines, even if there is a common minimum potency.

For live attenuated vaccines, virus titres or bacteria counts are predictive in monovalent vaccines. However, as it is known that there is immunological interference of virus components and relative virus titers are therefore important to consider. Historic data may not be sufficient to support CTC evaluations and label changes. This is because the quality of historic studies may be unclear or unacceptable or there may have been changes in the manufacturing processes over time that could negatively impact of the product’s stability under CTC temperature conditions. Even in situations where current clinical data may exist there can still be challenges. For example, clinical study data have shown that a lyophilised human rotavirus vaccine is still effective after storage at 37°C for seven days (11). However, no CTC label has been approved for this vaccine and it is unclear whether a clinical study report is available. CTC labels have been approved for various meningococcal and pneumococcal vaccines, where *in vitro* (physiochemical characteristics) and *in vivo* pre-clinical data (integrity of carrier protein) can be linked directly to clinical performance. This demonstrates that in principle, quality and stability data alone can be sufficient for a CTC label. For HPV vaccines, no surrogate marker or correlate of protection is established but quality and stability data alone are sufficient. In the US, CTC labels have been approved for both the currently available HPV vaccines; Gardasil can be elevated to temperatures at or below 25°C for 72 hours and Cervarix can be stored for 3 days between 20°C and 25°C or for 1 day between 25°C and 37°C.

Inadvertant temperature excursions should be considered separately from the planned temperature excursions which are the focus of this CTC initiative, given the different program objectives and field conditions related to CTC applications. Data from field studies (monitoring studies) are not be considered sufficient to change the label for CTC uses. These field studies are important but have a different scope and are intended to monitor practices, compliance and equipment during vaccination campaigns (e.g. the use and performance of VVM, temperature cards). When considering CTC labeling, it must be remembered that the product information, including the package insert and labelling, is a legal document. Off-label use is the responsibility of person administering the vaccine. Whereas, CTC labelling should be based on a high level of
evidence, such as that expected from a manufacturer’s study reports for stability and clinical programs. Published data, unrelated to a review process, may not necessarily allow for sufficient critical review since important information might be missing. This missing information could include the GLP compliance to standards related to any clinical studies as well as the performance and validation of the assays used. Finally, it is important to understand that there are different regulatory approaches and management practices for vaccination programs in various regions. Although it may be possible to implement best review practices and have more uniform information available (i.e. quality, non-clinical and clinical data) to support CTC product evaluations for label changes, the national/regional regulatory and vaccination programmatic needs will also influence outcomes.

Labelling of vaccines for CTC use

Ms S. Zipursky (Optimize) described the labelling vaccines for CTC use. Currently, 2 - 8ºC is the standard temperature at which vaccines are stored. From a programmatic perspective, the information that is on the labels needs to be clear for the conditions on the labels to be followed. WHO’s EPI program must develop and share guidance to ensure the conditions on the label are met in various settings (i.e. campaigns, routine use, birth dose, outreach). Countries have the choice to use or not to use the CTC flexibility. Vaccine is generally held in cold chain until it leaves the health centre. If CTCs are used, specific training is undertaken. For example, since thermometers are frequently not available during a vaccination campaign, staff are trained in the use of threshold indicators, which change instantly if exposed to 40ºC. To reduce vaccine losses, vials left over from the previous day are marked with a line and the numbers of marked and new vials are recorded on a CTC monitoring sheet. The marked vials are then used first on the next day.

Vaccine regulators must determine what data is required of manufactures to support CTC storage and delivery conditions in regions with limited cold chain, for products that have this capacity. It must be emphasized that some of the examples listed in Table 2 below may apply in one situation but not in all.
### Table 2 Examples of storage encountered by manufacturers

