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Meeting Report:

WHO workshop on implementation of international standards for quality control of polio vaccines including OPV and IPV

31 October - 2 November 2023¹

Holiday Inn Jakarta Kemayoran, Jakarta, Indonesia



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Executive Summary

The World Health Organization (WHO) has been developing international standards for biologicals including vaccines for more than 70 years which serve as the basis for setting up national requirements and for WHO prequalification of vaccines. Setting norms and standards, promoting, and monitoring their implementation are WHO's core functions. Live-attenuated oral polio vaccine (OPV) and inactivated polio vaccine (IPV) are used by the Global Polio Eradication Initiative (GPEI) and will still be playing a major role in the endgame of global polio eradication and beyond. In response to scientific and technological advances in the polio vaccines field, GPEI strategic needs including containment requirements, and to align with other recently published WHO general guidance as relevant, WHO has updated written technical standards/guidance for polio vaccines in recent years: IPV Recommendations amendment (2019), full revision of OPV Recommendations (2022), and Guidelines for the safe production and quality control of polio vaccines (2018 & 2020). Meanwhile, various international measurement standards and new quality control technologies (e.g., high throughput sequencing, HTS) for control of OPV and IPV have been developed and become available. It is important for manufacturers and regulators to be aware of current written and measurement standards and understand their proper use. In response to requests from stakeholders, WHO organized this workshop on implementation of international standards for quality control of polio vaccines including OPV and IPV². Main subjects of this workshop included:

- Update on current available written and measurement standards related to OPV and IPV
- Rationale and proper use of WHO written and measurement standards
- Elaboration on utility of HTS as a quality control (QC) test for OPV and IPV
- In-vitro D-antigen and in-vivo potency tests and standardization issues
- Vaccine stability monitoring considerations
- Production consistency issues & reference standards management

Participants included worldwide experts and representatives of stakeholders including vaccine manufacturers, control laboratories, regulatory authorities, and other international health agencies. During the workshop, the topics were discussed by providing lectures, case studies, and Q&A sessions. This Workshop provided a platform for networking, exchanging experiences and views among experts, manufacturers, and regulators on important issues related to poliovirus vaccine production, QC, and standardization. Questions about the use of International Standards, as well as selection, validation and calibration of secondary standards were raised by both national control laboratories (NCLs) and manufacturers. The role of monitoring programmes, trend analysis of in-house reference standards and stability studies including thermal stability test as an indicator of production consistency and accelerated stability tests to provide additional information on product characteristics were extensively discussed using case studies.

² OPV- Oral Poliomyelitis Vaccine. IPV- Inactivated Poliomyelitis Vaccine. The use of the abbreviation "IPV" refers to IPV derived from any strain. "wIPV" indicates IPV derived from wild-type strains only, and "sIPV" represents IPV derived from Sabin strains only.

This workshop was acknowledged by the participants to be helpful in improving or reinforcing their skills regarding QC of polio vaccines and increasing their awareness regarding recent changes in written standards. Challenges and further needs for support were identified during the workshop, regarding implementation of HTS as a tool for the QC of polio vaccines (including OPV, IPV, novel OPV), including the unavailability of a reference reagent / International Standards for HTS assay, standard protocol, assay equipment and bioinformatic pipelines. Participants recommended that WHO provide ongoing technical support so that they can continue to build upon what was learned at the workshop and strengthen their capacity for HTS assay. Other challenges identified included issues around the requirement of higher containment for performing assays with live type 2 poliovirus and shipping live poliovirus reference reagents, need for harmonized guidance for calibration of in-house reference standards for vaccine potency and additional quality attributes for monitoring the shift of standards replacements.

The workshop helped advocating WHO international standards as well as ongoing and upcoming collaborative studies on future standardization projects to raise awareness and interest.

1. Background

In 1988, the World Health Assembly adopted a resolution for the worldwide eradication of polio, marking the launch of the Global Polio Eradication Initiative (GPEI). Since then, the incidence of polio worldwide has been reduced by 99%, and the world stands on the threshold of eradicating a human disease globally for only the second time in history, after smallpox in 1980 [1]. The use of OPV developed by Albert Sabin has played a critical role in the progress of the GPEI. OPV was first licensed as monovalent OPV (mOPV) in 1961 and as trivalent OPV (tOPV) in 1963. Effective IPVs are also available, first licensed in 1955. OPV has proven to be both immunogenic and highly attenuated when administered orally to susceptible children and adults. The effective vaccination programmes implemented by WHO resulted in the declaration of the eradication of wild type 2 poliovirus in 2016 and wild type 3 poliovirus in 2019. Wild poliovirus cases have decreased by over 99% since 1988, from an estimated 350 000 cases in more than 125 endemic countries then, to just two endemic countries (with OPV and IPV still playing a major role in the endgame of global polio eradication and beyond. Setting norms and standards and promoting and monitoring their implementation are WHO core functions. In response to the scientific and technological advances in polio vaccines field, and GPEI strategic need, and to align with other recently published WHO general guidance as relevant, WHO has updated or revised written technical standards/guidance for polio vaccines including IPV Recommendations amendment in 2019 [2], full revision of OPV Recommendations 2020-2022 [3], Guidelines for safe production and quality control of polio vaccines in 2018 and 2020 [4,5]. Meanwhile, various international measurement standards and new QC technologies (e.g., high throughput sequencing, HTS) for control of OPV and IPV have been developed and become available to countries. Therefore, it is important for manufacturers and regulators to be aware of current standards and understand their proper use. During the process of developing those standards, issues have been identified among stakeholders and requests have been received by WHO to

