Conference Summary

11th WHO/UNICEF Consultation with OPV/IPV Manufacturers and NRA's
25 October 2012
Geneva, WHO/HQ, Salle C

Jointly Hosted by the World Health Organization and UNICEF
Chaired by
Dr R. Bruce Aylward, Assistant Director-General of Polio, Emergencies, and Country Collaboration
And
Dr Hamid Jafari, Director a.i. Polio
Conference Purposes and Goals

- Update manufacturers and NRAs on the current status of the global polio emergency action plan for both WPV eradication and cVDPV elimination
- Inform manufacturers on projected tOPV, bOPV1&3, mOPV1, mOPV3 and IPV demand for the period 2013-2016
- Bring manufacturers and NRAs up-to-date on pre & post-eradication risk assessment and the ongoing research and program of work to develop appropriate policies and products for managing these risks (including new developments in the elaboration of pre and post-eradication IPV policy)
- Strengthen existing collaboration between manufacturers and NRAs involved in the Global Polio Eradication Initiative

Polio Emergency & Endgame

Bruce Aylward, ADG-PEC, WHO
Polio Emergency & Endgame Plan: Strategy & Timelines

Dr Aylward welcomed all participants to the 11th consultation of Manufacturers and NRAs, underlining the criticalness of this meeting for the GPEI. New program changes and strategies mean new demands on manufacturers and their flexibility is greatly appreciated by our colleagues at WHO and UNICEF.

Dr Aylward began by providing the context in which the GPEI is currently operating. One year ago, 16 countries, 12 of which were previously uninfected, had WPV cases, some with both types 1 & 3. Outbreaks that affected both children and adults also demonstrated the crucial need for the global eradication of polio and the success of eradicating polio in India demonstrated this is possible. In April 2012, the WHA declared the completion of polio eradication to be a programmatic emergency for global public health. The 2012-13 polio emergency action plan launched at the time of the WHA has three major goals: (1) to assist Nigeria, Pakistan, and Afghanistan to achieve, by end-2012, the OPV coverage thresholds needed to stop virus transmission; (2) to ensure that the three reestablished polio transmission countries are again polio-free by end 2012; (3) to close the funding gap for polio eradication activities (now at a best case scenario of 320 million USD through end-2013). Program resources are now focused on chronically missed children. Furthermore, even though the funding gap meant a scaling back of OPV campaigns in some areas, all vaccine was utilized.

The Polio Emergency Action Plan has led to (1) a surge in human resources, with partners employing >4500 people in key polio-infected areas (i.e. Pakistan, Southern Afghanistan, Northern Nigeria, DR Congo, Chad); (2) a revamping of major program operations (e.g. monitoring, microplanning, supervision, etc.) to better understand and address the reasons for missed children; and (3) new accountability structures in Nigeria, Pakistan, and Afghanistan, which include the creation of presidential task forces that monitor districts and ensure elected leaders are held accountable for poor performance of OPV campaigns. Additionally, emergency centers have been activated at WHO and CDC to help partners and manufacturers communicate more quickly and coordinate seamlessly.

The impact of the EAP has been striking: October 2012 shows the lowest number of cases (75% reduction compared with 2011), countries (3 endemic and 1 re-established), and infected districts ever in history. Challenges are concentrated in parts of Nigeria, Pakistan, and Afghanistan; WPV1&3 co-circulate only in Pakistan and Nigeria. Furthermore, the decline in WPV3 continues, largely due to the introduction of bOPV, which manufacturers are responsible for bringing into the program so quickly. Although insecurity remains a concern for the program, polio workers continue to vaccinate in the field and the leadership in countries like Nigeria have become acutely aware of these risks and are adapting the program. The biggest challenge for the program is enhancing management: efficient microplanning, team assigning, supervision and operation in
Dr Aylward then described the polio endgame and its development. The goal is to complete eradication and containment of all wild, vaccine-related, and Sabin polio viruses in a 6 year program of work. As always, manufacturers will get five years of notice of any major changes in vaccine quantity and type that might be needed. In addition to completing the eradication of wild type poliovirus, the emphasis of the plan is on addressing the problems of cVDPVs and iVDPVs, with cVDPV type 2 being the most pressing. cVDPVs have increasingly been the cause of new polio outbreaks, with the highest burden being due to type 2, particularly in Northern Nigeria, central Africa and the horn of Africa. We now have a more robust understanding of the clinical consequences of cVDPVs, with solid evidence that they can become as dangerous as WPVs. In Northern Nigeria, for example, a study by Imperial College demonstrated that a cVDPV type 2 had regained all of the characteristics of a WPV2, including attack rate.