<table>
<thead>
<tr>
<th>Situation</th>
<th>Storage time and conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>In order to address lack of cold chain capacity at health centre level</strong></td>
<td>30 days minimum routine</td>
</tr>
<tr>
<td><strong>In order to address cold chain challenges/ice challenges at health centre level</strong></td>
<td>1 day minimum (with re-integration into the cold chain) ideal for routine</td>
</tr>
<tr>
<td><strong>In order to address lack of cold chain capacity at district level</strong></td>
<td>60 days minimum routine</td>
</tr>
<tr>
<td><strong>In order to address cold chain challenges at national level</strong></td>
<td>6 months minimum routine</td>
</tr>
<tr>
<td><strong>Campaign vaccines</strong></td>
<td>ideal minimum: 14-30 days</td>
</tr>
<tr>
<td><strong>Hepatitis B birth dose</strong></td>
<td>ideal minimum 30-45 days</td>
</tr>
<tr>
<td><strong>Routine vaccines</strong></td>
<td>ideal minimum 30-45 days</td>
</tr>
</tbody>
</table>

**Following discussions on labels and wording, the group agreed that:**

- Any recommendation on CTC conditions will be reflected in the package insert, not on the primary container or package
- The typical approved transport and storage conditions must be maintained until the CTC period just prior to use
- Statements on CTC conditions should be in a separate paragraph, under the conditions of use section. The CTC statement should include the temperature and time range and also the following information:
  - Whether or not the vaccine can be reintroduced to storage at 2 - 8ºC after a period under the CTC condition or if it must be discarded
  - Whether repeated withdrawals from the cold chain are possible
  - Clarification on how to handle the vaccine when it consists of two or more containers (components), for example involving reconstitution or mixture before use
  - For how long a reconstituted or mixed vaccine can be kept for use and under which conditions
Whether or not the WHO multi-dose vaccination policy is applicable for opened or un-opened vials

Examples for proposed CTC statements were discussed.

**Review of case studies on stability evaluation of vaccines under an CTC**

Four case studies were presented by manufacturers who produce prequalified vaccines.

Dr D. Felnerova (Crucell) discussed the stability data available for the birth dose of a hepatitis B vaccine, Hepavax gene. The antigen for this vaccine is produced in the *Hansenula* yeast strain and is produced in two formulations, for use in different situations. This vaccine is prequalified and has a 36 month shelf-life and meets VVM 30 requirements. It is available as 5 and 10 dose presentations with thiomersal or in a thiomersal-free formulation in monodose in vials and syringes.

The manufacturer has undertaken one stability study and the vaccine has been included in two other studies in which *in vitro* potency tests were used to assay vaccine stored at various temperatures for different periods of time. In the manufacturer’s study, 3 lots were held at 37 ºC and representative vials were tested using *in vitro* and *in vivo* potency tests along with all other final container tests at 0, 2, 4 and 6 months. The test results were within specification after the product was stored at 37 ºC for 6 months.

This vaccine has been tested in 19 clinical trials involving over 1400 adults and 1200 neonates and children. 600 million doses have been sold worldwide, which means that approximately 190 million subjects have been vaccinated. No reports on lack of efficacy have been received and the current database supports the favourable safety profile of Hepavax-Gene. There are publications that indicate existing use of Hepatitis B vaccines in CTC settings. However it was emphasized in discussions that the data must be available to allow a full CTC assessment.

The following issues will have to be considered
• Regulatory pathway: variation to the existing license or development of the CTC indication as a new product requiring a new license

• Involvement of the regulatory bodies
  • NRA in manufacturing country
  • WHO
  • NRA in importing country

• Requirements for licensure clarified up front with reference authorities

• Use in campaigns, routine or specific use – impact the requirements

• Validation of assays at the corresponding temperatures

• Additional testing

• Availability of the testing material at the end of shelf-life

• Availability of threshold indicator / expiry of VVM might be a limitation

• Manufacturer prospective: Costs/Efforts and Health Benefit to be balanced

• Support / advocacy: will WHO provide to ensure awareness and appropriate usage of the vaccine in the countries?

