Meeting Report

WHO Technical Working Group Meeting on Revision of the WHO Recommendations for the Production and Control of Inactivated Poliomyelitis Vaccines: TRS No. 910, Annex 1

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Executive summary

Inactivated poliomyelitis vaccines (IPV) are products that will play a critical role in the Polio Eradication and Endgame Strategic Plan (2013-2018). It is envisaged that IPV will be used instead of oral poliomyelitis vaccine (OPV) once the world is certified poliomyelitis (polio) free. Various approaches are being investigated in order to develop more affordable IPV produced from alternative strains to the currently used wild type strains (WPV) in order to meet the global demand and to satisfy the biosafety requirements which will be implemented after polio eradication worldwide. The World Health Organization (WHO) publishes technical guidance on the quality, safety and efficacy of vaccines intended to assist national regulatory authorities (NRAs), national control laboratories (NCLs) and manufacturers. In order to ensure that the written standards for IPV will cover the vaccines under development, WHO convened a technical working group on 14-15 May 2013 to discuss the revision of the WHO recommendations on the production and control of IPV which were adopted by the WHO Expert Committee on Biological Standardization in 2000. The attendees included experts from academia, NRAs/NCLs and industry from countries around the world who are involved in the development, manufacture, authorization and testing/release of IPV, including Sabin-based IPV (sIPV), and other new developments of IPV. During the meeting, critical issues for the quality control (QC) and evaluation of IPV (including sIPV) were identified and discussed and these will be taken into consideration in the revision of the WHO recommendations for the production and control IPV.

**Key words:** IPV, recommendations, quality control, standardisation

1. Introduction

An increasing number of industrialized countries are using inactivated poliomyelitis vaccine (IPV) as the vaccine of choice once the country has been declared polio-free. The Strategic Advisory Group of Experts (SAGE) on Immunization at WHO has been considering changing from live attenuated oral poliomyelitis vaccine (OPV) to IPV in routine immunization programmes, primarily to eliminate the burden of vaccine-associated paralytic poliomyelitis (VAPP), a rare adverse event associated with OPV, as one option for the post-OPV era. In recent years, the development of safe and efficacious vaccines that can be produced economically on a
large scale in developing countries, such as Sabin strain based IPV (sIPV), has been of great interest and SAGE has recommended that the development and licensure of such low-cost affordable IPV should be facilitated [1]. The rationale for using attenuated Sabin strains for manufacture of IPV is based on their lower virulence. Other ways to create non-virulent viruses to be used in IPV manufacture are also under investigation. So far two sIPV products, in combination with DTaP, have been licensed in one country and several other candidate sIPV are at an advanced stage of development. WHO is assisting vaccine manufacturers in low- and middle-income countries in developing sIPV through a technology transfer program [2, 3]. There are also new developments in the use of adjuvanted IPV and fractional dose IPV for intradermal (ID) use. In view of the complexity of the evaluation of such vaccines, in particular sIPV, and the extensive research work underway, it was recommended that a technical working group meeting, involving developers and manufacturers, regulators and researchers of IPV/sIPV, be convened by WHO to review available data and discuss how to address the critical issues to be included in the revision of the current WHO guidance document [4].

Dr David Wood (WHO) opened the meeting. He addressed the pivotal role of IPV in the new end-game strategy under the global polio eradication initiative (GPEI) and the need for regulatory convergence to harmonize regulatory decision-making which has been facilitated by WHO for many years. The revised international technical specifications for IPV will include new developments in IPV in light of global strategy for polio eradication. The aim of the revision is to define technical specifications for the assessment of IPV to promote improved quality, and ensure that safe and efficacious IPV are available for use in immunization programmes worldwide. The document will also facilitate increasing production capacity of IPV to meet global demands and facilitate strengthening of national capacity for production and regulation of IPV.

Dr TieQun Zhou (WHO) introduced the background for the project and outlined the objectives of the present meeting. The WHO, through its Expert Committee on Biological Standardisation (ECBS), is committed to providing both written standards and measurement standards for use worldwide. The WHO written standards are international technical specifications that help define safe and efficacious vaccines and facilitate international harmonization of vaccine evaluation and licensure. They are developed based on scientific consultation and international consensus involving researchers, regulators, manufacturers, and other interested parties and provide guidance to NRAs and manufacturers on assuring the quality, safety and efficacy of
vaccines. They are also used by Member States as the basis for establishing their national legislation for the regulation of vaccines and by WHO as the basis for the prequalification of vaccines procured by United Nations agencies. WHO written standards are living documents that may be revised in response to future scientific advances in the field. Current recommendations for the production and control of IPV were published in WHO Technical Report Series (TRS) No.910 [4]. Since then, a number of advances in scientific knowledge and vaccine development, such as use of alternative safer virus strains, new vaccine formulations and strategies, new quality control (QC) technologies and the global polio eradication programme ("end-game") [5], highlight the need for their revision. WHO initiated the discussion on the revision in 2012 and conducted a survey among worldwide IPV manufacturers to gather information on virus seeds, production and QC and to seek opinions on the revision of the current recommendations. A drafting group was set up by WHO to prepare a draft revision taking into consideration outcomes from previous discussions, information collected during a WHO survey among IPV manufacturers and the addition of guidance on non-clinical and clinical evaluation of IPV. The following issues were considered when preparing the revision: 1) updates of technology in IPV production and QC, new vaccine development in the pipeline in a global picture; 2) global polio eradication strategy and future trend of poliomyelitis vaccine use/development and bio-containment issues; 3) on-going and future scientific research areas and technology improvements; 4) updates of other general information in line with newly adopted WHO guidelines such as on stability, cell substrates and lot release. The purpose of this meeting was to bring together experts representing interested parties including regulators, manufacturers and other partners, to review available data and share experience on the development and evaluation of IPV/sIPV, exchange perspectives on the international technical specifications, review the proposed outline of the revision, identify and discuss critical issues to be further addressed, and discuss other aspects in the context of international standardization of IPV.

The meeting was chaired by Dr Elwyn Griffiths (UK) and the Rapporteur was Dr Morag Lennon (UK).

