Meeting Report

WHO/Paul-Ehrlich-Institut Informal Consultation on Scientific and Regulatory Considerations on the Stability Evaluation of Vaccines under Controlled Temperature Chain (CTC)

Paul-Ehrlich-Institut, Langen, Germany
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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

It is clear that immunization programmes in certain regions of the world face severe challenges with maintaining standard cold chain conditions (i.e. 2–8°C) for vaccines (1-2). These vaccine challenges can be reduced where vaccine specific stability assessments are able to demonstrate that a product can withstand a defined, planned period of exposure to elevated ambient temperatures (e.g. up to 40°C) within a “Controlled Temperature Chain” (CTC), while maintaining the key quality attributes necessary for clinical effectiveness (3-5). A critical feature of this approach is that a vaccine’s demonstrated CTC potential is explicitly approved by the appropriate regulatory authority and included in the product label. While the successful utilization of a CTC stability assessment has already been demonstrated in the field (6-7), there is still an urgent need to broaden the understanding of the principles involved and share best practices required to perform such assessments. Additionally, regulatory convergence on a global scale is also needed to advance these concepts and to support the implementation of the CTC approach.

With the objective of developing regulatory convergence regarding CTC vaccine stability assessments and support programme implementation, WHO in collaboration with Health Canada held a consultation in Ottawa from 4 to 6 December 2012. The workshop was to identify the issues which have to be overcome to develop CTC for vaccines. The participants considered: the design of stability studies required for this type of assessment, appropriate stability indicating assays, the best statistical methods to use for such evaluations, issues related to vaccines under development versus existing vaccines where some data may already exist; and when further clinical studies may be required in specific situations. These issues were further explored and broadened at a meeting held at the Paul Ehrlich Institut (PEI), Langen, Germany from 4 to 6 June 2013.

During the consultation in Ottawa in December 2012, participants suggested that the term “Extended Controlled Temperature Chain” (ECTC) may be more appropriate than CTC. This issue was again discussed in Langen and again the participants came to the same conclusion. However, understanding that the use of the term ECTC would have to be endorsed through the
appropriate WHO committee, for the sake of consistency, the term CTC is used throughout this report.

Key conclusions from the Langen consultation include: (a) that the CTC programme objective is to have an “on-label” use of vaccines outside of the normal cold chain requirements for as long as possible while maintaining the key quality attributes necessary for clinical effectiveness; (b) although not all vaccines would necessarily have the potential for a CTC label change, available information suggests that for some products, vaccine specific assessments based on appropriate validated stability indicating assays and real time stability data at the required temperatures (e.g. standard conditions (5°C) and a CTC upper limit (e.g. 40°C)) could support heat exposure at the upper temperature limit for defined periods of time while maintaining potency; (c) stability information to support CTC should be assessed using appropriate mathematical modeling, statistical analysis and information about rates of decay (e.g. linear regression or other suitable regression models); (d) for the purpose of CTC applications and label changes, at this time stability assessments should be limited to a single planned excursion from the cold chain (i.e. during the “last mile” prior to immunization) at the proposed temperature (e.g. 40°C) for at least three days prior to use but ideally for longer periods – while it was understood that it would be useful from an immunization programme perspective to have support for multiple exposures of individual vials of vaccine, this was considered to be too complex to assess and implement at this time; (e) Vaccine Vial Monitors (VVMs) are useful tools in providing information on accumulated temperature exposure and have been successfully applied to WHO prequalified vaccines for many years. However, since VVMs do not provide a direct measure of the inherent stability of a vaccine, the use of additional temperature monitoring tools, such as peak temperature indicators, has been shown to be a practical risk management tool in field situations to indicate that a predefined threshold air temperature has been reached. Collaboration of VVM experts, regulators and vaccine manufacturers should be encouraged in order to develop vaccine specific and/or region specific temperature monitoring tools; and (f) WHO should provide guidance on how to assess stability and approve labelling for CTC use, within the framework of complementary guidance for vaccine stability evaluation in general.

**Suggested Keywords:** World Health Organization; regulatory considerations; vaccine stability; cold chain; controlled temperature chain; statistical modelling
Background

Immunization programmes in certain regions of the world face severe challenges. One major challenge involves the requirement to store vaccines at 2–8°C, known as the cold chain, under field conditions where the absence of roads and electrical infrastructure hampers the timely transport of vaccines and appropriate storage at the site of immunization respectively. Additionally, the increasing cost of vaccine delivery due to cold chain requirements can also limit vaccine distribution in certain regions and therefore, the success of immunization programmes. Recognizing these challenges, both the WHO Strategic Advisory Group of Experts on Immunization (SAGE) (1) and the Immunization Practices Advisory Committee (IPAC) (2) requested the WHO Expert Committee on Biological Standardization (ECBS) to review and assess the possibility of planned temperature excursions that could support the “on-label” (as opposed to “off-label”) transport, storage and use of vaccines outside the cold chain in remote regions. In response to these requests, an initial WHO consultation was held in Ottawa from 4 to 6 December 2012. This consultation reviewed the scientific and regulatory considerations concerning the stability evaluation of vaccines under a Controlled Temperature Chain (CTC) system (3) and identified key issues which would form the basis for the development of future guidance (8). The WHO consultation in Langen continued and enlarged these discussions and agreed upon next steps and follow-up actions which are identified at the end of this report. Summaries of the presentations at the consultation are provided below.