In May of this year, the WHA declared the withdrawal of OPV 2 from routine immunization programs as near-term goal, followed by cessation of OPV 1 & 3 only after certification of wild virus eradication (i.e. after 2018). In September, the SAGE Working Group concluded: (1) that the risks associated with OPV2 cessation could be mitigated by the introduction of at least 1 dose of IPV in routine immunization programs prior to OPV2 cessation; (2) that the routine use of IPV should continue for at least 5 years after eventual bOPV cessation; (3) that an ‘affordable IPV’ for all environments would need to cost less than US$1/dose and preferably in the range of US$50/dose; and (4) that fractional IPV strategies, through either intradermal (ID) delivery or adjuvanted products for intramuscular administration, were the most promising approaches to ensuring sustainable access to affordable IPV products for all settings.

Dr Aylward then outlined the endgame timeline. Milestones include: (1) completing WPV eradication by the end of 2014; (2) withdrawing OPV2 from routine immunization programs in the period 2015-2016; (3) certifying global wild poliovirus eradication by end-2018; and (4) complete withdrawal of OPV use by 2020. These timelines could see the introduction of at least 1 dose of IPV in all routine immunization programs as early as 2015-2016.

The next steps for further consultation on, and finalization of, the Polio Eradication & Endgame Strategic Plan include: (1) the polio eradication Independent Monitoring Board (IMB) at the end of October 2012; (2) the SAGE meeting in November 2012; (3) the Polio Partner Group review in November 2012; and (4) the World Health Organization’s Executive Board meeting in January 2013.

The implications for manufacturers of all the new endgame strategy include: (1) increased OPV demand through 2019; (2) the need for all OPV-using countries to have access to a bivalent OPV for routine immunization purposes; (3) development and near-term introduction of ‘affordable’ IPV products.

**Hamid Jafari, Director a.i. POL, WHO**

**Projected IPV And OPV Demand 2013-2018**

Dr Jafari began by detailing the GPEI’s recent developments: India remains polio free one year after eradication, the fewest countries are infected with the fewest cases, SIAs continue globally, and short interval additional doses (SIADs) in endemic countries continue (putting heavy demand on vaccine supplies in Pakistan and Nigeria). WPV3 continues to decline, and cVDPV type 2 outbreaks persist (recently in Yemen).

Dr Jafari continued by laying out trends in vaccine use for 2012. bOPV remains in high demand due to continued WPV1&2 transmission in endemic countries and continued SIA activity, while the need to control cVDPVs keep tOPV demand high. Demand for mOPV1 has decreased thanks to fewer outbreaks. We may also see an increase in overall OPV demand due to the expansion of age groups targeted in special populations (Nigerian nomads and insecure areas in Pakistan and Afghanistan where limited access means people do not receive vaccine for long periods).

Dr Jafari then laid out the assumptions the program has for upcoming OPV projections, which can often be underestimated. OPV will be in high demand through the eradication of WPV and the tOPV to bOPV switch phase in 2015-2016 due to substantial SIA activity and continued routine immunizations. Just before the withdrawal of tOPV, manufacturers should expect high demands of tOPV for targeted campaigns to avoid insecure areas.
cVDPV type 2 risk. Some mOPV will be needed for outbreak response, as well. The aforementioned requirements do not include the stockpile or PAHO’s need for 80 million tOPV doses/year.

Concerning IPV, when the synchronized global switch from tOPV to bOPV occurs in 2015, all OPV using countries will introduce a single dose of IPV, with some countries preferring fractional dose. Dr Jafari presented the expected annual IPV demand by country for one full year, with the difference in requirements driven mainly by China and India and their choice to use either full or fractional dose (160m vs 78m doses respectively). This translates to a cumulative IPV demand from 2015-2018 at 310 million fractional doses and 640 million full doses.

In summary, there is a continued high demand for bOPV as well as tOPV until cessation, and current projections set need at 2 billion doses higher than those of June due to increased activities and contingencies in the 2013-2018 plan.