2. Current state of poliomyelitis eradication and biocontainment issues post eradication.

Dr Hamid Syed Jafari (WHO) described the new polio endgame strategy [5] and the important role of IPV in the future. He reminded participants that, in 1988, 125 countries had
endemic polio whereas in 2012 only three countries still had endemic polio cases, a 99% reduction. The need to synchronise the cessation of the use of OPV was identified in 2008 and withdrawal of the use of type 2 OPV (OPV2) began in 2012. In December 2012 there was the lowest number of polio cases from the fewest countries mainly as a result of the reduction in type 3 cases since bivalent types 1 and 3 OPV (bOPV) was introduced in campaigns in December 2009. Only Nigeria has had cases of type 3 polio in the last 12 months (the last case was reported in November 2012). During the past 6 months there have been cases of polio in Pakistan, Afghanistan, Nigeria and one case of cross border transmission in Niger. In addition, at the time of this meeting, there had been a single case of polio caused by wild type poliovirus (WPV) type 1 in Somalia and this was considered a major risk of spread as many children have not been vaccinated due to political situation. This outbreak has now increased and accounts for half the cases in 2013. The last WPV type 2 was detected in 1999 but between 2000 – 2011, 90% of outbreaks of circulating vaccine-derived-poliovirus (cVDPV) were caused by type 2 poliovirus. In the last 6 months, more countries have had outbreaks of cVDPV than cases of infection with WPV. In addition, there are 250 - 500 VAPP cases per year of which 40% are due to Sabin type 2 virus.

No cases of polio caused by WPV have been identified in India for over two years. In May 2012, the World Health Assembly (WHA) declared polio eradication an emergency for global public health and urged the Director General of WHO to rapidly finalise a polio endgame plan. In response to this global emergency, a Polio Oversight Board has been established comprising of the Director General of WHO and representatives from the United Nations Children’s Fund (UNICEF), the Centres for Disease Control, the Gates Foundation and Rotary International. Emergency operations centres have been activated and 5000 people are now involved in the eradication programme. National presidential focal points, emergency action plans, real time monitoring and accountability have been implemented resulting in a change in government operations.

The goal of the Polio Eradication and Endgame Strategic Plan, 2013 -2018 [5], is to complete the eradication and containment of all wild, vaccine-related and Sabin polioviruses. This plan involves poliovirus detection and interruption of the spread of poliovirus, immunization strengthening and OPV withdrawal, containment and certification and legacy planning. Timelines for each stage have been identified and one of the prerequisites to OPV withdrawal will be a WHA resolution in 2015 with international notification of type 2 polio cases and withdrawal of OPV2 use by 2016. Prerequisites for the cessation of the use of OPV2 include the validation of WPV
type 2 eradication and cVDPV type 2 elimination; the availability of a stockpile of monovalent OPV2 and response capacity; the availability of licensed bOPV in all OPV-using countries and an affordable IPV option for all OPV-using countries. If, in 2014, WPV type 1 virus spread continues, the use of types 1 and 3 bOPV will be important as interference with type 2 will be eliminated. In November 2012, SAGE recommended that all countries that use OPV should introduce at least one dose of IPV in their routine immunisation programmes to mitigate risks associated with the withdrawal of OPV2 [1]. Strategies for the availability of an affordable IPV include a fractional dose IPV for ID use being licensed, the use of adjuvanted IPV and the availability of sIPV that is now licensed in Japan as DTaP-sIPV. Other sIPV containing vaccines are at various stages in clinical trials in some other countries.

Poliovirus containment will be critical in achieving the eradication of polio and an updated Global Action Plan for laboratory containment of WPV (GAPIII) [6] is being prepared based on the new endgame strategy. This updated plan will include a containment policy for vaccine producers and a strategy for the establishment of an OPV stockpile. The need for OPV manufacturers to maintain production capacity after 2018 needs to be considered as stockpiles of monovalent vaccines will have to be retained and market authorisations maintained in case of emergency. A risk assessment will have to be undertaken to decide whether the use of IPV can ever stop. This decision will be influenced by non-public health issues such as the cost of adding IPV into combination vaccines.

Dr Jacqueline Fournier-Caruana (WHO), on behalf of Dr Christopher Wolff (WHO), outlined the management of the risks of facilities holding stocks of polioviruses in the post eradication and post OPV era. At that time laboratories and vaccine production facilities will be the only remaining source of polioviruses. Polioviruses will be needed after eradication of polio is achieved for vaccine production, vaccine quality control, diagnostic reagent production, stockpiles, reference functions, and research. The virus has limited survival in environment and there is no animal reservoir. Eradication of poliovirus will require minimizing the risk of reintroducing WPV and Sabin polioviruses from such facilities into environment and communities. The consequences of poliovirus reintroduction to circulation will be related to the size of susceptible population and likelihood of exposure to a facility-based poliovirus as well as the type of poliovirus and whether it is a wild or attenuated strain. However, at that time there will be very low tolerance for accidental reintroduction of virus as this will be perceived as an unnecessary compromise of a 20-
year, more than 4 billion USD global investment in the eradication program. During and after OPV2 cessation, enhanced control of Sabin type 2 virus will be required and after OPV cessation, Sabin reintroduction will have to be avoided.

GAPIII [6] aims to minimize risks associated with facilities holding polioviruses in the post eradication / post-OPV era. The implementation of this plan will have various phases linked to achievements in global polio eradication. GAPIII includes risk minimization through the destruction of unneeded poliovirus materials as well as material potentially contaminated by poliovirus and management of consequences of potential poliovirus release. The risk management strategy will be based on primary safeguards such as facility design and management, and oversight. Secondary safeguards include minimizing consequences through locating facilities in areas of high poliovirus immunity and tertiary safeguards such as location of facilities working with WPV in areas with low poliovirus reproductive rates. Containment goals can be achieved with a phased approach to OPV cessation. The next steps in the development of GAPIII are to reflect the OPV2 cessation timeline and the approach for novel production strains, international agreement on the timing and implementation of the plan, hopefully by the end of 2014, and a WHA resolution to that effect in 2015. GAPIII will have to be endorsed by all countries. Biocontainment considerations in line with GAPIII should be included in the update of the recommendations for IPV to be submitted to ECBS in October 2014.