organize implementation workshop to provide additional technical support. Therefore, this three-day workshop to facilitate the implementation of these written and measurement standards and discuss the issues identified was organized by WHO Headquarters (HQ) with assistance from WHO country office in Indonesia and Indonesian FDA from 31 October to 2 November 2023.

WHO has made extensive efforts to organize this workshop, invited NCLs, manufacturers and experts from worldwide countries who are involved in OPV (including novel OPV-nOPV) and/or IPV production and control, convened series of preparatory meetings with key experts to discuss and agree on technical topics of the workshop (see Appendix 1- Agenda). Despite various factors, there were total around 55 participants attending this workshop including 26 regulators from 17 countries across 6 WHO Regions, 18 manufacturers from 10 companies, and experts from PATH and other institutions, WHO staff from Headquarters, and WHO Country office in Indonesia (see Appendix 2- List of Participants).

This workshop was needed to communicate and reiterate the important changes made to relevant documents and make the participants aware of range of written and measurement standards available in the field of polio vaccines.

2. Opening and objectives of the workshop

To commence the workshop, Dr Tiequn Zhou (WHO/HQ, Switzerland) welcomed participants and invited Opening Remarks given by Dr Momoe Takeuchi, Deputy Representative of WHO Country Office Indonesia, and by Mrs. Togi J. Hutadjulu, Deputy Chairperson for drug, narcotic, psychotropic, precursor, and addictive substance control, The Indonesian FDA. The importance of assuring quality, safety, and efficacy of polio vaccines in the global polio eradication programme was highlighted well in the opening remarks. Dr Zhou informed participants of workshop arrangements. Mrs Teeranart Jivapaisarnpong (Thailand) acted as the Chair, Drs Javier Martin and Manasi Majumdar (Medicines and Healthcare Products Regulatory Agency, MHRA, UK) served as Rapporteurs of the workshop.

Dr Tiequn Zhou presented the background, objectives and expected outcomes of this workshop, as well as workshop preparation and arrangement. The main objectives of this workshop were: to provide updates on WHO standardization of polio vaccines (OPV, IPV) including written and measurement standards; provide lectures, case studies, and Q&A sessions to manufacturers and regulators to elaborate on important issues related to polio vaccine production and QC, including the rationale and proper use of WHO standards; and exchange experiences and views among experts, manufacturers and regulators, promote implementation of WHO standards into working practice, and identify future need for technical support. This workshop was expected to facilitate and promote the implementation of up-to-date WHO standards (written and measurement) for polio vaccines into manufacturing and regulatory practice.

Dr Ivana Knezevic (WHO/HQ, Switzerland) presented (virtually) an overview of the WHO biological standardization programme and updates on broad range of WHO biological

standardization activities including vaccines, biotherapeutics and cell & gene therapies, and outcomes of recent meetings of the WHO Expert Committee on Biological Standardization (ECBS).

3. Key Issues addressed in the workshop

3.1 Updates on WHO written and measurement standards for QC of polio vaccines (OPV, IPV)

Dr Tiequn Zhou provided an update on current WHO written standards for OPV and IPV, overarching WHO guidance for polio vaccines, WHO guidance on preparation and calibration of measurement standards and links to useful web resources [2-8]. The concepts and application of WHO written and measurement standards were also presented. Some key issues addressed in the current OPV recommendations in WHO TRS No. 1045, Annex 2 [3] are:

- Use of HTS in QC of OPV as an alternative to MAPREC assay.
- Analysis of whole genome mutational profiles generated by HTS as a possible future replacement of the MNVT and TgmNVT for routine lot release once manufacturing consistency has been established.
- Removal of rct40 test due to its insufficient sensitivity & implementation of GAPIV.
- Consideration of the design, manufacture, and QC of nOPV strains.
- Use of new non-pathogenic strains for the measurement of neutralizing antibodies to polioviruses.

Dr Zhou then discussed about the 2019 Amendment to IPV TRS 993 [2]. Some of the major key issues addressed in the last revision are:

- Modified definitions of “virus sub-master seed lot” and “virus working seed lot”.
- Modified requirements for confirming the genetic stability of attenuated vaccine seeds and monovalent virus pools to provide flexibility for vaccine developers.
- Additional cell substrates included that can be used for the effective-inactivation test.
- General safety (innocuity) test deleted.
- Updated recommendations for the evaluation of sIPV immunogenicity in nonclinical and clinical studies.