Challenges of delivering vaccines in developing countries; and the benefits of CTC

Ms Simona Zipursky (WHO) 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 (5).
One approach could be to consider that some existing vaccines may be more stable than their label indicates. This was explored by assessing the potency of an oral polio vaccine in a CTC condition in Chad (April 2010), where test vials were exposed to maximum ambient temperatures of 47.1°C for up to 86.9 hours. After testing by an independent laboratory in Brussels, Belgium, it was determined that despite these exposures, all vials tested met the minimum release specification. While it is understood that this type of information is insufficient to support a regulatory CTC label change and is not in agreement with the proposed approach for CTC stability assessments, it would be valuable for manufacturers to explore such excursion potential with their validated assays.

Based on more robust data sets and analysis supplied by vaccine manufacturers, countries such as Canada, the European Union (EU), South Africa and the USA already have vaccines licensed with “on-label” guidance when the vaccine is exposed to temperatures above 8°C. For example, Canada has already approved seven vaccines with this type of guidance and the specific wording approved for Prevnar 13, a Pneumococcal conjugate vaccine, is provided in the Ottawa CTC consultation report (8).

“On-label” approval for vaccines to be kept and administered at ambient temperatures, up to 40°C, for a single, product-specific defined period of time just prior to the administration of the vaccine, has been extremely helpful for immunization programmes in remote regions. It is worth noting that, prior to the planned excursion, the vaccine would continue to be kept in the traditional cold chain (normally 2–8°C) (6-7).

Recent studies in Benin and Chad have demonstrated the value and flexibility provided, when 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 required to maintain a cold chain are recourse intensive to manage, compete with other health care service needs and are costly. In areas where a cold chain is limited or not available, this problem is particularly pronounced. Some vaccines or their diluents are also damaged by freezing temperatures, which are most common during outreach activities and transport when vials are stored against frozen icepacks. In addition, the humidity found in vaccine carriers filled with ice, often results in the
loss of vial labels making the vaccine unusable. These challenges are particularly pronounced during campaigns, where hundreds to millions of people are immunized in a limited time span (generally 5 to 12 days). Such campaigns cause a substantial surge in the amount of vaccine to be stored and pose additional challenges for existing cold chain infrastructure. With the expansion of immunization programmes and the introduction of many new vaccines, often in single dose presentations, this problem is expanding. In some cases, the lack of cold chain capacity during large campaigns requires that temporary cold chains be established, which involves the installation of additional transport freezers and generators in order to make ice packs.

The use of CTC would expand the options for immunization strategies and ease the logistical burden faced when trying to deliver 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 heat stable vaccines and drugs and reduce the costs/constraints such as ice pack requirements imposed on transport and the need for specialized equipment. The more cold chain requirements for vaccines can be reduced, the easier the integration with other supply chains, such as 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 guidance to support these CTC evaluations, new technologies to aid implementation and support for field studies to assess these programmes and their impact. Supporting guidance from WHO (9-10) already exists for conditions similar to those of CTC for special strategies. One example is the Hepatitis B vaccine for the birth dose, which may be stored and used out of the cold chain (at ambient temperature) at point of use, whenever the regular cold chain cannot be maintained (e.g. in the lowest level health facility or by a midwife for home births). However, this is “off-label” use and it is hoped that additional regulatory pathways can be defined to allow vaccines to be licensed to reflect any additional stability potential rather than promoting the ‘off-label’ use. As part of these efforts, work is ongoing to identify and develop technologies needed to enable the implementation of CTC, such as peak temperature threshold indictors (to ensure vaccines are not
exposed to temperatures above the proposed 40°C) both as a standalone product and integrated with VVMs.

In October 2012, MenAfriVac, Meningitis A conjugate vaccine, became the first vaccine that was pre-qualified by WHO for use in a CTC, following a label variation granted by Drug Controller General India (DCGI). Guidance for the use of MenAfriVac in a CTC was developed and endorsed by WHO’s Immunization Practices Advisory Committee (11). A pilot conducted in Benin in 2012, vaccinated over 155,000 people using CTC. MoH/WHO conducted a post campaign survey with vaccinators and supervisors to capture their thoughts and perspectives on the CTC pilot. The survey revealed that 100% of supervisors and 98.7% of vaccinators would prefer to conduct their next campaign using CTC, if possible (6-7).

Key Principles on the Stability Evaluation of Vaccines under a Controlled Temperature Chain

This session summarized the outcome of the Ottawa consultation and provided background information on regulatory expectations and statistical considerations for the assessment of stability data to facilitate the use of vaccines under CTC conditions.

Dr Christoph Conrad, Paul Ehrlich Institut (PEI) presented an overview on the main topics discussed and the conclusions achieved during the Ottawa consultation, which are also summarized in the Ottawa report. The Ottawa consultation primarily focused on the regulators perspective on the quality, non-clinical and clinical data set needed to support CTC labels but also included case study presentations by manufacturers. It was concluded that the cold chain is critical and should be maintained whenever possible, but the CTC provides a useful option in situations where maintaining the cold chain is not feasible and limits immunization campaigns. Guidance on how to assess vaccine stability information for CTC is required by both developed and developing countries, since it is to be expected that there will be more requests for CTC guidance on labelling to support global vaccination campaigns. In the short term, priority should be given to vaccines used outside the routine immunisation programme, e.g. those used in
campaigns or to fulfill specific vaccination strategies. Examples are the Hepatitis B vaccine given as a birth dose, Yellow Fever vaccines, Human Papillomavirus (HPV) and Cholera. Inactivated Poliovirus vaccine (IPV) might be another example as Oral Polio vaccine (OPV) is phased out. In addition, new large distribution vaccines such as Pneumococcal and Rotavirus vaccines as well as combination vaccines are of interest. For some legacy products (products already available and licensed), no additional clinical or stability studies may be required to support the use for CTC, provided that the quality data available support the proposed application. However, additional statistical evaluation of the available stability data in addition to a review of manufacturing changes since the stability data was compiled, as well as a review of post-marketing data would be needed to confirm the currently available information for legacy vaccines. Quality data generated by sources other than the manufacturer or the National Regulatory Authority (NRA) approved external laboratories for the product would not generally be considered for a CTC label change. There are also limitations on the usefulness of data coming from reviews of published field studies because of limited information on the assays performed and non-availability of raw data. Stability information supporting CTC should be assessed using appropriate mathematical modeling, statistical analysis and rates of decay. It was found that additional guidance on the conduct of such assessments is required.