Questions have been raised about immunodeficient, long term secretors and the discovery of vaccine-derived polioviruses in sewage. The use of human antibodies and anti-viral drugs to treat chronic shedders is being investigated. The threat of bioterrorism and possibility of other releases along the lines of smallpox virus which is now held in only a few facilities will also have to be considered. OPV production will be required for emergency planning and the maintenance of a vaccine stockpile but will have to be performed under very high containment conditions (BSL 3+). WHO is discouraging the construction of new facilities for the production of IPV derived from wild type strains (wIPV) other than formulation and filling of final vaccine products from inactivated trivalent bulks supplied by current manufacturers.

3. Poliovirus strains used in IPV production

Dr Konstantin Chumakov (CBER, FDA, USA) reviewed the virus strains that are used for current wIPV production. The review is based on the feedback to a WHO survey among IPV
manufacturers conducted in 2012, as well as published literature [7, 8, 9]. Twelve manufacturers currently produce IPV or plan to do so in the future. Six of these will produce sIPV.

Mahoney strain was isolated in 1939 by Francis and Mack for a pooled stool from three healthy children in Cleveland, OH. It was used by Salk for preparation of IPV, and by Sabin for creation of Sabin 1 attenuated strain. MEF-1 was isolated in 1942 by a group of British doctors from a paralytic case among troops of the Mediterranean Expeditionary Forces in Egypt. Molecular studies conducted many years later have shown that nucleotide sequence of MEF 1 is the same as of Lansing, and that these strains may have resulted from cross-contamination early in their passage history. Saukett strain was isolated by Salk in Los Angeles, California, USA, from a paralytic case of poliomyelitis. Comparison of Saukett samples from different vaccine manufacturers and research laboratories showed that their nucleotide sequences are quite different [10]. The reason for these differences is unknown and is believed to be a result of extensive laboratory passaging. Some of the differences may involve antigenic sites and may affect antigenic properties. Because of this early passaging, the history of strains used in manufacture of IPV may be far from certain and it is important to thoroughly characterize sequences and antigenic properties of the currently used virus stocks.

Summaries of the origins of the Sabin strains used in OPV production are in the WHO Recommendations to Assure the Quality, Safety and Efficacy of Live Attenuated Poliomyelitis Vaccine (oral), which were revised in 2012 [11]. It was emphasised that the use of different strains, WPV and Sabin, will have implications for the standardization of vaccines and also for containment. The need to maintain passage history as growth in cell culture may result in mutations leading to antigenic changes was highlighted.

Participants agreed that an overview of virus seeds that are used in production now or may be used in the future should be included as an appendix in the revised WHO recommendations for IPV. Such strains include the WPV used in current IPV production and the attenuated Sabin strains which are considered to pose a lower risk and are being developed as alternative seeds. The document should also include a brief mention of the novel strains that are being derived by recombinant DNA technology and intended to be safer to use in vaccine production.
4. Review of current experience in development, production, QC and evaluation (non-clinical and clinical) of sIPV

Representatives of six manufacturers, including Intravacc [formerly The Netherlands Vaccine Institute, (NVI) and then the Vaccinology Unit of the Rijksinstituut voor Volksgezondheid en Milieuhygiene (RIVM), The Netherlands] who are transferring the technology for production of sIPV to manufacturers in developing countries, described their experience in the development, production, QC, non-clinical and clinical evaluation of sIPV and perspectives on international technical specifications. Representatives from NRAs in China and Japan also presented their experience in regulatory assessment of sIPV including major challenges.

Key issues identified in the presentations and discussions included the standardisation of sIPV potency assays and the availability of critical reagents as well as the need to understand the “equivalence” of D-antigen units (DU) between vaccines produced from Sabin or Salk strains. In addition, tests for strain identity, monitoring changes in the molecular characteristics of Sabin seeds, measuring effective inactivation and the need to perform \textit{in vivo} neurovirulence tests on virus harvests were also discussed. Clinical issues discussed included the need to ensure adequate immunogenicity of an IPV candidate vaccine against both WPV and Sabin strains, the use of comparator vaccines in non-inferiority trials, and the assessment of the immune response namely the comparison of seroconversion rate or geometric mean titers (GMTs). Issues relating to the production of affordable IPV through its administration of fractional doses by the ID route or through the use of adjuvanted vaccines containing lower doses of antigen were discussed. These are described in more detail below.

4.1 Production and quality control of sIPV

Dr Yoichiro Kino (Kaketsuken, KKT, The Chemo-Sero-Therapeutic Research Institute, Japan) described the production and control of the sIPV component of the DTaP-sIPV which is now licensed and in use in routine immunisation programmes in Japan. sIPV bulks are produced from the attenuated Sabin strains by Japan Poliomyelitis Research Institute (JPRI). DTaP-sIPV vaccines are formulated independently by Biken (The Research Foundation for Microbial Diseases of Osaka University) and Kaketsuken (KKT) and clinical assessment of these vaccines was undertaken in separate studies. The virus is grown in Vero cells obtained from ATCC and the master cell bank (MCB) and working cell bank (WCB) are produced by JPRI. The Virus Master Seeds (VMS) for sIPV were developed at JPRI and are different from those used for OPV.
production. In addition to the other tests, monkey neurovirulence test (MNVT), transgenic mouse neurovirulence test (TgmNVT), rct40 test, nucleotide sequencing were conducted on the VMS and virus working seeds (VWS) to verify the attenuation. The D-antigen content of sIPV concentrated trivalent bulk supplied to Biken and KKT is Type 1: 30 DU/ml, Type 2: 1000 DU/ml, Type 3: 1000 DU/ml.

The QC tests on DTaP-sIPV final product, specific to sIPV include potency assay in rats in which the national reference vaccine supplied by the NCL (National Institute of Infectious Diseases, NIID), Japan, and Sabin strains as challenge viruses are used. The specification for potency is that the test sample shall be no less than that of the reference following statistical analysis. An ELISA for determination of DU is also performed at JPRI which involves the use of a mouse monoclonal antibody as capture antibody and a rabbit polyclonal antiserum antibody as detector antibody. Pre-clinical studies in laboratory animals were undertaken for general pharmacology, single and repeated dose toxicity studies, and local irritation. The immunological potency was performed in monkeys.