• Training and supervision of health staff in using vaccines in CTC

Dr C. Lecomte (Glaxo Smith Kline, GSK) Vaccines, described studies on Cervarix HPV vaccine and the GSK approach in terms of vaccine thermostability. She emphasized thermostability of vaccines is key since temperature variations may happen at each step of the distribution chain from primary storage up to the health care professional. She referred to ICH and WHO documents on stability testing (12, 13) which summarise why supporting data are required and emphasize that heat impact on vaccines is cumulative. Each exposure to elevated temperature results in some degradation of the vaccine, even if the remaining potency is still above the level considered to be the minimal immunizing potency. GSK follows a two-step experimental approach in the design of thermocycling studies. Firstly, a study (pre-test) is conducted in order to set the most appropriate stressed conditions for a specific vaccine. Based on this pre-test, kinetics of degradation can be established and duration of vaccine exposure to the stress temperatures can be determined. Secondly, thermocycling studies are conducted on 3 consistency batches, according to the stressed conditions identified during the pre-tests. Using this approach, GSK has developed their concept of a stability budget (14). A stability budget
considers long-term, accelerated, extreme excursion, and temperature cycling studies to determine the amount of time out of storage (ToS) or time out of refrigeration (ToR) that a drug product may experience without any significant risk to its quality. The allowable time outside recommended storage conditions must be budgeted throughout each step of the distribution chain. Using such studies, vaccines are categorized according to the assessment of the available temperature cycling study data.

The initial stability package approved for Cervarix HPV vaccine did not contain out of the refrigerator conditions, and this was reflected in the initial Summary of Product Characteristics (SPC). The SPC was updated following a post-approval variation which included new thermocycling data. Prior to the submission of the variation, Cervarix had a shelf-life of 3 years and the label included the following precautions for storage: ‘Store in refrigerator (2°C – 8°C). Do not freeze. Protect from light’

The range of stability data submitted with the variation is listed in Table 3.

<table>
<thead>
<tr>
<th>Temperature cycling and stability data</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Syringes and vials</td>
<td>11 months at 2-8°C+ 1 month at 25°C + 48 months at 2-8°C</td>
</tr>
<tr>
<td>Syringes</td>
<td>9 months at 2-8°C+ 14 days at 25°C + 51 months at 2-8°C</td>
</tr>
<tr>
<td>Syringes</td>
<td>7 days at 37°C + 48 months at 2-8°C</td>
</tr>
<tr>
<td>Syringes</td>
<td>48 months at 2-8°C+7 days at 37°C</td>
</tr>
<tr>
<td>Syringes</td>
<td>60 months at 2-8°C+7 days at 37°C</td>
</tr>
<tr>
<td>Syringes</td>
<td>9 months at 2-8°C+ 7 days at 37°C + 51 months at 2-8°C</td>
</tr>
</tbody>
</table>

From these data and the calculation of the stability budget for Cervarix, the EU SPC was amended through a variation and after approval states:

*Shelf-life - 4 years. ‘Cervarix should be administered as soon as possible after being removed from the refrigerator. However, for the monodose containers, the stability has been demonstrated when stored outside the refrigerator for up to 3 days at temperatures between 8°C*
and 25°C or for up to 1 day at temperatures between 25°C and 37°C”. This variation was not approved by WHO as it did not meet VVM criteria.

Taking into consideration the GSK approach based on stability budget, vaccine categorization and thermocycling studies, combining long-term storage and temperature excursions, the following questions were raised for discussion:

- Is this approach aligned with the CTC concept?
- How to reconcile this stability budget approach, to a CTC or VVM assessment in terms of supporting data used, e.g. a temperature of 40°C vs. 37°C and the related stability plan complexity?
- How to translate a stability budget and supporting data into the WHO leaflet?
- What is the most appropriate wording to be used for time out of refrigeration excursions (vs. recommended storage condition terminology)?

Dr A. Laschi (Sanofi Pasteur) described their strategy for storage of vaccines outside of the recommended storage temperature of 2 - 8°C, with yellow fever as an example. This vaccine meets VVM 14 requirements and the vaccine and diluents are stored and shipped at 2 - 8°C. Local storage conditions are intended to be 2 - 8°C for both vaccine and diluent, according to the label, but frequently the diluent is stored at ambient temperature. The vaccine is to be stored at 2 - 8°C until the end of the immunization session (max 6 h) but in practice the diluent is cooled in ice just before use and once reconstituted, the vaccine is then kept in ice until the end of immunization session (max 6h). Both vaccine and diluents have a shelf-life of 3 years. Sanofi Pasteur has initiated a broad program to investigate the feasibility of vaccine for CTC applications. Under consideration is the appropriate approach to support temperature excursions during transport, distribution and to support storage under CTC conditions during “the last mile” prior to immunization, through the use of existing data and/or the generation of new stability data.