Presentations by Dr Heidi Meyer (PEI), Dr Dean Smith, Health Canada (HC), and Dr Phillip Krause (CBER, FDA) focused on the regulatory expectations on the quality, non-clinical and clinical data set needed for specific vaccines, on the design and parameters to be investigated in stability studies as well as statistical considerations for data analysis to facilitate the use of vaccines under CTC conditions. Dr Timothy Schofield (Medimmune) gave an overview on appropriate statistical methods recommended to be used for vaccine stability assessments as described in the WHO stability guidelines. These presentations are already summarised in the Ottawa consultation report or in the WHO stability guideline (12-14).

VVM and temperature monitoring of prequalified vaccines under a CTC

Dr Carmen Rodriguez Hernandez (WHO) gave an overview of the current WHO requirements for temperature monitoring and regulatory pathways for prequalification under CTC. Assessment
of the stability profile of vaccines at different temperatures is a main focus during the prequalification of vaccines to guarantee the quality, safety and efficacy of a vaccine throughout its shelf-life (15-19). Special consideration is given to the maintenance of cold chain conditions during shipping as well as the occurrence of cold chain excursions in the context of national immunization programmes worldwide. The fact that robust NRAs have thoroughly reviewed stability data during the registration process does not necessarily mean that the vaccine is programmatically suitable for use by some United Nations (UN) countries where environmental conditions and handling of the vaccines are different from those of the country of origin. A Vaccine Vial Monitor (VVM) is a tool recommended by WHO to detect vaccine cumulative exposure to extended temperature. VVMs are available in four different time and temperature dependent categories: VVM30, VVM14, VVM7 and VVM2. The upper limit for 95% of VVM30 to reach end point is 30 days at 37°C, while for VVM2 it is two days at 37°C. For each vaccine, a specific VVM category is selected by WHO based on the stability data available for the vaccine under evaluation and submitted to WHO in the prequalification dossier. Guidelines for using vaccines in a CTC are under development by WHO.

Dr Thaddeus Prusik (TempTime Corporation) described the principle mechanisms of the VVM in use by WHO. The VVM is a time-temperature indicator for monitoring heat exposure of the final container during its storage. VVM2 was the first VVM commercialized in 1996 and was designed specifically for OPV according to WHO’s specifications. It is printed on a vial-label, applied to the vial cap or on an ampoule neck as appropriate. Three additional categories (VVM7, VVM14 and VVM30) were developed in 1998 after WHO consultations with vaccine manufacturers and are defined by the upper limit of the number of days at 37°C for 95% of VVMs to reach the end point. Thus, for example, VVM2 on OPV (one of the most heat-sensitive vaccines in WHO prequalified vaccines) reaches its end point in 48 hours at 37°C, whereas VVM30 on Hepatitis B (one of the most heat-stable vaccines) takes 30 days to reach its end point at this temperature.

The active region of the VVM is the color changing reactive portion which is based on the solid state polymerization of colourless diyne diurea monomers to highly colored polymers following temperature exposure. The colour changing portion is light at the start and progressively and
irreversibly darkens. The colour change is faster at higher temperatures and follows the Arrhenius kinetic. The combined effects of time and temperature cause a gradual, predictable, cumulative and irreversible colour change from lightly coloured to dark. Dr Thaddeus Prusik (TempTime Corporation) clarified that the VVM does not show vaccine potency and that the colour change of the VVM is not stability indicating. In fact, the VVM was developed for monitoring the temperature exposure of vaccines and shows a Health Care Worker if a product has been exposed to excessive heat over time. Extremely high temperatures or temperatures below the freezing point can be factors that very quickly affect the potency of a vaccine. However, the VVM was not designed for proposed 40°C CTC temperature, nor was not designed to register information regarding freezing conditions that may also contribute to vaccine degradation. Moreover, the VVM does not differentiate between continuous exposure to slightly higher temperatures (>20°C) or peak exposures to very high temperatures, e.g. temperatures > 42°C. Therefore, the company is currently developing combined VVMs, which are capable of providing information on the continuous heat exposure as well as on peak exposures to very high temperatures.

OPV was the first vaccine to use a VVM. Thermal stability requirements laid down in WHO guidelines (12, 20) were used as a guide to form a basis of a classification framework that would give some guidance in the field. Thermal stability testing remains a part of the lot release requirement for live attenuated vaccines. In no case was a VVM category assigned to a product without analysis of the manufacturer’s own data on their specific product and in some cases this was tested by WHO contract laboratories as well.

Moreover, it was confirmed that the VVM is outside of regulatory oversight in most countries although there was a discussion as to whether VVMs should be part of the regulatory approval process.