Dr QiHan Li, (Institute of Medical Biology, Chinese Academy of Medical Science) and Dr Changgui Li (NCL, China) described the advances and challenges in the development of sIPV in China. In the 1980s, the Chinese government, supported by the World Bank, initiated a project to develop sIPV and a bioreactor has been used since 1994. The VMS from WHO which are used for OPV production are used for sIPV production and must be approved by the NRA. The manufacturer must make no more than two passages of the working seed lot passage from master seed in Vero cells. The history of the strain must be traceable with the source supported by documentation. The control of Sabin virus seeds includes identification by the neutralization method and genotype identification by RT-PCR and monkey neurovirulence (as for OPV). In addition, tests for sterility / mycoplasma / SV40, adventitious agents (cell culture and animal test), titre and immunogenicity tests of vaccine lots in rats. Cell substrates are tested according to the requirements prescribed by the China Pharmacopeia, which are generally consistent with WHO requirements. The source and passage history of the Vero cells must be documented and it must be tested according to the Chinese Pharmacopeia requirements which are consistent with WHO recommendations. The cell substrates must be shown to be suitable for the fermentation/ microcarrier process, giving a suitable virus yield and have previously been used for vaccine production. The cell bank in current use was obtained from the European Collection of Cell Cultures (ECACC)
at P134. The MCB is at P136 and WCB at P141. Production passage must be less than P150. The production process, control and quality testing of monovalent pools, trivalent and final bulks are as described in the current WHO recommendations for IPV [4]. The storage period of intermediates must be approved.

Dr Wilfried Bakker (Intravacc, The Netherlands), reported that Intravacc have produced three master seed lots, three working seed lots, six monovalent pools, two pre-clinical final lots (high dose: plain and adjuvanted) and 6 clinical final lots at different dose levels, plain and adjuvanted, of sIPV under cGMP. These lots have been fully QC-tested. Phase I clinical trials in adults have been conducted in Poland and Cuba and a Phase I/IIa trial in infants in Poland. The production process is currently being optimized and initial process specifications developed using a scale-down model of the wIPV production process [12]. New master seed lots have been prepared by a single passage of the WHO Sabin seeds i.e. Type 1: WHO / Behringwerke 1976 SO+1, Type 2: WHO / Behringwerke 1976 SO+1 and Type 3: Institut Mérieux 1963 (457-Pfizer) RSO1. The new master seed lots were produced under cGMP and are well characterised. Animal-derived materials (porcine trypsin and bovine serum) used were tested according to current European Union (EU) guidelines. The absence of SV40, SIV, STLV, Simian cytomegalovirus (sCMV) and retroviruses in new master seed lots was shown by a contract laboratory. A risk assessment showed that it is highly unlikely that infectious adventitious viruses that could potentially have been introduced during the production process of the original WHO Sabin seed lots are still a risk during the use of the final inactivated vaccine in clinical trials. Major differences in the culture conditions of sIPV, compared with the culture conditions of wIPV, are the use of a lower culture temperature (32.5°C) for all three types to prevent reversion to neurovirulence. This is even lower than that recommended in the current WHO recommendations for OPV: (33°C - 35°C). A multiplicity of infection of 0.01 was used for all three types. Sephadex A50 columns were used for ion exchange chromatography. Clearance of host cell proteins and residual DNA in sIPV was comparable to wIPV production. Purity (ratio total protein and D-antigen) was < 0.1 µg/DU for sIPV. Kinetics of inactivation by formaldehyde are comparable between sIPV and wIPV.

Intravacc has also produced clinical batches of sIPV using Al(OH)₃ as adjuvant and this has resulted in an increased potency of sIPV in rats. The use of known and novel adjuvants in new formulations in the future may require additional QC testing. Stability tests on sIPV final lots
based on D-antigen content (and rat potency data) indicate that sIPV final lots, both adjuvanted and non-adjuvanted, are stable for at least 30 months. sIPV batches have been released using current IPV requirements. Appropriate OPV QC tests such as MAPREC/rct40 were added to indicate molecular consistency and as an indicator of biosafety. Furthermore working seed lots were tested for neurovirulence in monkeys. Repeated dose toxicity and local tolerance study in rabbits indicated that both adjuvanted and non adjuvanted sIPV are safe to use in a phase I clinical trial.

Dr Sudhakar Konda (Panacea Biotec, PBL, India) described the technology transfer project initiated in collaboration with Intravacc. Intravacc had already tested the antigenicity and immunogenicity of sIPV in animals in the 1990s and confirmed this in preclinical trials and Phase 1/2a clinical trials. Panacea is the first partner selected by WHO/Intravacc for this technology transfer project with the ultimate aim of establishing an sIPV production process based on Intravacc’s sIPV technology. Intravacc will make available the required cell and virus seed materials, QC reference materials along with all the necessary documents for the development of sIPV. In addition, Intravacc will transfer the QC testing procedures, including Sabin specific analytical methods, working and reference standards for initial start-up until in house reference materials are prepared by Panacea. At present, the training of personnel, process reproducibility and analytical method standardization studies are being undertaken by Panacea along with scale up activities, including facility readiness, and validation and process reproducibility at pilot scale. It is envisaged that the partially optimized process will be demonstrated by Intravacc personnel at the Panacea facility. The sIPV production process of Intravacc is based on a scale-down model of the current wIPV process using serum containing media. Intravacc has a program in place for process optimization (relating to the yields of all the three serotypes), to establish a process at an affordable price. It is proposed that the current yield, achieved, for timing reasons, under non-optimized conditions, during the production of clinical lots, will be improved at small-scale and transferred to the Panacea site. This process will be further used to produce material for a phase I/II clinical trial. Once the material for this trial has been generated, scale up of production will be initiated. After scale up and required validation of assays, consistency batches will be produced for a phase III clinical trial at the production scale.

Dr Tiziano de Rosa (Crucell) described the development of an “affordable” IPV using WPV grown in the PER.C6® cell line which is a human retina cell immortalized by adenovirus E1.
It is stable without antibiotic selection pressure and grows in serum-free medium. It has been established for bio-pharmaceutical manufacturing PERC6® derived products that are used in various clinical trials around the world. It has a well-documented history and an FDA Advisory Committee endorsed its use as cell substrate for vaccine manufacture in 2001. Safety testing has been updated to include risk assessments for adventitious agents. Process intensification (PIN) using bioreactors is accomplished by a 10 fold increase in cell density, exploiting the unique properties of PER.C6® which results in increased capacity and a reduction in the cost of goods. The use of this process resulted in a 20-fold increase in yield at 10L Scale with the PER.C6® PIN process compared to Vero cells. An efficient downstream process for harvests resulted in a highly purified monovalent bulk. Rat potency tests were performed in collaboration with NIBSC and showed a comparable potency profile between our first monovalent (type 1-Mahoney) IPV batch, and international IPV reference standards produced on VERO cells.