Dr Javier Martin (MHRA, UK) provided an overview of available international reference materials for OPV and IPV. OPV is a live attenuated viral vaccine prepared by serial passage of poliovirus that leads to virus attenuation therefore critical QC tests in OPV production are: Virus identification, Virus concentration, Neurovirulence test in monkey neurovirulence test (MNVT), or poliovirus receptor transgenic mice neurovirulence test (TgmNVT), Genetic markers using MAPREC/HTS and Thermal stability. On the other hand, IPV is prepared by inactivation of live poliovirus with formaldehyde leading to destruction of infectivity. Critical QC tests in IPV production are: Virus identification, Virus concentration, Effective inactivation, D-Antigen content after inactivation, *in-vivo* potency, adjuvant adsorption. Absolute measurement is required for the quality assessment and licensing of biological products for human use to ensure safety, efficacy, and consistency. There is a fundamental

need for reference materials to support biological standardisation. Reference standards need to be robust, fit for purpose and shared widely and often gets used up and need replacement. WHO plays a global role in biological standardization by developing international norms and standards through WHO guidelines and recommendations to assure the quality, safety, and efficacy of biological products which includes the establishment of WHO Biological Reference Materials. NIBSC produces >95% of International Standards for biological medicines. Reference standards help establishing consistency of vaccine production. The use of reference standards allows comparison of vaccines from different manufacturers and vaccines from different batches of the same manufacturer. It also helps develop and characterise new vaccines. Dr Javier Martin then provided an updated list for the WHO International standard and reference reagent that are useful in standardizing assays for polio vaccines like potency assay, cell sensitivity standards, International Standard for anti-poliovirus sera, International Reference Reagents for neurovirulence assays that are available in NIBSC catalogue, International Standards and Reference Reagents for MAPREC, International Standards for D-antigen and Reference Reagents for IPV and sIPV. Dr Martin also provided plans for the establishment of new international standards for nOPV products and HTS assays. The use of S19 hyper-attenuated poliovirus type 1, 2 and 3 Reference Reagents to support serology QC assays in low containment was also described.

3.2 Use of molecular tests in the QC of OPV and IPV

Dr Kostya Chumakov (George Washington University, United States) provided a historical overview of the development of OPV and scientific understanding of the molecular basis for attenuation of poliovirus which highlighted the need of monitoring vaccine genetic stability/consistency initially using the MNVT. He described the development of the molecular MAPREC test and transgenic mouse tests to replace MNVT at different production stages. He then explained the regulatory role of MAPREC in passing or failing a vaccine in conjunction with MNVT or TgMNVT [9]. However, MAPREC tests can provide information about only one/two genomic positions. MAPREC test requires highly skilled personnel and specialized equipment. In addition, mutations probed by MAPREC assay are of no significance for quality control of nOPV vaccines. Therefore, a test method that can scan the genetic profile of poliovirus entire genome like HTS [10] will be highly desirable and have the prospect of replacing animal testing and MAPREC as well for routine lot release.

Dr Tong Wu (Health Canada) then provided an overview of definitions and applications of HTS mentioned in Annex 2 TRS No 1045, Annex 3, TRS No 1024 [2,3].

Dr Kutub Mahmood (PATH, United States) described the alternatives to animal testing for vaccine release of polio vaccines and how PATH is supporting various projects related to standardization and safe production of polio vaccines.

Dr Javier Martin gave a detailed overview of OPV safety testing through time and reiterated the important role that HTS can play in molecular characterization of poliovirus vaccines. He covered in detail two ECBS endorsed WHO collaborative studies which were carried out in recent years to investigate the utility of HTS assay as an alternative to the MAPREC assay [11,12]. Both studies showed excellent correlation between MAPREC and HTS result for

Type 1, 2 and 3 poliovirus. He then delved into detailing the role HTS can play in characterizing the whole genome. Centre for Biologics Evaluation and Research (CBER), at the US Food and Drug Administration's (FDA) and MHRA have been working closely in developing methodology for whole genome HTS analysis of polio vaccines. He explained how whole-genome single nucleotide polymorphism (SNP) profiles were highly consistent between vaccine products from the same manufacturer. Different vaccine seeds and associated products were found to contain unique SNP profiles. These results suggest that whole genome HTS analysis has a great potential as a QC test for OPV, measuring vaccine production consistency and potentially replacing neurovirulence testing using animals.

Dr Manasi Majumdar (MHRA, UK) provided details of the ongoing work carried out for a collaborative study aiming at establishing reference reagents to be used for the HTS method for genomic consistency. The main objective of the collaborative study is to establish reference reagents suitable for measuring neurovirulent domain V mutations and/or whole genome sequence analysis. She presented the data regarding candidates developed at MHRA to be included in the collaborative study, shared details regarding the collaborative study workflow and SOPs developed with the participants. The vaccines tested so far in the study showed HTS to be a sensitive tool for monitoring consistency of production and identifying outliers. Caveats of the study being inconsistency of molecular profiles does not necessarily mean that a vaccine lot is unacceptable. It suggests that conditions of virus growth have changed, this is a red flag and may require investigation.