For the transport / distribution excursions, a typical study design will include 1 lot of liquid or freeze dried vaccine and diluent for reconstitution. Vials of vaccine will be subject to the stress conditions in parallel with vials from the same lot in typical real time conditions (+5°C) in annual stability studies. Vials will initially be stored at +5°C (to simulate the period before
distribution) for between 6 and 12 months; a second period simulating the distribution process at +25°C (for approximately 7 days for sensitive vaccines and 1 month for other vaccines) and then a third period at +5°C till the expiry date. Test points will be time 0, annually and the end of shelf-life. Samples will be tested for physico-chemical parameters (appearance, pH, residual moisture for freeze-dried vaccines) and potency. Low temperature excursions studies will also be performed. For the “last mile” CTC studies, through the internal Immunization Practices Network, Sanofi Pasteur made the strategic decision in 2011, to assess the possibility of using some vaccines at “ambient” temperatures, up to 40°C for a limited period of time immediately preceding administration. Vaccines to be studied will include products used in mass campaigns or emergency diseases such as Yellow Fever, Cholera, Meningitis, Polio, Influenza, JE and Dengue. A collaboration has been signed with PATH and WHO to undertake a pilot study using Stamaril, since this vaccine is often used in program circumstances where maintaining a 2 - 8°C cold chain is not possible or is extremely challenging. The study will start before the end of November 2012. If the results are satisfactory, the new recommendation will be implemented for Stamaril from 2014. This pilot could open the way to other vaccines used in campaigns.

The stability studies are designed to support distribution conditions and end-user administration at controlled temperatures (up to +40°C) and will include the expected local distribution duration (days), the predicted temperature exposure range and the time out of refrigeration that the vaccine will experience during the local distribution and the end-user administration (after reconstitution and after first opening). The 10-dose freeze-dried vial and the 10-dose diluent (NaCl 9%) in polypropylene ampoule (bottle-pack) will be used. Studies are under consideration in order to generate data allowing defining the CTC conditions for Sanofi Pasteur Yellow Fever vaccine in order to determine:

- If the vaccine and the diluent are both stable at the proposed 40°C for a defined period
- If the reconstituted vaccine can be stored under CTC, when the vaccine and diluent have been stored under CTC for the maximal defined period. Reconstituted multi-dose presentations should also be considered, when in use in such CTC applications.
Two studies will include three commercial batches, with one batch close to the end of the shelf-life and another study will include two batches, according to guidance (CPMP/QWP/2934/99), with one batch close to the end of the shelf-life. The results must comply with approved specifications defined for storage at +5°C, to facilitate a comparison between data obtained at +5°C and at +40°C and the statistical analysis. It is then hoped that the labeling for storage and transport can be changed from ‘STAMARIL® should be refrigerated for storage and transport, between 2°C to 8°C. Protect from light’ to ‘In situations where maintaining the 2°C to 8°C storage immediately prior to administration is not possible, both STAMARIL® and its diluent can be stored at temperatures not exceeding 40°C for up to XX days, provided the VVM has not yet reached its endpoint and the expiry date has not been reached’ (under discussion). It is hoped that the labeling for reconstitution and administration would also be changed. The duration of storage claimed would be ‘Immediately prior to reconstitution (providing that VVM and threshold indicator placed on the tertiary packaging supported product use): 4 days at +40°C prior to reconstitution’ like MenAfrivac to take into account the potential occurrences of Cold Chain Break and after reconstitution: 6 hours at +40°C. These proposals for revisions to the labeling are under discussion with the Health Authorities.