4.2 Additional QC issues

4.2.1 Assays for effective inactivation

Dr Javier Martin (NIBSC) presented critical issues identified in the QC and regulatory considerations of wIPV and sIPV. He highlighted that the demonstration of effective inactivation is reliant on a sensitive test for residual infectivity. Historically, kidney cells from some monkey species, such as those of the genera Macaca, Cercopithecus and Papio, have appeared to be more sensitive than those from other species. If other tissue culture systems, including continuous cell lines, are used, they should have been shown to possess at least the same sensitivity as monkey kidney cells. Manufacturers may be able to demonstrate this through the use of virus titration standards and the assay of partially inactivated samples. Some manufacturers treat inactivated virus preparations with bisulphite to neutralize residual formaldehyde, followed by dialysis, before testing for effective inactivation as residual formaldehyde might be toxic to cell cultures. The assay of virus D-antigen content after dialysis would indicate virus loss during the dialysis process. Monoclonal antibodies can detect structural changes in formaldehyde treated virus and this could be investigated as a test for consistency.

4.2.2 Identity (serotype and strain)

Dr Martin discussed assays for strain identity which is currently shown by serotype neutralization. New tests such as the use of strain-specific monoclonal or polyclonal antibodies in ELISA or neutralization tests could be used. Molecular assays including conventional reverse
transcriptase polymerase chain reaction (RT-PCR), restriction fragment length polymorphism (RFLP), real-time RT-PCR or standard or deep nucleotide sequencing may be used to differentiate strains (i.e. wild or attenuated). Such new molecular tests could also provide information on genetic stability of vaccine seeds and consistency of vaccine production.

4.2.3 Reversion to virulence of sIPV

Dr Stéphane De-Walque (GSK) reviewed the evaluation of reversion to neurovirulence of Sabin strains. Attenuated Sabin strains used in manufacture of OPV or sIPV can regain neurovirulence during propagation in cell culture and, because of this genetic instability, it is proposed that all purified monovalent pools are tested for neurovirulence before inactivation. This test may be performed in the monkey or mouse neurovirulence tests or by molecular marker e.g. MAPREC. Several approaches are being taken to develop stable attenuated strains, namely codon de-optimization and modification of the 5’ non coding region. Specific testing programs for the neurovirulence of IPV vaccine manufactured using such strains needs to be considered. During discussion it was agreed that testing every lot for neurovirulence is a biosecurity issue and that consistency of production may be demonstrated in other ways.

4.2.4 Potency assay and standardization

During the discussion, participants agreed that one of the major issues to be addressed in the revised WHO recommendations for IPV was potency evaluation which includes an in vitro assay for antigen content and an in vivo assay for immune response. In both tests, the results obtained with the test sample should be compared with those obtained with a reference preparation calibrated by comparison with the WHO International Reference Preparation. In-vivo potency in rats is considered the ‘Gold standard’ since immunogenicity profile in rats is correlated to the human response. It is used to demonstrate consistency of production during vaccine development and to demonstrate equivalency between the vaccine and a reference vaccine shown to be satisfactory in human clinical trials to support manufacturing changes. A D-antigen ELISA has been established as an in-vitro potency test and is used for formulation of vaccine and to check the consistency of production. Both in vivo and in vitro potency assays must be validated. However, some laboratories have found that the results of in vivo assays are dependent on the strain (Sabin or wild type) used in the virus neutralization test to assay the rat sera. In addition, one manufacturer had found that an alternative type 3 antibody was required for sIPV in the D-antigen ELISA and stressed that 1 DU of wIPV may be different from 1 DU of sIPV. Another
manufacturer noted that Sabin type 2 immunogenicity is weak and when sIPV was formulated on the basis of the rat test, the antigen content may need to be adjusted. It is therefore difficult to compare products in such tests as the assays performed by manufacturers and control laboratories vary. This was demonstrated in a collaborative study in which all 14 participants used different assays/reagents. Dr Martin reported that the use of the surface plasmon resonance technology (Biacore) as an in vitro potency assay [13, 14] gave a good correlation with ELISA and that there are fewer sources of variability in this system as no capture antibody is required.

4.2.5 Assay of adjuvanted IPV

Adjuvanted vaccines are being developed to facilitate the availability of ‘affordable’ IPV. However, the use of aluminum hydroxide as adjuvant interferes with the D-antigen ELISA and full desorption is difficult.

4.2.6 Waiver of in-vivo assay

Some authorities permit the in vivo assay to be omitted following assay validation, establishment of production consistency and demonstration that sub-potent batches are identified by both assays. This may be achieved by testing sub-potent batches, produced experimentally if necessary (e.g. by heat treatment at 45°C), or other means of diminishing the immunogenic activity. Dr De-Walque mentioned that GSK found both the in-vivo and in-vitro potency tests were able to detect antigen degradation. However, the in-vitro test allowed earlier and more accurate detection of the degradation as compared to in-vivo test. In-vitro potency is therefore a valuable tool to follow production consistency and may be used as the only potency test after a waiver is granted to terminate in-vivo testing. In-vivo assays would still be carried out when re-qualification of the manufacturing process is needed such as when there is a significant change in the manufacturing process of the antigens or their formulation. It was proposed that clear criteria, based on scientific evidence, would be required before the waiving the in vivo test could be included in the revised recommendations.