The main conclusion from all the presentations given related to HTS as a replacement for an animal testing for genomic consistency can be drawn as below:

Step 1: During the establishment of OPV production first several batches of vaccine should be tested in animals as well as by generating whole genome single nucleotide polymorphism (SNP) profiles by HTS.

Step 2: New manufacturer or major change in production conditions, new seed virus, etc should trigger step 1.

Step 3: Only after consistency of manufacture is established, HTS can be used to test for conformity of molecular composition of each new batch of OPV to the historical profile of mutations.

Step 4: If the SNP profile of a new batch of vaccine, falls within pre-defined statistical release criteria, it can be released without performing NVT.

Step 5: If the SNP profile of a new batch of vaccine falls outside pre-defined statistical release criteria: Careful review of the specific sequencing data should be conducted. Based on the results, animal testing should be performed. If the result of animal testing is acceptable, the SNP database should be updated.

Dr Julia Panov (University of Haifa-UoH, Israel) then presented the ongoing collaborative UoH/PATH/George Washington University/MHRA/CBER-FDA work on developing the code-free bioinformatics platform for quality control and analysis of HTS polio-vaccine

samples. HTS data contains a lot of valuable information on virus mutability and its specificity to batches of samples. However, the sequencing data may be contaminated by other sequences such as host and bacterial sequences as well as sequencing artefacts due to sample preparation and sequencing procedures. The QC part of the platform (VacQC) was developed to identify possible contamination and artefacts in the sequencing reads and to clean the data for further analysis. The main analysis part consists of alignment of reads on the reference genome, variant calling, and statistical analysis of found statistically significant mutations. In the developed no-code platform, the VacMut pipeline consists of the following steps:

- (i) Determine mutation variants and their frequencies.
- (ii) Correct mutation variant frequencies for variants that are statistically deviating from expected values due to low coverage by HTS reads.
- (iii) Perform unsupervised clustering of samples based on whole genome mutation variant frequency profiles.
- (iv) Determine differentiating variants in each pair of clusters of samples as well as cluster-specific variants.

Dr Panov presented the October-2023 version of the developed platform: quality control oriented VacQC and machine-learning based VacMut pipelines. Then she gave an online demonstration of the pipelines VacQC and VacMut and provided links to the participants to test the pipeline with Demo data.

Dr John Konz (PATH, United States) then provided a presentation on establishing HTS for quality control of novel OPV2 (nOPV2). He started with describing the construct and phenotypic attributes of nOPV2 and how HTS is first used in the development (characterization of seed and vaccine bulks) of nOPV2 and later used in understanding the genetic evolution of the virus in vaccinated human subjects. He described his group at PATH has strong collaboration with Andrew Macadam's group at MHRA, where they designed experiments to understand the impact (*in-vitro* and *in-vivo*) of the variants seen while vaccine production or evolution of the virus seen in the stool samples of the human subjects. Data generated confirmed the superior genetic and phenotypic stability of shed nOPV2 strains compared to shed Sabin-2 and suggest that nOPV2 should be associated with less paralytic disease and potentially a lower risk of seeding new outbreaks [13]. Due to the early involvement of HTS technology in developing nOPV2 vaccines there was ample evidence regarding key mutations (Variants of Interest; VOI) that should be targeted for quality assessment of nOPV2 bulks produced. He listed the VOI and the impact that can be caused by those mutations. He then described about validation and study design considerations to study these VOI using HTS [14].

Dr Catherine Milne (The European Directorate for the Quality of Medicines, EDQM, France) presented points to consider in the validation of HTS in context of QC of OPV and IPV. She pointed out different potential applications of HTS for polio vaccines and highlighted the parameters to be considered in the validation in the different contexts with examples.

(i) In the context of absence of neurovirulence/molecular consistency

- for OPV, as replacement of MAPREC test and/or for whole genome molecular consistency.
- for nOPV and sIPV seed, whole genome molecular consistency.

(ii) In the context of detection of adventitious viruses

- for cIPV, sIPV, nOPV, bOPV, mOPV, can be used for detection of adventitious viruses in Cell banks, Viral Seed lots, and Single harvests.

Dr Milne then provided an update on the EDQM/Ph. Eur. Texts related to HTS: Ph. Eur. chapters 5.2.3 & 2.6.16 mention HTS and foresee its use as part of the testing strategy for extraneous agents. However, HTS methods were not described in detail in any regulatory document and no guidance for their validation was available. This prompted the elaboration of a general chapter, 2.6.41, on HTS for the detection of extraneous agents in biological products intended to be a non-binding general chapter that includes description of the technology/methods and workflow and guidance on validation of HTS methods. The availability of regulatory standards including validation guidelines in the Ph. Eur. will serve as a reference for regulators and manufacturers. HTS is planned to be introduced in the revised ICH Q5A guideline (Viral safety evaluation of biotechnology products). She also mentioned that FDA has recently developed panels of viruses as reference preparations for HTS that were adopted by WHO ECBS and will serve as useful tools in this context.