**Case studies on stability evaluation of vaccines under a CTC**

Five case studies were presented by NRAs and manufacturers who produce prequalified vaccines.
Case Study No. 1
Investigation of a vaccine batch stability failure, the role of appropriately established release specifications in the identification of the issue and the application of these principles to CTC stability assessments - Dr Michael Pfleiderer (PEI) and Dr Ralf Wagner (PEI)

Dr Ralf Wagner (PEI) shared PEI’s regulatory experience and the company’s root cause analysis related to an Out of Specification (OOS) issue for the potency of a Japanese Encephalitis (JE) vaccine Ixiaro. Ixiaro is a liquid; aluminum hydroxide adsorbed inactivated JE vaccine (JEV) containing 6µg total protein per dose. It is indicated for active immunisation against JE from two months of age. The final potency specification is related to the minimum amount of vaccine antigen required to induce neutralizing antibodies in mice that are able to reduce plaques by at least 50% (effective dose 50/ ED50) in the Plaque Reduction Neutralization Test (PRNT). As with all such assays, the inverse relationship between an ED50 value and the vaccine potency means that the lower the ED50 value, the higher the potency.

The original Final Vaccine Lot (FVL) shelf-life granted in the EU is 24 months. In Canada the cumulative shelf-life of the combined Final Bulk Vaccine potency (FBV) and FVL was 18 months. Additionally, Health Canada (HC) used appropriate statistical methods to analysis the potency stability data in order to establish testing and potency release specifications for the FBV to ensure that the product would meet its end of shelf-life potency requirement. In a situation where this FBV potency limit was not met, an abbreviated stability testing programme of the FVL would be required at 11 and 15 months. These lot release and testing requirements were established through the initial Canadian IXIARO review/approval process and are described in the HC portion of this Case Study (below). Since authorization of IXIARO in the EU in 2009, PEI has conducted potency testing for the release of vaccine batches to the European market and the PEI test data is also used to support lot release decisions by HC.

In 2011, a Final Vaccine Lot (FVL) which had been placed into the abbreviated stability programme due to a failure to meet the HC required FVB potency specification, also failed to meet the potency specification at the 11 month post release test date. Following further evaluation the affected lot, was recalled from the market (Canada and EU). An extensive investigation was
initiated by the company to identify the root cause for the potency OOS. Analysis of the collective evidence indicated that the quality of the aluminum hydroxide in the affected lot likely caused enhanced JE-antigen degradation resulting in a decrease in potency during storage. The main findings included: identification of a higher metal ion content in the affected AlOH lot, that these metal ions, primarily Cu(II) ions, can lead to degradation of JEV neutralizing epitopes and other FBL batches formulated with the affected AlOH lot also showed enhanced epitope degradation and loss of potency upon storage. Another important outcome of these extensive investigations was that both the company and PEI were able to significantly reduce the PRNT test variability as well as improved the inter-lab comparability of their results, where one key change involved the use of a common source of mice for the tests.

Regulatory measures to deal with the issue included the implementation of specific new acceptance criteria for heavy metal ions in the aluminum hydroxide (i.e. copper, iron, nickel) by a formal variation procedure, the strengthening of the potency specification at time of release (more stringent limits for the amount of protein capable of inducing neutralizing antibodies) and the routine retest of each FBL at six months with an additional specific action limit. Follow up investigations revealed that two lots used in clinical trials were also manufactured with alum hydroxide lots that had enhanced metal ion content, which most likely caused accelerated antigen degradation and reduced potency over the shelf-life. However, to date there is no indication that this potentially reduced potency in those cases has had a significant impact on the immunogenicity in humans.

Dr Dean Smith (HC) continued with some further information on the HC stability analyses for Ixiaro, which permitted the identification of the potency OOS and the lot recall in Canada and the EU. Additionally, the potency stability data available at the time of the original IXIARO approval was used in an interactive tutorial to highlight the principles involved with a statistical approach required for a CTC analysis.

The central observation of the HC analysis of the initial IXIARO stability data was that the potency declined from the lot release date to the end of shelf-life. When such a potency decline is evident, it is essential to establish a release potency limit. This lot release limit must take into
account the decline in potency while in storage, such that by the end of the proposed shelf-life the minimum potency value established in the clinical trials is maintained. The HC lot release model, involving a statistical analysis of the rate of decay in potency for the stability lots at 2 to 8°C and the minimum end of shelf-life potency was described.

Another key lesson from the IXIARO experience was the importance of having a sufficiently sensitive and robust potency assay that can detect changes in product quality. Results from an assay with these attributes can then provide a meaningful basis for the establishment of the release and end of shelf-life specifications. The insensitivity of many in vivo multi-immunization (e.g. “prime and boost”) potency assays is also described in the Ottawa CTC consultation report (presentation by Dr. Tong Wu, (HC)). With IXARIO, the 1st generation potency assay was a two injection (prime and boost) model, whereas, the 2nd generation assay was a more sensitive single injection model with an improved dose response curve (i.e. with a steeper slope). With the implementation of 2nd generation assay and more manufacturing experience, Intercell could consistently demonstrate release potency values at the Final Bulk Vaccine (FBV) level well below the HC release specification (e.g. generally two fold more potent than required). Analysis of additional stability data that followed the OOS, demonstrated that the rate of decline in potency seen earlier in the shelf-life tended to be reduced at later time points and an extension of shelf-life was granted to 24 months in the EU, Canada and USA.

CTC assessment principles: Accelerated stability data (e.g. at 25 or 40°C storage conditions) for a product that is to be held at 5°C can also be considered as “real time” data when evaluating a product’s CTC potential at 25°C or 40°C respectively. With this in mind, an initial CTC evaluation was performed for IXIARO based on the 25°C and 40°C “accelerated stability” data provided during the original submission. It was noted that the data collection points were not optimized for a CTC evaluation (i.e. only one month intervals) and this analysis was only for demonstration purposes for this WHO consultation. The central principle of a CTC evaluation considers the potency loss during routine storage (i.e. 2–8°C) in addition to the potency loss at the maximum CTC temperature (i.e. at either 25 or 40°C in this case).
The assessment concluded that with the original stability data and the statistical assessment of the rate of decline in potency over the initially approved 18 months, there was no CTC stability potential. However, if the shelf-life was reduced to 17 months, two days of CTC excursion could be provided for. Further reductions in shelf-life possibilities and/or changes in release specifications to enhance CTC potential could also have been explored. Since the stability data at 40°C failed specifications prior to the first one month test point, no CTC assessment was possible for that temperature condition.