**Meredith Shirey, Chief Vaccine Center Supply Division, UNICEF**

**Key Updates On Polio Procurement And Supply Through UNICEF**

Ms Shirey began with an overview of OPV procurement for 2012: tOPV and bOPV are now mostly used with 1.3 billion doses of OPV procured this year. The weighted average price increased slightly this year due to the loss of product from lower priced manufacturers, requiring additional awards for higher priced products. Ms Shirey demonstrated on a map that the destination of vaccine is aligned with program priorities. Everything contracted was used with the exception of product that was not available to the program when it was needed and as planned (due to delisting of OPV from two manufacturers and reduction of not enough supply from a third).

2012 has been a complex year for supply and demand, particularly due to the delisting of two manufacturers that created a gap of over 400 million doses. However, other manufacturers’ flexibility meant this delisting had a minimal effect on program activities. Looking at tOPV supply and demand for 2012-2013, Ms Shirey noted a decrease in tOPV availability in January and that supply (also used in routine) has been tight for the majority of the year and remains tight through the end of this year. During this year, PAHO had a hard time accessing tOPV, so UNICEF reallocated quantities to meet PAHO’s request. Further, a higher demand than what was forecasted for tOPV meant manufacturers had to work quickly to fill the additional need, for which UNICEF is very appreciative. For bOPV (only used in SIAs), there were some tight periods but the overall supply was acceptable. Overall, through adjustments in SIA activities and responses of the industry, UNICEF was able to meet demand, but Ms Shirey reminded participants that when supply dips below 20 million doses, this can pose problems if unforeseen situations arise. UNICEF has utilized most of the mOPV1 on contract and some manufacturers still have mOPV3 in stock. Although mOPV demand is just for response to outbreaks, UNICEF has alerted the program of availability of mOPV3 stored with manufacturers.

Ms Shirey continued with tender updates, laying out the complex year ahead. Following the initial discovery of a 300 million dose shortfall for Q1 2013, UNICEF and other partners succeeded at mitigating this gap thanks to Manufacturers and other partners’ efforts. Although the supply situation has improved for early 2013, it is still tight and demonstrates the importance of getting additional manufacturers’ products licensed in countries to provide the program and UNICEF greater flexibility to manage supply. Concerning the tender this year, it has a duration of 4 years plus 1 year possible extension (2013-2016/17). Thanks to more visibility, there is more steady pricing and continued bulk production. The objective of the 2012 tender was vaccine security, with an emphasis on meeting the high demand (particularly in 2013-2014), achieving lower pricing, spreading out of bulk risk, and sustaining bulk production through OPV cessation. Ms Shirey provided an additional thank you to the manufacturers for the collaboration in reducing the WAP from .1350 USD to .1323 USD based on the awards.

Ms Shirey gave a brief overview of the IPV tender that was conducted in the first half of 2012 (covers September 2012 – December 2013). It is expected that the offers received were not indicative of the long-term market price of IPV; however, there has been demonstrated movement towards a decrease in long-term market price of IPV and indication that there will be sufficient supply should there be a large uptake. Furthermore, pricing could be lower if there is sufficient demand and program policy for full dose IPV. The next steps for UNICEF and vaccine procurement rely on the timing of the tOPV to bOPV switch and the IPV
demand and supply. Important to note is the close coordination and careful planning with industry and partners around the timing of the switch to ensure manufacturers are not left with type 2 bulk.

**Pieter Neels, CHMP Member, FAGG**

**Regulatory Issues And Pathways For ID IPV And New IM Products (Adjuvanted IM IPV)**

Dr Neels prefaced his presentation by explaining that it would reflect his personal viewpoint and not the stances of any of the organizations with which he works. Dr Neels began by explaining how immunological data should be obtained and presented using a standard approach in each study report (slide 4): responders with 95% confidence interval, “non-responders” characterizations, GMCs/GMTs ratios calculations, reverse cumulative distribution curves, data on antigen specific T-cell responses.

Non-inferiority criteria was explained through the example of a recent multi-valent vaccine (Hexaxim) containing polio 1/2/3 (slide 5) whose license was based on the following criteria: (1) response rate as positive after dilution 1/8; (2) non inferiority delta margin of 5%; (3) at least 95% responders; and (4) GMT shown in different vaccination schedules. This approach is acceptable, but it must be situation linked to OPV given at EPI schedule + ID IPV where no extrapolation to other schedules or situations will be allowed. Following with surrogate marker for protection, Dr Neels mentioned Plotkin, who published a threshold for protection ([http://cid.oxfordjournals.org/content/47/3/401.full](http://cid.oxfordjournals.org/content/47/3/401.full)) at 1/8 = 1/4 dilution; however, in the case of Hexaxim, EMA/CHMP takes a conservative approach to this topic, using 1/8 instead of 1/4. Furthermore, in Germany, three different cut-off values have been indicated ([http://www.biomedcentral.com/1471-2334/2/2](http://www.biomedcentral.com/1471-2334/2/2)), but as they are not yet validated, they cannot be used in a regulatory environment.