3.3 Standardization of potency tests for OPV and IPV

Dr Javier Martin provided an overview of current potency tests for OPV and IPV. He outlined the range of Polio vaccines that have been used in the past, present or can be used in future; like monovalent OPVs, bivalent OPVs, trivalent OPVs, novel monovalent OPV, novel trivalent OPV, conventional IPV, Sabin based IPV, hyper-attenuated strains based IPV, virus like particles and RNA vaccines. He then outlined the flow chart for the production of OPV and IPV vaccines and described that for the OPV testing the main QC tests are focused around identity, potency and consistency (attenuation) of production. For IPV, vaccine's identity, titre are important but after inactivation of the virus In-vitro potency assay to establish D-antigen content is very important. If, it is a new manufacture or a new formulation then along with D-antigen content in-vivo potency assay using rat or transgenic mouse plays important role in initial characterization of the new product.

Dr Manasi Majumdar then provided an update on standardization of potency test for OPV. Key points in the current WHO TRS for OPV [3] related to potency assays for OPV were discussed. A detailed overview of potency tests for OPV was provided, including details of collaborative study [15], assay format, testing parameters, interpretation of results, assay validity, compliance with WHO specifications, routine data monitoring and data trending. The use of reference standards in the assay as well as antibody reagents required for potency assays for bOPV and tOPV were discussed. Details of the upcoming collaborative study to establish the 1st WHO international standards for nOPV1, 2 and 3 potency assays were provided.

3.3.1 Standardization of in vitro potency tests for IPV

Dr Kostya Chumakov provided historical background and scientific rationale on the D-antigen ELISA potency test for IPV. Original D-antigen units were arbitrary and based on agar immunodiffusion test. He further elaborated on the proper use of the sIPV D-antigen International Standard [16], assignment/meaning of SDU. Differences in the antigenic properties of cIPV and sIPV products mean that a different WHO international standard as well as different D-Ag units are required for cIPV and sIPV products, respectively. Universal antibody reagents and associated method for potency testing of both sIPV and cIPV products were validated and adopted by ECBS and may be used as an option for manufacturers and NCLs upon demonstration of suitability for specific products.

Dr Alison Tedcastle (MHRA, UK) provided key aspects of the in vitro D-antigen potency assay for IPV including the choice of references, D-Ag specific antibody reagents and assay format [16]. The main conclusion from the session were that:

- A new sIPV International Standard 17/160 has been prepared, validated and approved by ECBS. 17/160 reference material was arbitrarily assigned potency of 100 SDU (new established unit used for sIPV only).
- Universal potency reagents based on human monoclonal antibodies have been prepared and validated. The universal potency reagents can be used to test potency of both Salk and Sabin IPV upon demonstration of product specific suitability.
- Only homologous D-antigen International Standard must be used in conjunction with these reagents. Heterologous D-antigen International Standard, results in poor agreement between labs.
- The universal potency reagents are available from the NIBSC/MHRA catalogue. Manufacturers are free to choose whether to use universal reagents or to prepare their own reagents. In either case they must demonstrate their suitability for the intended purpose with the specific product.
- New IPV manufacturers could benefit from adopting fully validated reagents and the test protocol.
- Formulation of IPV-containing products is different (e.g., adjuvants, combination vaccines). Therefore, the protocol for testing final products must be validated by each manufacturer.

3.3.2 Standardization of in vivo potency tests for IPV

Dr Javier Martin provided a historical overview of in-vivo potency assays for IPV, showing the rat assay as the most suitable test due to a high antibody titre, good linear dose response and to better resemble the antibody response in humans. D-Ag values might provide indication of virus/protein quantity in IPV samples but do not tell us much about the immunogenicity of vaccine preparations. In-vivo laboratory potency assays are very useful for early vaccine development stages (for both IPV and VLP preparations), assessment of the effect of mutations that arise during virus cell growth, vaccine dose finding determination, and establishing batch release quality control assays. Following establishment of consistency of vaccine production, in vivo assays can be waived in favour of in-vitro potency assays

provided full correlation between in-vivo and in-vitro assays has been established and has been approved by the NRA.

Dr Alison Tedcastle provided a detailed methodology including description on inoculation of rats, titration of sera (for each serotype), selection of challenge virus strains and back titration of virus challenges. She provided examples of calculating relative potency and validity and data trending options. She then outlined an ongoing collaborative study to look into the utility of S19 being used as challenge virus for *in-vivo* potency assays. S19 strains are genetically stable and include a portfolio of strains containing the capsid proteins (and thus having the antigenic properties) of the Sabin live attenuated vaccine strains or the wild strains used most commonly in the production of inactivated polio vaccine. S19 strains can be used at BSL2 containment level and are a safer alternative than using wild strains for QC assays.