Case Study No. 2a

The CTC approval for the MenAfriVac, Meningitis A conjugate vaccine:

Dr Sunil Gairola (Serum Institute of India, SII) reported on the epidemiology of Meningitis A (MenA) in Africa and development and especially stability studies of MenAfriVac, a freeze-dried MenA Tetanus toxoid conjugate vaccine. Following a severe MenA epidemic in 1996 in Africa a Meningitis Vaccine Project (MVP) was initiated in 2001 supported by the Bill & Melinda Gates Foundation in partnership with WHO/PATH. Vaccine development took place at different sites (SynCo BioPartners, Amsterdam; Aerial France; CBER/FDA, USA and SII, India). MenAfriVac was prequalified by WHO and launched in December 2010 and by the end of 2012 more than 100 million people had been vaccinated in the African Meningitis belt and no epidemics occurred in the vaccinated areas.

Upon review of updated stability data provided to the DCGI, the initially granted two years shelf-life was extended to three years. Analysis of the stability data in terms of VVM assignment resulted in a VVM30 designation. However, as suggested in Dr Thaddeus Prusik’s presentation, an analysis for the assignment of a VVM serves a very different purpose relative to a CTC stability assessment and this is explored further in the 2b case study below.

Up to 15 lots were investigated in 2–8°C (36M to 42M), 25°C (6M) and 40°C (4W/8W/15W) stability studies that also addressed different dosage forms and changes in the manufacturing process. Accelerated stability studies at 40°C (following 36M storage period at 2–8°C) were
performed at two, four, six and eight week time points. Free polysaccharide and molecular size distribution (MSD) were considered important stability indicating criteria. Additional reconstitution studies of the freeze-dried antigen component with the diluent at 2–8°C and 25°C confirmed acceptable stability for 24 hours at both conditions.

To explore the possibility for limited storage outside the cold chain (below 40°C) HC reviewed the available stability data, which included studies at 5°C, 40°C and studies with the reconstituted product at 40°C for two, four, six and eight hours. Several analysis were performed but the key quality attribute assessed was the rate of increase in free polysaccharide, which supported storage of the product for up to four days at 40°C followed by a maximum of six hour storage after reconstitution at the same temperature. DCGI approved CTC storage conditions are reflected in the wording on the container labels as well as in the product insert.

Case Study No. 2b

CTC assessment principles for a mock polysaccharide conjugate vaccine:

Dr Tong Wu (HC) presented data on methodologies and analysis to support CTC. Both published data and mock data was used for the case study. The model vaccine used for the HC standard storage condition (i.e. 2–8°C) and CTC (40°C) stability assessments was a Diphtheria toxoid-polysaccharide conjugate. Since free polysaccharide (PS) is a quality attribute that is clearly linked to the clinical performance for PS conjugate vaccines, this was the key parameter assessed using the following specifications: total PS: 8-12 µg/dose, free PS: not more than (NMT) 15% at release NMT 25% at the end of shelf-life.

The mock 2–8°C stability data set included eight lots stored between 18M and 36M, with test time points at 0M, 3M, 6M, 9M, 12M, 18M, 24M, 30M, and 36M. The mock data was developed based on HC’s general experience with conjugate vaccines but did not represent data from any specific product. Using the mock data, a statistical evaluation\(^1\) of the accumulation of free PS

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\(^1\) Statistical analysis is used to determine the rate of change of a key stability indicating parameter (e.g., free PS or potency) and the precision of that determination. This may be performed by linear regression for a specific parameter against time or with other appropriate techniques. For the free PS data in this mock data set, a linear mixed model was used for the analysis (Ime4 package of the R language, 95% percentile distribution). These types
over time was performed. Under the 2–8°C condition the analysis revealed an increase of free PS of about 10% at 24M and 15% at 36M. As stated in the first case study (No. 1 above) when a key stability indicating quality attribute such as free PS (or potency in the IXIARO situation) is known to change over the shelf-life of the product, it is critical that a release specification be established. In this case study, free PS is an impurity and as such the release specification must take into account the rate of accumulation for free PS while in storage, so that by the end of shelf-life the maximum acceptable level linked to the clinical performance of the product (i.e. efficacy and safety) is not exceeded. Using the statistical evaluation mentioned above, the free PS stability data, the specifications listed above and assuming the “worst case scenario” in which lots are released at the highest level permitted by the specification, a 24M shelf-life was determined and a “release model” was established (14). On the other hand, if the rate of accumulation of free PS is not considered and the only the total free PS levels for the lots are evaluated at face value (i.e. the “best representation” of the stability data) a 36M shelf-life could be accepted. This is because the highest free PS lot at release in the study was well below the NMT 15% free PS release specification and this resulted in 21.4% free PS at 36M.

From these examples it can be seen that if the rate of accumulation of free PS and worst case factors are not taken into account, this can result in an over-estimate of the shelf-life period, since this approach would not consider lots released that are near the NMT 15% free PS limit unless they were represented in the data set. Importantly, the statistical evaluation also demonstrated that lots released at 15% free PS would reach approximately 25% free PS at 24M and 30% at 36M based on the rate of free PS accumulation.

