DCVMN 3R Program
PSPT Project Kickoff meeting
Tuesday 29th September 2020

Attendees: Anissa Wari Murti (AWM), Arjen Sloots (AS), Arun Bhardwaj (AB), Christina Von Hunolstein (CVH), Coenraad Hendriksen (CH), Deepak Mahajan (DM), Elizabeth Ika Prawahju (EP), Gopal Singh (GS), Irma Riyanti (IR), Jim Saylor (JS), Marta Prygiel (MP), Maya Ramdas(MR), Muhammad Erdiansyah (ME), Pavel Mitrenga (PM), Pavlinka Stoyanova (PS), Pradip Das (PD), Sivakumar Sakthivel (SS), Sreenivasulu Reddy B (SR), Sri Wahyuningsih (SW), Stan Deming (SD), Sunil Gairola (SG), Supaporn Phumiamorn (SPh),Tana McCauley (TMC), Ute Rosskopf (UR), Wiriyarmarst Jaroenkunathum (WJ), Zulfa Noerhidayati (ZN), Sonia Pagliusi (SP), Laura Viviani (LV), Nora Dellepiane (ND), Benoit Hayman (BH) and Sonia Villaseñor (SV)

Opening and participants presentation

CVH opened the meeting by introducing herself. Each of the participating manufacturers and NCLs introduced themselves and gave a brief description of the wP batch release information used in their laboratory.

LV gave a short background on how will DCVMN manage the project. SP will be the project and administrative director. LV will be the project manager. DCVMN is going to manage the relationship with NIIMBL, participating labs, the Steering Group, Intravacc, CMO and the independent statistician; coordinate the signature of the Consortium agreement; and organize all the virtual meetings as well as the distribution of the PSPT coating antigen.

The project will have the support of a Steering Group which will provide scientific and technical advice and will meet quarterly. The members of the steering group introduced themselves.

Description and initial discussion on the in-house validation study

CH explained the three main aspects of the project:

- The main focus is the in-house evaluation of validity of the PSPT, as a replacement of Kendrick Test (KT)
- Another focus is implementing the consistency testing approach in the laboratories for batch release tests
- The third focus is that the study will be based on an in-house validation

As an in-house validation study, each manufacturer will use their own batches, apart from the NCL, which will receive the batches from one of the manufacturers for which they perform the release testing. Each lab will produce their own data on KT and PSPT test, which will be validated separately by each lab. For this study, commercial batches will be used that are (or have already been) tested by routine batch testing in the KT at each manufacturer. As a minimum 3 different final lots of vaccines need to be used in the study. A volume of one of these batches will be used to produce an altered batch which potency will be determined in KT and PSPT. Laboratories can test more batches in the study and it will be possible to use different types of wP vaccines (DTP, Penta, etc.). However, each kind of vaccine will need to be tested according to the study protocol. In this study, there is also a need to link the results of the PSPT with the KT and the additional wP Regional Reference Standard. The results need to be consistent with the already produced batches test in use.

CH then explained the possible design of the study. *For manufacturers*. One Regional Standard and one batch will be used as in-house references The 2 homologous consecutive batches produced will be tested against their own in-house reference standard. Then labs shall prepare an altered batch based on a volume of one of the three wP batches to get a vaccine batch with an altered potency (higher/lower). Each lab will decide which of the 2 consecutive batches to alter. The *NCL* will perform the tests using 3 batches and the altered batch, which will be provided by the manufacturers. The altered batch can be prepared in different ways, for example, diluted, heated or frozen. Common procedures to alter the batch will be shared with the laboratories. KT results are obtained as part of the routine batch release, so an additional KT test should only be performed in batch number 4 (altered one). All four batches shall be then tested by the PSPT test. If it is not possible to test all the products in one experiment, the samples can be divided, but in each animal study to be performed, the in-house reference preparation and the regional standard shall always be included.

Two sets of data will be obtained; one is to demonstrate the relevance of the PSPT for consistency testing and the other to demonstrate the reproducibility of the PSPT for consistency testing. Data will be used for statistical purposes to rank vaccines against potencies 1-4 in KT and PSPT. Potencies of vaccines 2, 3, and 4 will be related to the in-house reference 1, and potencies of batches 2,3 and 4 can be expressed in % of potency of batch 1 or in IU/ml if the regional standard was included in the study. Regarding demonstration of reproducibility, the hypothesis is that the 95% intervals of the PSTP test will be smaller than those of the KT.

An extension has been added in the study to link the PSPT consistency data to data obtained from the conventional KT potency test. For that, the Regional Reference wP Standard needs to be included together with the 4 batches produced by each manufacturer. The study design of the test is the same; there is no double testing. If any participant decides not to include a reference preparation, although it is preferred, the results will only be used for consistency evaluation and not for the link of PSTP consistency data with KT data. CH showed also the parameters that will be analyzed at the end of the study designed for consistency and link KT-PSPT. A final consensus is still necessary.

Questions and Answers

Question 1 (SP): Are regulators encouraged to test the same kind of vaccines from different manufacturers in one test or the same kind of vaccines from the same manufacturer.