3.4 Scientific and regulatory considerations for management of reference standard

Dr Tong Wu gave a presentation on the critical role played by reference standards in vaccine quality control assays [17,18]. The main conclusions from her presentation were: The composition and storage conditions of In-house reference (IHRS) may be different from the vaccine product. However, it is important that the IHRS and test samples should have similar dose response curves. It is important to preserve the integrity of IHRS and reduce the need for frequent replacements that may lead to drift. Effective IHRS management, ensure IHRS replacements are comparable to 1st IHRS. The assigned value of an IHRS replacement should be based on a large data set. Equivalence assessment should examine equivalence assessments of all previous IHRS. This will improve the detection of a drift in relation to the 1st IHRS. Periodically testing IHRS against the IS if available is recommended. Establish, monitor, and trend the range and the mean value of a “specific activity” for each antigen during routine commercial manufacturing and the qualification of an IHRS replacement. This will improve the detection of a drift.

3.5 Considerations for stability and consistency of polio vaccines

Dr Catherine Milne presented a talk on considerations regarding stability and consistency of polio vaccines including definitions to distinguish the two different concepts. Like any other vaccines polio vaccines are subjected to stability and consistency evaluation which should be addressed by strategies approved by the NRAs as part of licencing and updated as necessary through the product lifecycle [17]. The choice of stability indicating parameters for live-attenuated polio vaccines should include potency tests (titre) and can be directly studied on the intermediate and/or final lot. For inactivated vaccines e.g., cIPV, sIPV, potency/content assays are used but are only relevant if demonstrated to be stability indicating – this is a critical consideration for method development in particular for *in-vitro* assays where the stage of testing (and presence of other components) may impact their relevance. Parameters other than potency-indicating ones could also be considered since they indicate changes in vaccine quality but with unknown effects on efficacy and safety e.g., appearance and pH. Shelf-life of final products and storage times of process intermediates should be established based on real-time, real-condition stability studies and approved by the NRA. Consistency parameters should ideally be relevant to potency, safety, or efficacy. Examples of relevant consistency

tests for different stages of production for OPV, nOPV, cIPV and sIPV were shared. Acceptable limits are defined based on links to clinical data.

Method and process performance and their variability should also be taken into consideration when defining the acceptable limits. Specifications should be established for the parameters monitored for stability and consistency. Any confirmed out of specification (OOS) results should be considered noncompliant. Appropriate regulatory actions should ensue and an investigation into the root cause should be carried out and, once identified, corrected. In addition, Trend analysis of quantitative data (both stability and consistency) is expected and shifts in trends should be investigated to identify root causes and implement any necessary corrective actions. Appropriate statistical analysis is used to identify out of trend data. The use, and appropriate monitoring of suitable reference standards was also highlighted as critical to successful stability and consistency programs. She reminded that changes in production process, control methods or reference standards require specific actions to ensure that control strategies for stability and consistency remain suitable and provided examples of relevant actions.

4. Key issues raised during case studies and discussions

Two case studies were provided in the workshop which included presentation, group work, group report and conclusion of findings. The first was designed around reference standards management e.g. use of monitoring programs, trend analysis of in-house reference standards and the comparability of sequential replacements and their impact on product consistency have been extensively discussed.

Overall, participants actively applied the scientific principles correctly and identified additional quality attributes for monitoring the shift of standards replacements. During this case study both NCLs and manufacturers asked relevant questions regarding the use of International Standards, selection of secondary standards, validation, and calibration of secondary standards for vaccine potency assays. The moderator for the case study Dr Tong Wu led this useful discussion on troubleshooting real life challenges in the process of manufacturing polio vaccines. She pointed out relevant WHO guidance documents including manuals and shared her own experience. The need for further guidance in this area was identified.

The second case study was designed around vaccine stability evaluation. The use of monitoring program, trend analysis of product consistency, stability evaluation and the role of thermal stability test and accelerated thermal stability tests have been extensively discussed among manufacturers and NCLs. Participants provided correct responses to the questions based on a product release model. Participants also actively discussed the application of stability characteristics at high temperature to support manufacturing changes. Extensive discussions took place regarding thermal stability test (as an indicator of production consistency) and accelerated thermal stability tests (providing additional information on product characteristics and may aid in assessing comparability should the manufacturer change any aspect of manufacturing). The general consensus is that this Thermal Stability test as defined in TRS 1045 [3] is not needed for stability monitoring for OPV, it is an indicator

of production consistency. Monitoring of release specification versus end of shelf-life specification was also discussed.