4.2.7 Regulatory evaluation of sIPV

Dr Kazuhiko Katayama (National Institute of Infectious Diseases, NIID, Japan) considered how an NRA should evaluate a vaccine with regard to safety and efficacy and the need to use an animal model and/or an in vitro test system to estimate vaccine safety and efficacy. In Japan, the NRA reviews the summary lot protocol, performs a test for effective poliovirus inactivation on the trivalent sIPV bulk and a potency test on the final product using the rat model. At present, primary
monkey kidney cells are used in the test for effective inactivation but Vero cells will be used in the future. The rat potency test is performed on DTaP-sIPV final product and utilizes reagents supplied by NIID (i.e. the national reference, challenge viruses (Sabin strain) and standard neutralizing antibodies against polioviruses). The potency of the test sample should be no less than that of the reference upon statistical analysis that is a parallel line quantitative analysis. Development of the national reference vaccine for the rat potency test included three potency tests performed in five different laboratories and the vaccine manufacturer. References established are:

- first generation national reference #05J that contains PV1:2:3=3:100:100 DU / 0.5 ml/dose
- Second national reference #09A was prepared with double the concentration compared to #05J that contains PV1:2:3=6:200:200 DU / 0.5 ml/dose
- Third generation national reference #12A was prepared as for #09A i.e. 6:200:200 DU / 0.5 ml/dose
- The national reference #05J and #09A were stable at -80 degree for 3.5 - 7 years

4.2.8 International standard for IPV

Dr Martin gave an update on the international standards (IS) for IPV. An International Reference Preparation (IRP) of poliomyelitis Vaccine (Inactivated) was established by the WHO Expert Committee on Biological Standardization in 1963 [15]. This preparation was a trivalent blend prepared in 1959 in primary monkey kidney cells from type 1 (Mahoney), type 2 (MEF) and type 3 (Saukett) strains of poliovirus. After preparation of the IRP, significant advances in production and control of IPV occurred and vaccines of increased potency and purity were developed. A new reference material, 91/574, was established by the WHO Expert Committee on Biological Standardization as the 2nd WHO International Reference Reagent (IRR) for in vivo and in vitro assays of IPV [16]. A potency of 430, 95 and 285 DU per ml was assigned to poliovirus type 1, 2 and 3, respectively. Problems in the use of this preparation were identified. However no standard was established following a collaborative study in which two candidate materials were evaluated in duplicate along with two other preparations including the biological reference preparation supplied by the Directorate for the Quality of Medicines & HealthCare (EDQM), as a bimodal distribution of vaccine potencies for IS candidate samples was observed. Eight laboratories obtained values close to expected values but six laboratories obtained values 30-60% lower than the expected values. The results did not correlate with any particular method or reagents used or experience in performing the test. A high inter-laboratory variability for IS
candidate samples (30-70%) was observed and average potency values for candidate samples were 20-30% lower than the expected values. Nevertheless intra-laboratory variability was low for all samples and no significant inter-laboratory variability for one sample was observed suggesting that the variable results might be product-specific. Further efforts to establish a 3rd IS for IPV are underway and a second collaborative study to assess the suitability of another batch of vaccine as a replacement IS has been undertaken and preliminary results suggest that the results may be better.

In a study investigating the use of the D-antigen ELISA with sIPV in which 14 laboratories participated, the standard error of the mean was 94.6% and 12.3% for sIPV and wIPV, respectively. One laboratory got higher potency for sIPV, possibly due to the capture antibody used. The differences might be due to antigenic structure of the virus strains in the IPV and the extent of antigenic modification which depends on virus/formaldehyde concentration. Alterations induced by formaldehyde have different effect on different epitopes and strains, which means that measurement of IPV D-antigen content and assessment of correlation between in vitro and in vivo potency for different IPV products is very difficult. During the discussion it was agreed that the standardisation of sIPV may require the use of common reagents. The need for an International Standard for sIPV was discussed as comparing sIPV target doses between manufacturers remains difficult.

4.3 Clinical evaluation of IPV

Dr Yoichiro Kino presented the findings of the clinical trials on DTaP-sIPV vaccines including phase I studies for safety evaluation in healthy male adults against a placebo by BIKEN and against DTaP by KKT. No serious adverse events were observed in either study. Phase II dose finding studies involving three doses were also performed by BIKEN and KKT. Following these studies a vaccine containing 1.5, 50 and 50 DU /dose (the medium dose) for type 1, 2 and 3, respectively, was selected for further investigation. Randomized, double-blinded and controlled phase III clinical studies were undertaken in healthy infants and children (3 to <74 months of age) by BIKEN and KKT. Since wIPV was not licensed in Japan when these clinical trials were conducted, it was not possible to compare the response of sIPV with that of wIPV. DTaP-sIPV induced antibody responses against both Sabin virus and WPV that were higher than the protective level. He concluded that the DTaP-sIPV vaccine has similar safety profile to the DTaP vaccine and induced significant neutralizing antibody response to both Sabin and WPV without interfering
with immunogenicity of the DTaP components. The DTaP-sIPV was licensed in Japan in July 2012 and has been used in routine immunization programmes in Japan since last November.

Dr QiHan Li presented clinical development of sIPV in China. A phase I clinical trial was conducted in China from August 2008 to May 2009. Adverse events were monitored and the vaccine was found to be safe and able to induce good immune response as determined by the detection of neutralizing antibodies. OPV was included as a comparator in this study. A phase II trial began in July 2009 and finished in June 2010. In this trial, seroconversion rates of almost 100% were achieved as indicated by the induction of neutralising antibodies. Homologous Sabin strains were used in these assays and titres were higher than had they been performed using WPV. An sIPV booster was given at the age of 18-month, which resulted in a 30-fold increase in titres, even with a low dose. A randomized, blinded, positive controlled phase III study (non-inferiority) was completed in October 2012. 600 two-month-old infants were given sIPV and 600 infants were given wIPV. Blood samples were taken before immunization and one month after the third dose and tested for neutralizing antibodies. Cross-neutralization studies were performed by CDC, Atlanta, US and the antibodies induced by wIPV and sIPV were shown to neutralise WPV and endemic strains from Africa. Antibodies against the WPV type 3 strain (Saukett) were low. Antibodies dropped at low levels after one year but increased after a booster dose. The data collected from the clinical trial confirmed the safety and efficacy of sIPV and antisera from recipients of sIPV were shown to be capable of neutralizing WPV, pandemic, cVDPV and immunodeficiency-related vaccine-derived poliovirus (iVDPV) strains. Nevertheless, the NRA was concerned that only Sabin virus was used in the neutralization test and they queried whether a neutralization antibody titer of 1:8 is protective as titres against WPV are lower than against Sabin virus. During the discussions it was emphasised that WHO needs to consider the difference in neutralising antibody titres induced by sIPV, which are higher against homologous Sabin strains compared to WPV, and the implications on a seroconversion titre of 1:4 - 1:8, which is considered indicative of protection. The question of what vaccine could be used as a comparator vaccine if wIPV not licensed in countries where trials are performed was also raised.