Answer 1 (CH): The NCL shall test 3 batches from the same manufacturer to look for consistency in one manufacturer. However, it would be interesting for the NCL if they have another manufacturer of the same kind of vaccines to see if they can reproduce the findings for the other manufacturer using in common one vaccine.

Question 2 (UR): If for example, if an Indonesian NCL that tests Indonesian produced pentavalent and DTP vaccines are also testing samples from India, there will be an imbalance because we have many manufacturers participating from India. What is the distribution and how is it going to be mapped? What is the design and who is testing what?

Answer 2 (CH): Before starting the study, the laboratory shall indicate what are they going to do. If there is an imbalance, there is still a possibility to discuss and modify the design of their studies.

Question 3 (UR): Do NCL only test the vaccines from manufacturers of their country or from other countries

Answer 3 (CH): NCL will normally only test the vaccines from manufacturers of their country, unless they also regularly test vaccines coming from other manufacturers from other countries.

Answer 3 cont. (CVH): NCL will perform PSPT on the vaccine it is receiving from the manufacturer, and can perform the study on only one kind of product from one manufacturer. The respective NCL will decide whether to transfer this method for other products from other manufacturers. The study is very complex. It is not feasible to perform the study using many products.

> *Comment (SPh):* In Thailand it is not possible to find 3 consecutive batches of the same type of vaccine from one single manufacturer. This is a limitation for the Thai NCL to perform the consistency test. They might have DTP, DTP-Hep B and pentavalent, depending on the imported product. CH suggested to request an outside collaborating institute to provide 3 consecutive batches that have been tested by KT so that the NCL will be able to participate in the study. The case needs to be discussed further (**Action**)

Question 4 (SG): Request on clarification on consecutive lots, because if we say consecutive lots, it does not make a difference between different bulks. If consecutive lots come from the same pool of wP bulk it makes no sense to compare consistency, it should be specified that they should come from different bulks of wP. In addition, when altering a batch, if somebody uses freezing the potency goes very high. He also suggested to fix a norm to alter the batch so that the alteration for all manufacturers remains one method to have the consistency in terms of altering the batch.

Answer 4 (CH): Frozen and thawed vaccine will have a higher potency but the objective of the study is to demonstrate consistency, so that a batch deviating from other batches is suspicious of being non consistent. So, there would not be a problem in including frozen and thawed vaccines. But if you want to do a sub potent batch it will be more relevant to use dilution or heating. Regarding the three consecutive lots coming from different bulks of pertussis, it is acceptable but it is not acceptable having the three lots coming from three different types of wP vaccine.

> *Comment (UR):* While it might be difficult to achieve use of 5 bulks of diphtheria might be suggested and 3 final bulks of wP pertussis to produce different final vaccines. CH said this will be needing further discussion (**Action**).

Question 5 (EP): Should one run the test with the two methods KT and PSPT.

Answer 5 (CH): The test is run only once, not several times. The KT is part of the routine test as part of the batch release. It is not necessary to do them at the same time, if there is not a long-time gap between running the KT and PSPT.

Project Work Plan presentation

LV reviewed the timelines; the project has a 17-month timeframe, ending on Jan 31, 2022. Each laboratory would use the data generated from the PSPT for the implementation and regulatory acceptance of the PSPT. If the project successfully demonstrates in-house validation, all results will be published and shared with the WHO, to make sure that PSPT will be used for releasing wP containing vaccines. LV said the coating antigen for ELISA will be shipped from *BioLyo Technologies* to the labs as a research material under an MTA. This material shall be used for the project only. A renegotiation for the future use for this material will be needed. DCVMN will have a consultant to work on a business plan. CVH stressed time is tight, so everybody needs to be transparent and inform immediately of any difficulties, as to find a solution. SP added the database will be electronically built by DCVMN for the consortium members to input the data and will be anonymized, so nobody will know from which lab a dataset originates. The DCVMN secretariat will eventually know but will not disclose which lab submitted which data.

SPh said that, in Thailand, they must apply for animal ethical approval in October. She requested to get the SOP by mid-October. LV offered that CHV and CH will do their best to deliver, SPh confirmed a draft could be sufficient (**Action**). LV invited the other participants to contact her in case they have any other time constraints. CH said that regarding the SOP, each laboratory will have to decide the number of animals to be used per dilution, and then decide on the number of products to be included in the test. The SOP will only provide the number of dilutions. UR asked if the number of animals to be used by each laboratory will be decided by each lab. CH said for the PSPT study we will give an indication, but it depends on the strain of animal used, also the quality of the animals is an issue. The SOP will set a range, but each laboratory will decide the number of animals to use, however UR said she will not recommend go with 10 mice but above.

CVH thanked all the participants; the questions raised in the chat will be answered afterwards in writing and will also be taken into consideration while preparing the SOP and related documents together with CH. Also, they will prepare a questionnaire to find what will be done in every laboratory. If there are other ideas for the steering committee, please submit by email to LV.

Meeting closed at 14:33

Notes taken by SV

Christina Von Hunolstein
Chair of PSPT Steering Group

Laura Viviani
DCVMN Project Manager

Nyon, October 9th, 2020