Concerning label changes, there may be a future possibility of adding a paragraph in the summary of characteristics in order to give ID injection with 1/5 dose of existing polio vaccines on top of at least 3 doses of OPV. This is only a first step, however, and if the desire is to eventually use ID instead of OPV in primary series much more data will be required and it will be a challenge to get non-inferiority in EPI schedule. Additional pathways include adjuvants to reduce dose. There is no problem with the Alum adjuvant and dose reduction as long as non-inferiority can be demonstrated with one large clinical trial. Concerning newer adjuvants (like AS03 or AS04), there will be a heavy risk management plan and it will be carried out in a very detailed way.

Discussion is ongoing about regulatory pathways to license an ID or adjuvanted new polio vaccine through Article 58 or line extension to the existing national licensure. In countries where OPV is not used, ID IPV would not be on top of OPV, so they will need good non-inferiority data to move forward. Through Art 58, CHMP can evaluate a data package and it can provide an opinion for use of the product outside the EU; however it might be risky to look at an old product dossier like IPV that could not meet the 2012 standards.

**Chris Wolff, Chief a.i. SSS, WHO**

**Global Action Plan For Containment: Current Status And Next Steps**

The objective of containment is to minimize the risk of reintroducing facility based wild and Sabin polio viruses to post-eradication/post-OPV communities. Strategies to accomplish this include risk elimination and risk management. Mr Wolff then detailed the GAP III strategy of risk management: primary safeguards include minimizing risk through facility design, management, and oversight (BSL requirements, legal frameworks, accreditation). GAP III secondary (facilities in areas of high immunity) and tertiary (facilities in areas with low poliovirus reproductive rates) safeguards breakdown for WPV/cVDPV and Sabin facilities as outlined on slide 6. Tertiary safeguards will be applicable only to wild polioviruses.

Mr Wolff continued by laying out the four implementation phases of the Global Action Plan to Minimize Risk: (1) national facility survey and inventory (now being conducted); (2) establishment of national long-term virus policy and regulation (after phase 1); (3) global destruction and containment of polio materials (1 year after last WPV/at tOPV to bOPV switch); and (4) global destruction and containment of OPV/Sabin materials (at global OPV cessation). The timeline of containment is superimposed with the endgame.
Remaining issues and next steps for containment include the completion of inventories in polio free countries (India) and of Sabin 2 materials, finalization of GAP III with governing body approval (to be submitted to the WHA as part of the end game strategy), collaboration with member states on regulatory framework, and the establishment of an expert body for evaluating profiles of candidate vaccine seed strains.

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**Research & Product Development for the Endgame**

**Hiromasa Okayasu, Medical Officer RAP, WHO**

**GPEI Program To Develop Affordable IPV: Update**

Dr Okayasu began by providing the background of the 2012 WHA Resolution that not only endorsed the tOPV to bOPV switch, but also expressed alarm over current IPV price and the lack of medium and long-term IPV prices. The WHA requested WHO to work with partners and manufacturers to enhance IPV affordability and availability. Dr Okayasu then laid out the GPEI approaches to affordable IPV.

The short-term plan is to develop and license an affordable IPV option before bOPV switch (planned for 2015). This plan includes the exploration of an alum adjuvant and fractional dose with ID IPV. Three short-term affordable options include (1) pride reduction of wIPV (IM full dose with no need for regulatory approval, but the current price is too expensive for developing countries); (2) fractional wIPV using ID (no adjuvant needed, but the regulatory pathway is complicated and there is concern over lower GMT and low acceptability by some countries); and (3) adjuvant wIPV using IM (well established with Alum, simpler development and regulatory process than ID, but much clinical study is needed over next 2-3 years). Either the fractional ID or alum adjuvant IPV has the potential to get down to less than $.50/dose for 1/5 dose.