Dr Monique van Oijen (Intravacc) presented phase I safety and immunogenicity trials in adults that have been performed by Intravacc on the sIPV whose production is being transferred to manufacturers in developing countries. Non-adjuvanted sIPV (20-32-64 DU) showed a safety profile in adults comparable to Al(OH)₃ adjuvanted sIPV (10-16-32 DU) and wIPV and no related
Serious adverse events following immunization were observed. The immunogenicity of Sabin poliovirus type I, II and III was also comparable to wIPV [17]. A dose escalation safety and immunogenicity trial in infants has almost been completed. Different doses of non-adjuvanted sIPV (20-32-64 DU, 10-16-32 DU, 5-8-16 DU) and Al(OH)₃ adjuvanted sIPV (10-16-32 DU, 5-8-16 DU, 2.5- 4-8 DU) were compared against wIPV. The immunogenicity of all vaccines has been investigated by comparison of neutralizing antibodies against both WPV and Sabin poliovirus strains. Preliminary conclusions of this clinical trial indicate that sIPV is well tolerated and immunogenic in infants. According to the regulatory authorities in the EU, sIPV is required to be non-inferior to wIPV with respect to immunogenicity and safety. Non-inferiority with respect to immunogenicity could be shown by comparison of seroconversion rates only. However additional long term studies might be needed to investigate whether comparison to seroconversion rates only is sufficient to provide long term protection. Questions raised were whether

- Seroconversion rates should be non-inferior against Sabin and WPV. This might depend on administration of sIPV pre or post eradication of polio.
- The safety profile could be different from wIPV when using known or novel adjuvants. What is acceptable?
- Is the safety profile of an adjuvanted vaccine acceptable if the frequency of one local adverse reaction after adjuvanted sIPV is higher than after non-adjuvanted sIPV in phase III trials?

Dr Emmanuel Vidor (Sanofi Pasteur) discussed the evaluation of neutralizing antibodies responses induced by sIPV. He considered that poliovirus neutralizing antibody assay results cannot be directly compared across clinical studies due to assay differences including the readout (cytopathic effect versus cell growth inhibition measurement), the strain used (Sabin strains versus WPV), the cell line HEp-2 Cincinnati cells, L20B cells versus Vero cells, the viral inoculum size (100 or 200 CCID₅₀) and incubation time and the range of 2- or 10-fold serial dilutions. The reference serum also varies as does the incubation and agitation times and the endpoint calculation e.g. ED50, PRNT, metabolism inhibition. In addition, results may be expressed as:

- Observed or adjusted post-vaccination titers accounting for pre-vaccination maternal antibody decay,
- Sero-conversion: % with ≥ 4-fold increase (on observed or on adjusted titers),
• sero-protection or sero-prevalence i.e. % with sero-neutralization titers ≥1:8 [1:10] (or 1:4 [1:5]),
• GMT or median titers or titers expressed in 1/dilutions or in I.U.

Another complicating factor is the fact that, in the clinical studies, poliovirus neutralizing antibodies are induced through a wide range of immunization regimens including wIPV only, sIPV only, or both wIPV and sIPV, OPV only, sequential IPV followed by OPV or sequential OPV followed by IPV, or IPV and OPV co-administered for at least one of the immunization series. Assay variability can result in different conclusions when there are differences between laboratories and assays. In these studies:

• Evaluation of wIPV-induced neutralizing antibodies with a Sabin strains-based assay give lower titers compared to a WPV-based assay
• Evaluation of OPV vaccine-induced neutralizing antibodies (and possibly sIPV-induced antibodies) with a Sabin strains-based assay give higher titers compared to a wild type strains-based assay (more visible on post-dose 3 time point)

Questions which came out of the study are:
• whether the antibody paratope profiles induced by OPV (and also sIPV) are the same as those induced by wIPV?
• are the lower WPV (and VDPV) neutralizing antibodies induced by sIPVs compared to wIPVs clinically meaningful / relevant?
• which of assay results should be used in non-inferiority testing for regulatory purpose?
• is GMT a meaningful endpoint to complement post-vaccination sero-protection / sero-conversion rate endpoint?

4.4 Regulatory considerations for fractional dose and adjuvanted IPV

Dr Pieter Neels (Federal Agency for Medicinal and Health Products, Belgium) discussed the regulatory issues and pathways for IPV administered by the ID route and adjuvanted IPV given intramuscularly. He noted that the Committee for Medicinal Products for Human Use (CHMP) clinical evaluation of new vaccines is applicable to the evaluation of IPV and includes consideration of the immunological data, percentage of responders, geometric mean concentrations (GMCs / GMTs, reverse cumulative distribution curves). When available, data on antigen specific T-cell responses should be presented.
A recent new multivalent vaccine which contains IPV produced by Sanofi Pasteur, SP Hexaxim, has been licensed based on non-inferiority criteria using different schedules. The surrogate marker for protection cited by Stanley Plotkin [18] i.e. a seroneutralisation titre of 1 in 4 or 1 in 8 is accepted. CHMP normally takes a conservative approach and requires a titre of 1 in 8 instead of 1 in 4. However in studies in Germany, cut-off values in International Units have been used to determine immune status against polio. The results of this study indicated that there were different cut-off levels for antibodies against different types of poliovirus. However, the use of different levels for the different poliovirus types is not acceptable due to lack of standardisation.

Licensing the ID route versus the IM route using a non-inferiority approach is acceptable provided that 95% are responders and that a delta of 5% is obtained based on 1 in 8 (or 1 in 4) dilution in the non-inferiority hypothesis tests. However, this is linked to the schedule used i.e. OPV given following the Expanded Programme of Immunisation (EPI) schedule plus ID. No extrapolation to other schedules and situations is permissible. Nevertheless, not all NRA are happy to introduce an ID route as there may be consequences to national labeling and vaccination programmes.

Vaccines with aluminium-based adjuvants have been used extensively in immunization programmes worldwide with well-demonstrated safety profile. However, the use of Pandemrix containing ASO3 adjuvant resulted in narcolepsy and the use of this adjuvant is not acceptable in the EU. The use of such adjuvants also greatly increases the costs per vaccine dose. All vaccines in the EU are penta- or hexa-valent vaccines and there will be reluctance to license monovalent vaccines for ID use or to license a new adjuvanted vaccine. Discussion is on-going on the regulatory pathway to licensure of an ID/IPV and regulatory consensus has yet to be reached.