Additionally, it was again noted that data generated with insensitive “prime boost” in vivo potency tests should not be used to support the extension of vaccine shelf-life at 2–8°C. Only appropriately-designed sensitive in vivo potency tests, that have been validated using lots shown to be effective in clinical trials, should be used to support shelf-life extensions at 2–8°C or to support CTC assessments.
CTC studies:
Stability studies to support CTC assessments must be based on real time real condition studies and should include additional characterization tests. A minimum of four weeks data with weekly test intervals at the CTC condition, for an otherwise well characterized vaccine, can suffice for statistical analysis. Quality data alone were considered sufficient for protein-polysaccharide conjugate vaccines since these vaccines are: 1) more stable than protein vaccines 2) there are several key quality attributes related to clinical performance (e.g. total and free PS; Nuclear magnetic resonance (NMR) which can confirm PS structure and appropriately designed and sensitive in vivo potency assays can ensure carrier protein integrity.
Ideally, worst case stability scenarios (e.g. storage at 2–8°C for 24M followed by four weeks at 40°C) should be included in the design for a product intended for a CTC application. The evaluation of changes in rates of increases in free PS over shelf-life (i.e. non-linear accumulation) should also be considered.

Setting of appropriate specifications is a key issue and ideally should be supported with satisfactory immunogenicity and safety data, preferably with clinical lots approaching the specification limits during product development. The 25% free PS limit assigned to this model vaccine was assumed to be supported by clinical lots reaching approximately 20% free PS. It was highlighted that a major factor for limiting free PS is its potential link to hypo-responsiveness, which is less well documented for conjugate vaccines. Even for this model vaccine it was noted that the setting of a 25% free PS limit should have ideally been supported by product specific clinical experience.

CTC investigations at 40°C included studies for up to eight commercial lots, which were tested at 0, 1, 2, 3, 4, 6, 8, 10, 12 and 14 weeks for several key quality attributes including; total and free PS, and free protein. For the reasons already stated the final analysis focused on changes in free PS and in vivo potency data. Statistical analysis of the 40°C data revealed a mean free PS increase of 1.5–2.0 % following the first week and 3.2– 4.2% increase following the second week at 40°C storage. The “release model” free PS limits indicated previously (i.e. 15% at release and NMT 10% increase at the end of shelf-life) was applied for CTC evaluation.
Assuming an estimated increase of free PS of 9.6% in 24M at 2–8°C and, an estimated increase of 2.1% in seven days at 40°C, the maximum storage period at 40°C was determined to be three days. *In vivo* (potency) studies which measure functional immune responses (i.e. Rabbit complement Serum Bactericidal Assay or rSBA) were also considered important to monitor carrier protein integrity at 40°C storage conditions. The need to use sensitive *in vivo* test methods was again illustrated with several examples. One example from a published study illustrated the problems with multiple immunizations (i.e. prime and boost) of the test animals which resulted in a shallow dose response curve making the method insensitive to all but largest changes in the product quality or quantity (see also the Dr Tong Wu’s (HC) presentation in the Ottawa CTC report) (8). Additionally, *in vitro* data collected on a vaccine indicated that no changes in antigen integrity had occurred at 2 - 8°C storage, for up to 42M. However a time dependent loss of antigen integrity was observed at 40°C storage even using an insensitive *in vivo* test (data points at 0M, 1M, 3M and 6M data with rSBA and IgG titer assay data). It was speculated that this might be due to increase of free PS in combination with conformation changes of the carrier protein. However, when an in vivo test is not sensitive, such a result must be interpreted with caution. For this case study, the recommendation for a CTC label of three days at 40°C was not changed in spite of the in vivo results that were supportive of a longer CTC period because the assay was assumed to be of the insensitive prime boost design.

**Next steps related to the CTC claim include based on the mock data set described:**

a) establishment and implementation of sensitive *in vivo* test (i.e. using the steepest portion of the dose response curve and establish specifications based on clinical experience);

b) estimate free PS in first two weeks more accurately (add more time points);

c) establish vaccine failure monitoring where vaccines are used under CTC conditions; and

d) perform investigations on storage at 40°C after reconstitution applying multiple withdraws from multi-dose containers (e.g. assay free PS and preservative effectiveness).

**Contrast of a VVM assignment for the mock vaccine versus a CTC evaluation:**

Using the real time free PS mock data at 2–8°C, 25°C and 37°C, Dr Tong Wu (HC) demonstrated that even for a VVM assignment, an analysis using rates of accumulation of free PS during entire shelf life as the worst case provides a more appropriate and conservative
assignment than one that only considers the absolute free PS values in mock data set. For example, using same product specifications as before (i.e. 15% at release and NMT 25% at the end of shelf-life) the assignment using free PS accumulation rates was VVM14, versus VVM30 when only the absolute values for free PS were used. However, the main point that was highlighted by Dr Wu (HC) was the difference between the assumptions behind a VVM assessment and a CTC assessment. An assignment of VVM30 implies that a product can be exposed to 37°C for at least thirty days before specifications are exceeded. However, the statistically based CTC stability assessment in this case study, assumes that the product can be held for its full three year shelf-life at 2–8°C and then it still has the capacity to withstand a planned excursion of 40°C for three days, without altering the vaccine’s clinical performance. It was made clear that these are two very distinct sets of assumptions and conclusions.