Dr D. A. Hokama (Bio-Manguinhos) reported the Stability Studies on 3 multidose presentations of Biomanguinis yellow fever vaccine, all of which are prequalified by WHO. A stability study undertaken in 2006 on 10 dose vials held at 37º for 6 months, included the following tests: Appearance, pH, Residual moisture, Protein, and Potency. This study indicated that the 10 dose vaccine maintains its potency for 6 months at 37°C. Additional studies were initiated in 2012 under the Optimize Project in collaboration with WHO, PATH and Fiocruz. The study is divided into 4 parts:

1) Vaccines and diluents maintained for 28 days at 40°C.
   Every 7 days tests for potency, residual moisture (vaccines), pH and conductively (diluent) would be conducted.
2) Vaccines and diluents held at 40°C. Reconstituted vaccine would be held at 40°C for 8 hours and tested for potency and sterility.
Vaccines and diluents held 2 to 8ºC. Reconstituted vaccine would be held at 40ºC for 8 hours and tested for potency and sterility.

3) Vaccines maintained at 2 to 8ºC and diluents at 40ºC. Vaccine would be reconstituted, maintained at 2 to 8ºC for 8 hours and tested for potency and sterility.

4) Vaccines with VVM 14 and 30 stored at 2-8ºC for approximately 18 months, would be placed at 40ºC for 07 and 21 days, respectively, and returned to 2-8ºC until the end point of the VVM. At each test point, potency and residual moisture would be determined.

Data are still being generated from these samples but preliminary results of this study indicate that the potency and moisture content of the 5 dose yellow fever vaccine are within specification for 21 days at 40ºC. In order to use the results of accelerated studies to predict vaccine behavior over long time periods, a study was conducted in 2000 to evaluate the relationship between temperature and potency loss on 5 dose vials using the Arrhenius Equation. The temperatures used were 32ºC, 37ºC and 42ºC. A review of the data from the Arrhenius study and the preliminary results from the Optimize study indicated that vaccines had similar behavior in the two studies.

**Summary of discussions**

**Issues raised**

**Management of stock**
UNICEF manages their global vaccine stock by filling the requests for a specific vaccine with the available stock. Therefore, considering the implementation of CTC for a specific product when used in campaigns but not when used in routine immunization programs is logistically difficult. This issue should be taking into consideration when evaluating CTC options for vaccines potentially used in both settings (i.e. campaigns and routine immunization).

**Vaccine stability**
The stability of vaccines may vary over its shelf-life. For example, the decay rate for a key parameter (e.g. potency) may be greater initially and may level off at the end of the shelf-life or...
vice versa. Therefore, when evaluating the effect of temperature on vaccine stability it is important to understand how individual products behave and how exposure to different temperatures affects product shelf-life. This is particularly important to consider when exploring the possibility of returning vaccines to the cold chain after a CTC exposure.

Samples for CTC studies
The group noted that it is sometimes problematic to obtain end of shelf-life samples for use in stability studies.

Frozen samples
Although risk of freezing is not part of scope, it must be prevented from happening.

VVMs
VVM assignment is established from 3 different lots and three data points are estimated each time at 37°C, 25°C and 5°C. Vaccines do not need to follow the Arrhenius equation exactly to have a suitable VVM applied. During the discussion, concerns were raised that in CTC evaluations the results may be in conflict with the VVM number assigned to the vaccine.

Stability budget
Another approach to evaluate the effect of temperature exposure on vaccine stability is the so-called ‘stability budget’, which takes into account the ‘excess’ potency of the product. CTC is a part of the total stability budget that includes the internal and external time out of refrigeration, this approach can therefore be used to establish CTC when statistical evaluation is undertaken.

The consistency approach
The group considered whether the consistency approach to evaluate product quality is appropriate when looking at samples stored at different temperatures. It was agreed that the assays which may be used in CTC evaluation need to be considered carefully but in general the consistency approach was useful.

What temperature
The group considered which temperature and time should be considered in CTC evaluation. For campaign use in countries with high ambient temperatures, exposure is generally <37°C with short peaks at 40°C. Therefore, the use of 40°C is appropriate. The evaluation should be based on real time stability studies.