Dr Kutub Mahmood (PATH) described the regulatory challenges for fractional dose and adjuvanted IPV. Global IPV implementation in routine immunizations will require more than 600 million doses of IPV annually. The production of affordable IPV with reduced antigen content will have to be achieved by the use of adjuvanted IPV or fractional dose IPV for ID use. At present wIPV is supplied by four manufacturers and sIPV will be produced in several others after WHO supported technology transfer by Intravacc to developing country vaccine manufacturers. Licensed wIPV contains 40 : 8 : 32 DU although fractional doses (1/2, 1/3, 1/5, 1/10) are being evaluated. In addition one sIPV is being evaluated at various doses containing 45: 64: 67.5 DU
(high), 30: 32:45 DU (medium), and 15:16:22.5 DU (low). The Japanese (JPRI/Kaketsuken) licensed DTaP-sIPV combination vaccine contains 1.5: 50 : 50 DU units.

In 1955, Salk published a paper [19] in which the use of different quantities of vaccine given intramuscularly were compared with 0.1ml given ID and it appeared that the ID dose was equal in effectiveness to 0.25ml given intramuscularly. Fractional dose ID delivery devices are available and several clinical studies have been undertaken with varying results and issues raised.

- seroconversion of one dose IPV was lower in ID (59 percent) than IM (100 percent);
- fractional ID doses of IPV at 2, 4, and 6 months induced similar levels of seroconversion, but significantly lower titers than IM; ID produced immune response, not inferior to the IM after immunization 6,10, and 14 weeks;
- fractional ID doses of IPV at 6, 10, and 14 weeks of age resulted in suboptimal immunogenicity, compared with IM.

Several additional studies with ID disposable-syringe jet injectors are planned. Product registration of fractional dose ID IPV in which the product is the Vaccine + Device will be country specific and the mandatory label change will require filing a supplement to the license application. The use of a 1/5 or 1/10 dose will have to be established and immunogenicity monitored. The introduction of adjuvanted IPV will also result in several challenges. Such adjuvants may include aluminium salts, monophosphoryl lipid A, oil in water emulsions such as MF59, ASO3 and whole-cell pertussis based combinations. Clinical studies are needed to determine safety of adjuvanted vaccines and compatibility with other combination vaccines and assessment of long-term safety with other vaccine immunizations in EPI schedule may be required. Training and programmatic materials for IPV administration (e.g., wrong dose or route) is required, including having significant resources to train health workers at all levels. Dose-sparing options are considered viable options only for low/lower middle income countries.

During discussions participants considered that it will be challenging to get an ID IPV plus device licensed by 2015 in the EU where combination vaccines are used and ID administration will not be performed. WHO is discussing these issues and the design of trials as the use of IPV will support the switch from trivalent OPV to bOPV. A review of fractional dose ID administration prepared by PATH shows some benefit on cost as the devices would also save time during administration of vaccine especially if it is required for mass campaign.
5. Conclusions

Participants reviewed a proposed outline of the revised recommendations on the second day of the meeting. The discussions focussed on critical issues relevant to the production, QC, nonclinical and clinical evaluation of IPV and containment of live virus during the production process. Consensus was reached on the following issues which will serve as the basis of further revision of the recommendations for IPV.

5.1 The scope of the updated recommendations will encompass IPV derived from 1) the WPV that have been used in manufacture of IPV for many years; 2) the attenuated Sabin strains that have been used in manufacture of OPV; and 3) new alternative strains with improved biosafety that are under development, including those derived by recombinant DNA technology. The guideline will not cover vaccines which are based on virus like particles (VLPs) and replicons. However, some aspects of the current document may be relevant and should be taken into consideration during their development.

5.2 Production in monkey kidney cells will no longer be included in the recommendations as no manufacturer of wIPV or sIPV use these cells.

5.3 Biocontainment is a key issue especially in post-eradication era and it has implications on the current revision of the IPV recommendations (TRS 910). It was proposed that the revised recommendations should be in line with the updated GAP III. Containment at various stages in endgame will be dealt with in GAP III and reference will be made to this document.

5.4 Virus strains for production should be identified by nucleotide sequence analysis. Strain identity (i.e. to differentiate Sabin strains) using suitable molecular technique and serotype identity using neutralization assay should be determined in the production process.

5.5 Additional tests such as MAPREC and neurovirulence tests i.e. the monkey neurovirulence test (MNVT) or the transgenic mouse neurovirulence test (TgmNVT), nucleotide sequencing were proposed for sIPV virus master and working seeds.

5.6 The need to perform *in vivo* neurovirulence tests on every sIPV harvest to verify attenuation and production consistency was discussed.

5.7 The provision for omission of the test for absence of infective poliovirus on the trivalent bulk should be included in the revision.
5.8 The provision for omission of in vivo rat potency assay for IPV lot release and whether the D-antigen content assay may be omitted on the final product if it was performed on the final bulk should be included in the revision.

5.9 Sequencing requirements and neurovirulence tests on monovalent pools and as part of nonclinical testing should be considered.

5.10 The standardisation of sIPV potency assays, the availability of critical reagents and the “equivalence” of DU in vaccines produced from Sabin or WPV strains and strains derived by recombinant DNA technology should be addressed.

5.11 The evaluation of immunogenicity in animal models should be considered and the equivalence between tests in rats, mice, humans.

5.12 The comparison of the immunogenicity of vaccines manufactured from different strains should be addressed.

5.13 The standardisation of assays for serum neutralising antibodies should be discussed including the need to include recently circulating WPV and VDPV strains as challenge virus in the neutralization test.

5.14 Consideration should be given to what may be used as a comparator vaccine in countries where wIPV are not licensed.

5.15 Issues for consideration in the clinical evaluation of the vaccine including immunogenicity endpoints and whether comparable GMTs are required for non-inferiority in terms of immunogenicity will be addressed.

5.16 The revised recommendations should include information to facilitate the production and quality control of ‘affordable’ IPV i.e. adjuvanted vaccines or vaccines to be administered by the ID route.

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