Case Study No. 3
GSK’s concept of a stability budget approach for CTC applications:

Dr Diane Doucet, GlaxoSmithKline Biologicals SA (GSK) described GSK’s concept of a stability budget approach for a mock vaccine. The supporting stability data should consider findings affecting product potency, purity as well as other quality attributes. Dr Diane Doucet (GSK) emphasized that external conditions, accidental exposures during transportation and the cumulative heat impact on vaccine stability are critical. The concept of stability budget derives from the Parenteral Drug Association Technical Report #53 (21) and considers long-term, accelerated and Temperature Cycling Studies (TCS) 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 ToS/ToR must be budgeted throughout each step of the distribution chain. In such studies vaccines are categorized according to their available TCS data. GSK follows a two-step approach in designing TCS. In a first test series, the most appropriate stress conditions for a specific vaccine are set based on the profile in accelerated stability studies and the target product profile. Based on this pre-test, kinetics of degradation can be established and duration of vaccine exposure to the stress temperatures can be determined. Secondly, TCS are conducted on three consistency batches, according to the chosen stress conditions. Shelf-life is estimated based on the results of stability indicating tests (e.g. in vitro
potency results by ELISA) in comparison to long term stability. The TCS results at different temperatures i.e. 25°C and 37°C, are reconciled in the thermostability budget approach based on the comprehensive model. From these data, GSK calculates the ToS/ToR which can be used for the information provided to the Health Care Professional (HCP) and evaluating the requirements for the label and recommended wording. The ToS/ToR at the HCP level developed in the stability budget approach could be used in the context of the CTC. During discussion, the issue for an adequate stability wording in the leaflet and provided to the HCP, was raised. The group agreed that all recommendations concerning CTC usage need to be included in the Product Information Leaflet (PIL) in a separate paragraph with very clear information/guidance to the HCP (e.g. “Vaccine must be stored at 2–8°C, but in case of excursions up to 40°C, vaccine can be stored for three to five days before administration”). However, the risk of unknown excursions was noticed. The stability budget and the budget allocation per time bucket, assigned to the different parts of the supply chain cycle, are defined to mitigate this risk. In any case, in absence of information, the assumption is that the bucket allocated to the specific supply chain cycle is fully used.

Another topic discussed was on reconcilement of the information provided by VVMs and a CTC label and revealed that the CTC/VVM programmes have divergent regulatory and scientific objectives. This raised concerns about CTC evaluations because they might conflict with the specific VVM assigned to the vaccine. The group agreed that the use of the VVM would need to be aligned with the CTC concept when product specific CTC statistical evaluations are conducted.

Case Study No. 4

Sanofi Pasteur’s application of statistical principles to the stability evaluation of vaccines:

Dr Alda Laschi, Sanofi Pasteur (SP) described and discussed their strategy for stability data evaluation and predictions based on the model with a live attenuated multi-dose freeze-dried viral vaccine. Quantitation of live virus was selected as the stability indicating parameter. Quantitative raw data for live virus were presented at four different temperatures and dependent on the temperature, this parameter was determined at different time points and time spans
(temperature, time span: 5°C, 42M; 25°C, 9M; 37°C, 42 days, and 40°C, six days). Data from at least three lots at each temperature were collected. Data evaluation was performed according to International Conference on Harmonization (ICH) Quality part 1 revision E by an analysis of covariance (ANCOVA) (22). Linear regression analysis was found to be useful in order to streamline differences between lots, define confidence limits for a given slope and define specifications at release and for shelf-life. Nevertheless, in order to obtain significant results large amounts of experimental data are necessary.

Dr Alda Laschi (SP) presented the concept for a “toolbox” for stability prediction. Available data from ICH or stress studies, as well as preliminary and development data serve as a starting point. For meaningful simulations good knowledge of the vaccine characteristics is beneficial. Several models could be available for adaptation to all kind of products. The selected model and the underlying mechanisms of degradation should be validated, preferably based on real data. The models could be applied to simulate stability of early stage development products as well as the stability of marketed products. The application of these models allows for the prediction of long term stability, single or multiple temperature excursions during shelf-life, as well as the influence of temperature excursions prior to use. It was clarified during the discussion that while modeling methods such as those described are potentially useful from a product development perspective, for a CTC evaluation, only real time data at the desired normal storage condition and maximum CTC temperature would be considered support for label change.

Case Study No. 5

Merck’s approach to stability budget assessment for CTC applications:

Ms Sally Wong (Merck) discussed the application of a stability budget approach based on the stability profile of Gardasil, a recombinant quadrivalent Human Papillomavirus (HPV) vaccine. Among different methods used for stability monitoring, the In Vitro Relative Potency (IVRP) method was selected as the most relevant indicator for the loss in potency over time at the 5°C storage condition. The potency loss rate was identified to be sensitive to temperature as well. Additionally, calorimetric methods showed that no thermal transitions, such as unfolding of protein, appear below 50°C. Release specifications were set and the IVRP results obtained on a
low dose clinical lot were used to support minimum specifications at end of shelf-life. Contributions to the stability budget from release to end of shelf-life were analyzed, taking into account the different steps of the supply chain, from filling of the final bulk to administration of the vaccine. Based on the availability of low dose clinical results, further clinical data were not deemed necessary to support temperature excursions within the defined stability budget. A stability study at 40°C for a maximum of 30 days, on three lots that are at the end of their shelf-life is proposed in order to support a claim for CTC. A VVM30 category for Gardasil is deemed adequate for cumulative monitoring of excursions, but an additional CTC 40°C allowance time, documented for the end customer in the prescribing information, would be outside the VVM categorization.

Subsequent discussions dealt with the question if 37°C or 40°C data are necessary. This was considered to be a regulatory issue that would require consultation with the relevant competent authority. If 40°C data are deemed necessary, these data might be estimated by modeling, taking in account data on potency decay obtained at lower temperatures but that this would have to be considered in the context of the other characterization data for the product at or above 40°C.

Summary of discussions

Issues raised: General

Alignment of "stability budget" (or "potency budget") with "CTC"
Stability budgets must take into account the ‘potency loss of the product throughout the self-life under the normal storage condition as well as any planned CTC excursion. The CTC excursion is therefore only a part of a product’s total stability budget that must also include the scheduled TOR during manufacturing, shipping etc. in addition a vaccine’s CTC potential.