**Ability of assays to detect changes in product quality**

Manufacturers should consider the ability of an assay to detect changes in product quality. Potency assays are key parameters to be used in the evaluation of a CTC.

**Age of product**

The need to test vaccines of different ages clinically was discussed. The group agreed that this would depend on the product but that knowledge of the potency at the time of use would be required if this were pursued. The use of aged lots versus lots that had been subjected to forced degradation before the clinical studies was also discussed. In choosing an approach, the objective of the study should be clearly defined and the product should be well characterized under relevant stress conditions before deciding which approach would be most appropriate.

**Statistical model vs single-point model**

Regardless of what method is used to set release criteria or shelf-life, the specific tests and data that support that decision are amenable to statistical analysis and such analysis should be considered in support of CTC related applications. Moreover, statistical analysis can help to determine the risks that are being taken even when a single-point model is used. Both models have been applied to the determination of shelf-life or release models of products, but there are distinct advantages with statistical modeling and several limitations with the single-point model.

Using statistical modeling to set shelf-life and release criteria will assure that the product will behave as predicted by these statistical models. Using the single-point method without also performing statistical analysis on the conclusions, risks that the product will not behave as predicted, potentially leading to failure of product before the end of its predicted shelf-life. Alternately, the product could be filled at higher levels than needed to maintain potency through shelf-life, in turn leading to safety or supply problems. When quantitative data are not available, statistical modeling is more challenging, but can still be performed by examining the proportion
of lots that pass or fail at a given time point, allowing calculation of the likelihood (and the confidence in that calculation) that the product would fail at other time points. While an accepted LL is needed to use statistical methods to set release criteria, such that a product will maintain a potency at least equal to that LL through its shelf-life, any release model (whether based on LL or not) can be subjected to statistical analysis to determine how low end-expiry potency could become under that model, and a determination can be made regarding whether that level is acceptable. Regardless, because CTC applications represent a stress to product filling and release models, it is particularly important that they be based on a sound scientific foundation.

It would be helpful if the national regulatory authorities from all countries in which prequalified vaccines are manufactured could meet to discuss these models. Consensus is required as to how data in support of CTC should be analyzed. There is no common view in the EMA Biologics committee and Brazil currently accepts the single-point model because there is insufficient information on relative merits of statistical modelling in contrast to the single-point model. In countries where appropriate statistical input is not readily available, the single-point method is easier to interpret but may give wrong information (less precise and not able to accurately predict shelf-life or needed release potency). If assay variability is low, this can be satisfactory but if the assay has high variability there are problems in the justification of the shelf-life.

**Conclusions**

The group agreed that:

- The cold chain is critical and should be maintained when possible, but that CTC provides a useful option in situations where maintaining the cold chain is problematic and is preferable to off-label use.

- Guidance on how to assess vaccine stability information for CTC is required by both developed and developing countries. In future there will be more requests for CTC guidance on labelling.
The discussions at the meeting have been helpful and the meeting report would inform other regulators about windows of stability regarding controlled temperature chains, as well as providing guidance manufacturers during the development of new products with a CTC license.

The discussion of the key issues will form the basis for the development of guidance and there are now opportunities for regulators and manufacturers but also VVM experts to address these issues.

Priority CTC products in the near term will be those used outside of the ‘routine’ immunization program, for example, those used in campaigns and special strategies, such as the hepatitis B birth dose, yellow fever, HPV and cholera. IPV also needs to be considered as OPV is phased out. New, large distribution vaccines such as pneumococcus and rotavirus as well as combination vaccines are also of interest, as are new products under development.

For legacy products, no additional clinical studies are required to support CTC use. However additional statistical studies may be undertaken on available data. In most cases, clinical data are not needed, but post-marketing studies may provide confirmatory information.

The information on the product label (e.g. indication, dose, storage conditions etc.) are regulatory decisions based on vaccine-specific clinical and quality information. The product label (e.g. carton, vial, insert etc.) is a legal document, the responsibility for this information is with the manufacturer and subject to approval by a regulatory authority. Therefore, it is the responsibility of the manufacturer to generate and submit this information. Published available data or information generated by other sources (external laboratories) is not generally used due to the potential bias, lack of control of assays/reagents etc. For current vaccines, there are limitations to the usefulness of data reviews of published field studies as they are proof of principle.
only as there is often little information on the assays performed and raw data is not available for further analysis.