The last session of the workshop was dedicated to participating NCLs and manufacturers to share their challenges and perspectives in implementation of WHO international standards for polio vaccines by following a template of focused questions sent by WHO to participants before the meeting. Participants took active part throughout the workshop and stirred useful discussion on real life challenges in manufacturing poliovirus vaccines. Regarding implementing HTS technology, 4 labs have experience with the technique. The majority of other labs do not have much experience in HTS technology; however, they are keen to learn and implement. Participants requested more detailed guidance on HTS such as assay procedures, validation, data analysis (e.g., bioinformatics) and establishment of pass/fail criteria. The ongoing WHO Collaborative study on HTS standardization for MAPREC replacement/genomic consistency is expected to provide more information. A study protocol developed for the HTS standardization study was made available to all study participants. Following the completion of HTS standardization study, a hands-on workshop for study participants and other interested labs will be carried out, and also to disseminate the study results and as a part of implementation of HTS in participating labs.

Questions about the use of International Standards, as well as selection, validation, and calibration of secondary standards for vaccine potency assays were raised by both NCLs and manufacturers. WHO guidance documents including manuals for this are available and presented in the workshop. More elaborations on real practice might be needed. There was desire for replacing *in-vivo* potency assay for IPV with *in-vitro* potency assay. *In-vivo* rat assay is still needed, in particular, for new vaccine development.

The meeting was well received by all the participants and there were requests that such meetings should be organized more frequently where labs can share issues and challenges that they are facing with assays over the years in network interactions. All participants contact details were shared to facilitate building such network. Meeting presentations, and relevant information have been shared by WHO with workshop participants, this enables the participants to access the scientific presentations after the workshop.

In conclusion, this workshop provided up-to-date information on WHO international standards and standardization of assays for QC of OPV and IPV, provided guidance and elaborations on the proper use of the standards, discussed challenges in the subjects and informed of ongoing collaborative efforts towards standardization. It provided a good forum for exchanging experience and perspectives among experts, regulators and manufacturers in the QC of polio vaccines. This workshop was proved to be a good opportunity to promote use of WHO standards and advocate ongoing collaborative studies to attract interest of participation by manufacturers and NCLs.

Authors

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Appendix 1: Agenda

WHO workshop on implementation of international standards for quality control of polio vaccines including OPV and IPV³

31 October- 2 November 2023

Holiday Inn Jakarta Kemayoran, Jakarta, Indonesia

Pre-meeting on 30 October 2023 is starting at 9:00 attended only by WHO, facilitators, invited speakers, to review agenda, presentations, case studies, and prepare for subsequent workshop. (Coffee breaks, lunch included)

Chair: T Jivapaisarnpong

Rapporteurs: J Martin, M Majumdar

Day 1, 31 October 2023, Tuesday

Session I. Opening of the meeting

8:00-9:00	Registration	<i>Participants</i>
9:00-9:30	Opening Remarks & Welcome Speech	<i>WHO/CO, Indonesia</i> <i>Chairperson of Indonesian</i>

FDA

	Housekeeping announcement	<i>T Zhou/Juliati</i>
	Taking group photo	<i>All</i>
9:30- 9:40	Background, objectives and expected outcomes of the workshop	
	WHO DOI assessment statement	<i>T Zhou</i>

Session II. Updates on WHO standards for quality control (QC) of polio vaccines (OPV, IPV)

9:40- 9:55	Update on current WHO written standards for OPV and IPV	<i>T Zhou</i>
9:55- 10:20	Overview of available international reference materials for OPV and IPV	<i>J Martin</i>
	Discussion	

10:20-10:50 Coffee break

Session III. Use of molecular tests in the QC of OPV and IPV

³ OPV- Oral Poliomyelitis Vaccine. IPV- Inactivated Poliomyelitis Vaccine. The use of the abbreviation "IPV" refers to IPV derived from any strain. "wIPV" indicates IPV derived from wild-type strains only, and "sIPV" represents IPV derived from Sabin strains only.

- 10:50-11:30 Overview of molecular methods and their utility in the QC of polio vaccines
K Chumakov
- *Provide historical background and scientific rationale for the molecular methods and their potential use in the QC of OPV and IPV*
 - *Explain principles of High Throughput Sequencing (HTS) - use as a replacement of MAPREC vs. whole genome HTS as a potential replacement of animal neurovirulent tests, etc.*
 - *Elaborate on consensus sequence issue for OPV, sIPV*
- 11:30-11:45 Recommended use of HTS in current WHO TRS Recommendations for the control of polio vaccines
T Wu
- *Current WHO TRS recommendations regarding the use of HTS for QC of OPV, IPV*
- 11:45- 12:30 Ongoing effort towards HTS standardization for QC of polio vaccines
J Martin/M Majumdar & K Mahmood
- *Developing SOP and International Standards for HTS*
 - *Use of HTS as an alternative to MAPREC*
 - *Whole genome HTS analysis replacing animal neurovirulence tests*
- 12:30-13:30 Lunch Break**
- 13:30- 14:30 Case study: Establishing HTS for QC of novel OPV2 (nOPV2)
J Konz
- *Share experience of HTS assay development and validation in the case of nOPV2, how to set up assay validity and criteria, analytical method and data interpretation, any special considerations for HTS.*
- Discussion
- 14:30- 15:00 Points to consider in the validation of HTS in the context of QC of OPV and IPV
C Milne
- 15:00- 15:30 Coffee Break**
- 15:30- 16:10 Bioinformatics considerations in HTS analysis
J Panov
(remote presentation)
- 16:10- 16:40 Update on WHO biological standardization activities
I Knezevic
(deferred presentation in session I) *(remote presentation)*
- 16:40- 17:30 Round-table discussion, Q&A about issues in this session, and feedback on Day one
Facilitators, speakers, and participants