Term definition: CTC (WHO/IPAC) vs ECTC (Ottawa/Langen meeting)
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. During the consultations in
Ottawa (2012) and again in Langen (2013), the term Controlled Temperature Chain (CTC) and its definition were reviewed. It was proposed that the term Extended Controlled Temperature Chain (ECTC) may be more appropriate. However, the term CTC is used throughout this report to avoid confusion as the use of ECTC will have to be endorsed through the appropriate WHO committees, e.g.: SAGE.

The ECTC 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 ECTC, allows a specific vaccine to be kept and used at ambient temperatures, e.g. 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.

**Vaccine stability vs VVM:**

**diverging regulatory, scientific and immunization programme views**

The stability of vaccines generally varies over shelf-life (e.g. potency) and products behave individually to exposure to different temperatures, which determines a product’s shelf-life. This is particularly important to consider when exploring the possibility of returning vaccines to the cold chain after a CTC exposure. CTC evaluations are a regulatory issue and submissions for CTC label changes should be based on actual stability data to support the planned use of a product out of the cold chain for a defined period of time and defined temperature range. In contrast, VVMs are monitors of temperature exposure, not unlike thermometers, except that a VVM measures accumulated temperature exposure but which is not specific to a particular vaccine stability profile.
Options that may increase flexibility for limited storage outside the normal cold chain:

- reduction of the approved normal shelf-life at 2–8°C;
- provision of stability data that support storage beyond the shelf-life already approved by the competent authority;
- amend (i.e. tighten) product release speciation’s within the approved ranges to enhance CTC potential;
- reformulation of the product to specifically increase thermal stability or increase of overages on a case by case basis, which would result in a new product.

How to promote stability studies and data analysis supporting the CTC concept?

- reviewers/regulators and industry should consider specific training for CTC evaluation including mathematical modeling;
- guidance on the use of already existing data in CTC application for legacy products should be developed;
- understanding that most vaccines do not adhere to Arrhenius kinetics, guidance on the use of Arrhenius modeling (e.g. interpolation for decay rates estimation) should be considered.

Issues raised regarding CTC labelling:

- wording should be instructive and informative (e.g. specific maximum temperature, maximum time of planned CTC excursion);
- an informative summary of the stability data supporting limited storage outside the cold chain should be provided in the product insert.

Peak temperature recording:

- use of peak temperature indicators (indicating e.g. single temperature excursion above 40/42°C or even 50°C) are considered mandatory.
Conclusions:
The group agreed that:

- for the majority of vaccines, the rate of potency decay is lower when the product is stored at 2–8°C;
- the cold chain is critical and should be maintained where possible, but at least for certain vaccines - CTC will provide a very useful option in situations where maintaining the cold chain is not feasible and limits immunization programme effectiveness;
- guidance on how to assess stability and labelling for CTC has to be provided;
- further information sharing and training opportunities with regulators, vaccine manufacturers and VVM experts are required;
- priority products are Hepatitis B-birth dose, Yellow Fever, HPV, Cholera, IPV, Pneumonia, Rotavirus, Combo, new vaccines, etc.
- appropriate real-time data are required to support CTC product label changes;
- 40°C is considered a target CTC temperature if supported by stability profile of the vaccine;
- at least 3 days is the minimum time for excursion outside the cold chain for logistic reasons;
- temperature monitoring must be assisted by appropriate peak temperature indicators.

Recommendations
Considerations on drafting CTC-specific guidelines:

- CTC data should be assessed using appropriate mathematical modelling, statistical analysis and additional guidance/training on how to perform these studies is needed;
- the CTC programme expectations are for:
  – a single planned excursion just prior to use (e.g. the “Last Mile”) at temperatures up to 40°C as the short term goal;
  – multiple planned excursions ("Cycling") would be considered a longer term goal.
- stability studies & data analysis requirements:
  – shelf-life estimation at 2–8°C, 25°C, 37°C and/or 40°C must be based on sufficiently sensitive, robust and validated potency or other stability indicating assays. These key
quality attributes must be assessed over the full normal shelf-life (i.e. at 2–8°C) and the proposed CTC condition, be based on the rate of decay (i.e. potency) or the accumulation of stability indicating impurities (e.g. free PS for conjugate vaccines) and consider worst case lot release scenarios against specifications linked to the product’s clinical performance (i.e. efficacy and safety).

**Special consideration on VVM selection for WHO-PQ vaccines/peak temperature indicator:**

VVMs have shown to be effective for the intended use, which is to detect cumulative temperature exposures. It is understood that a VVM does not show vaccine potency and the colour change of the VVM is not stability indicating. However, the VVM was not designed to meet the CTC programme objectives and is not sensitive to freezing conditions that may also contribute to vaccine degradation. Moreover, the VVM does not differentiate between continuous exposure to slightly higher temperatures (>20°C) or peak exposures to very high temperatures, e.g. temperatures > 42°C. Therefore, peak temperature indicators should be developed in combination with VVMs, which would then be capable of providing information on the continuous heat exposure as well as on peak exposures to the maximum CTC limit (i.e. 40°C). Additional monitoring by peak temperature indicators is also needed to support CTC programme implementation in order to detect single course temperature excursion, above a critical threshold temperature for vaccine label requirements.

**Proposed follow-up actions:**

Further points for action include:

a) to develop CTC specific guidelines that could be integrated into a subsequent revision of the existing WHO vaccine stability guidelines — such an approach would provide consistent guidance with regard to the stability evaluation of vaccines in general;

b) to develop plans for training and sharing of best practices for regulators performing CTC stability assessments; and

c) provide an update on each of these proposals to the ECBS in 2014.
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