**Recommendation**

Given the importance of assessing CTC using the best approaches, it was the consensus of the participants that stability information to support CTC should be assessed using appropriate mathematical modelling, statistical analysis and rates of decay. Additional guidance on how to perform these studies is required.

Recommended by the group, a follow-up meeting was held in PEI, Langen, Germany, June 4-6, 2013.
References


2. Guidelines on the international packaging and shipping of vaccines (WHO/IVB/05.23)


6. Guideline for establishing or improving primary and intermediate vaccine stores (WHO/V&B/02.34)

7. ICH Guideline Q6B. Test procedures and acceptance criteria for biotechnological/ biological products (CPMP/ICH/365/96 September 1999)


human rotavirus vaccine (RIX4414) after storage at 37 degrees C for seven days. Human Vaccines.;7:74–80


13. Temperature Sensitivity of Vaccines (WHO/IVB/06.10)

Appendix 1

Labels and where the CTC information should appear:
Information on CTC should be described in the product leaflet/package insert to provide information for medical practitioners. The statement on CTC should be a separate paragraph, in the ‘conditions of use’ section. No CTC statement should appear on the vial or syringe itself or on the boxes.

Information on CTC should be clear, concise and specific. If the vaccine consists of two or more components (e.g. lyophilised vaccine and diluent), CTC information should be given for all components of a specific vaccine.

Information to be included in CTC statements should consider the following, if applicable:
- Range of temperature or maximum temperature
- Range of time or maximum time at a specific temperature
- Time after opening (or reconstitution or mixture), if applicable
- Advice on unopened vials exposed to CTC (e.g. discard or return to cold chain)
- Single or multiple periods of excursions within the maximum length of time allowed.

Proposed text for single use alternate storage conditions
In situations where the 2-8°C cold chain cannot be maintained [immediately prior to administration], the vaccine [and its diluent or other component] can be kept for a single period of time of up to [x days or x weeks or x months] at temperatures of up to [x°C]. At the end of this period, the vaccine [must be discarded] or [can be returned to the cold chain]. [After opening [or reconstitution or mixture], the vaccine can be kept for [x hours or x days] at temperatures of up to [x°C] at which point it must be discarded].

Proposed text for multiple use alternate storage conditions
The vaccine [and its diluent or other component] can be kept for up to [x days or x weeks or x months] at temperatures of up to [x°C]. At the end of this exposure period, the vaccine [must be discarded] or [can be returned to the cold chain]. [After opening [or reconstitution or mixture], the vaccine can be kept for [x hours or x days] at temperatures of up to [x°C] at which point it must be discarded].
Appendix 2

Parameters to consider for the decision on the potential need for clinical data

I. In general:

All evaluation and assessment should be done by considering both, the safety and the efficacy of the vaccine to be used under CTC conditions.

The final decision should be based on an appropriate benefit/risk assessment. This is in particular important in the context of the evaluation of clinical data.

II. The issues which influence the need of clinical data to support the use of a vaccine under CTC conditions can be divided into two main areas:

a. The proposed conditions – temperature and duration
   - Clinical data might be needed if the maximum temperature or the duration of the excursion is likely to influence the integrity of the product in a manner that cannot be properly assessed though an analysis of quality or non-clinical data.

b. Product related issues
   - All components of the product should be considered (e.g. antigen/conjugate, excipients, adjuvants, …)
   - History (knowledge) of the product - what kind of stability related information do we have already about the product and its components
   - As supportive information: what kind of surveillance data are already available
   - How relevant are the assays to predict clinical performance of the product
   - Specificity of the assays used (for potency, characterization, …)
   - What are the characteristics of the assay? Are they suitable for the intended use?
   - Are the set specifications appropriate? Do they need to be revisited (e.g. is there a need for higher release specification? Would such a change of the specifications have an impact on the safety of the product?)
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