17:30 Closure of Day 1

Day 2, 1 November 2023, Wednesday

Session IV. Standardization of potency tests

9:00- 9:20 Overview of current potency tests for OPV and IPV, applicable International Standards (ISs), ongoing standardization activities in this regard

J Martin

- *In vitro and in vivo potency assays*
- *Recommendations in WHO TRS for OPV & IPV in terms of potency*
- *Any critical “gaps” at present*

9:20- 9:40 Standardization of potency test for OPV

M Majumdar

- *Proper use of IS*
- *nOPV potency testing, need for standardization and ongoing effort*

9:40- 10:10 D-antigen ELISA potency test for IPV: scientific rationale and historical background

K Chumakov

10:10- 10:30 Discussion, Q&A

10:30-11:00 Coffee break

11:00- 11:30 Standardization of D-antigen ELISA potency test for IPV

A Tedcastle

- *Elaborate on i) proper use of D-antigen ISs (for wIPV & sIPV), and new WHO RR (monoclonal antibodies-HuMAbs adopted by ECBS 2022), ii) assignment/meaning of unitage, interpretation of results, example of SDU calculation; iii) calibration of working standards, interpretation of results*
- *Introduce the D-antigen ELISA method- recommended accompanying method with HuMAbs (WHO RR), key considerations for implementing the method, available support to global labs*

11:30- 12:00 Scientific and regulatory considerations for management of reference standards

T Wu

- *Rationale of IS vs. secondary standard*
- *Reference replacement in the context of OPV/IPV*

12:00- 12:30 Discussion, Q&A

12:30-13:30 Lunch Break

13:30- 14:10 Standardization of in vivo potency assay for IPV

- 1) History of in vivo (rat) potency assay for QC of IPV and current use

J Martin

2) In-vivo potency testing for sIPV *A*
Tedcastle

14:10- 15:00 **Case study (*participants will be split into groups to work on the case study*)**
Reference standard for the lifecycle management of IPV *Lead: T Wu*
- Introduce case study
- Group work

15:00-15:30 Coffee Break

15:30- 15:40 Group work (continue)

15:40 -16:30 Group 1- 4 reports on case study (5-8 min/group)
Conclusion

16:30- 17:00 Round-table discussion, Q&A about issues in this session, and feedback on
day two *Facilitators, speakers, and participants*

17:00 Closure of Day 2

Day 3, 2 November 2023, Thursday

Session V. Ensuring vaccine stability and production consistency

9:00- 9:30 Considerations on stability and production consistency of polio vaccines
C Milne

9:30- 10:30 **Case study (*participants will be split into groups to work on the case study*)**
Key principles of stability evaluation in the context of OPV *Lead: T Wu*
- Introduce case study
- Group work

10:30-11:00 Coffee break

11:00- 11:10 Group work (continue)

11:10- 12:10 Group 1- 4 reports on case study (5-8 min/group)
Conclusion

12:10- 12:30 Round-table discussions focusing on issues in this session
Facilitators, speakers, and participants

12:30-13:30 Lunch break

13:30-14:00 Round-table discussions focusing on issues in this session (continue)
Facilitators, speakers, and participants

Session VI. The way forward- implementing international standards into manufacturing and regulatory practice

14:00- 15:00 Each participating **NCL and manufacturer** to present up to 5 minutes (following WHO template) on the plan of implementing WHO standards into their work practice & the need for future support (e.g., proposed topics for future WHO implementation workshop).

National Control Laboratories

- 1) RIVM, Netherlands
- 2) SCIENSANO, Belgium
- 3) NIFDC, China
- 4) NQCLDF, Indonesia
- 5) NIID, Japan
- 6) NCL, Russia
- 7) NDCCL, Saudi Arabia
- 8) NCLBP, South Africa
- 9) NIFDS, South Korea
- 10) IBP, Thailand
- 11) CDSCO, India

Manufacturers

- 1) Bharat Biotech, India
- 2) Biological E, India
- 3) Panacea Biotech, India
- 4) Serum Institute of India
- 5) Biofarma, Indonesia
- 6) BBIO, Netherlands
- 7) Chumakov Institute, Russia

15:00-15:30 Coffee break

15:30- 17:00 Presentations by NCLs and manufacturers (*continue*)

17:00 Summary, conclusion and closure of the workshop

Rapporteurs, Chair, & T Zhou

Appendix 2: List of Participants

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