Dr Okayasu then detailed immunogenicity and dose sparing studies in rats completed by Infectious Disease Research Institute (IDRI) in which neutralizing antibody titres with adjuvant for 1/2, 1/6, and 1/30 dose were higher than normal full dose (slide 6 and 7). Next, Dr Okayasu covered the objectives of ID IPV development (obtaining label change of IPV to include 1/5 dose with ID administration for supplemental dose in RI and SIAs and developing and licensing ID devices appropriate for developing countries). Studies in Oman, the Philippines, India, and Cuba all targeted these objectives with varying outcomes (slide 10). Follow-up studies are being conducted on ID IPV development in Cuba, India, Jordan, Bangladesh, and China (slide 12) to target a number of objectives, including one dose boosting effect after OPV series and ID device comparison. There is also significant support of ID device development occurring with companies Bioject (ID Pen development, supported by WHO/PATH) and Pharmajet (WHO prequalified Stratis jet injector and WHO/PATH support of clinical evaluation of Tropis). As always, discussions with NRAs and manufacturers is essential in order to work towards an IPV label change and prequalification of ID devices.

Dr Okayasu also detailed the long-term plan for developing a safer and affordable IPV before OPV cessation (planned around 2018). This plan includes sIPV development and alternative IPV strains. Five manufacturers in three countries – Japan, China and Indonesia – have provided proof of concept of sIPV and WHO/RIVM have collaborated to demonstrate the commercial feasibility of sIPV development. WHO/RIVM’s collaboration has isolated a key challenge in sIPV development – type 2 production yield – but their lab-scale production data demonstrated that it is possible to produce Sabin IPV at a lower cost than that of Salk IPV. In parallel, studies continue in Poland and Cuba to assess safety and immunogenicity of Sabin IPV and four partners have been selected for future technology transfer so far. An additional long-term option is alternate IPV strains, the development of which was stimulated by the Polio Research Committee.

Finally, an IPV demonstration project is underway in Indonesia to show the feasibility of affordable IPV and its benefits (i.e., prevention of cVDPV emergence). The study attempts to verify that OPV vaccine virus disappears from the environment after OPV cessation and demonstration the operational feasibility and immunological equivalence of replacing OPV with IPV in a tropical setting of a developing country. Results of this study show that Sabin virus disappeared from the environment within 3 weeks of OPV cessation and
no cVDPV emerged over 5 years. No major operational problems were encountered and a post-switch seroprevalence survey is pending, but should be high.

In conclusion, the development and introduction of affordable IPV is a prerequisite for the endgame strategy and a top priority identified by the WHA. There are multiple approaches to address this challenge, including developing different affordable and safe options and conducting IPV demonstration projects to show feasibility and benefit of including IPV in routine schedule. There is sufficient evidence that IPV can be affordable through adjuvant and/or IPV administration (within 2-3 years). Additionally, the methodology to produce Sabin IPV at a lower cost has been proven at lab-scale and is underway to demonstrate it at commercial scale within 18-24 months.

Dexiang Chen, Portfolio Leader/Senior Technical Officer, PATH

PATH’s Work To Apply Adjuvants To Inactivated Poliovirus Vaccine

Mr. Chen began by detailing the IPV adjuvant project. Its goal is to develop a low-cost IPV through antigen dose reduction using adjuvants and to achieve a 5-10 fold dose reduction. The strategy is to evaluate and compare several advanced adjuvants with PATH’s role being the development of PCPP-IPV formulation and coordination of a head-to-head comparison of different adjuvants (PCPP, Alum, delta, CAF01) and formulations currently under development.

PATH examined PCPP based on the literature reports that PCPP, compared to aluminum salts, was more potent and has no associated depot formation. Additionally, there were no alarming safety issues in pre-clinical and clinical studies. The strategy is to mix trivalent IPV at a reduced dose with a selected PCPP dose and review results in mice and rats. Primary serology is serum neutralization titres and secondary serology is serum and mucosal antibodies measured using ELISA. Aluminum is the control with selected buffer (slide 10). The adjuvant effect for IM immunization in mice is that in general, both alum and PCPP gave modest effect in neutralization titres, but the boosting effect seen with ELISA is more significant. For ID immunization in mice, PCPP does not appear to offer an advantage over IM. Both PCPP and alum caused some degree of histopathology at the injection sites. The next steps are to complete an investigation and optimization of PCPP’s adjuvant activity and safety, to determine the dose-sparing effect, and to compare this effect with other adjuvants (i.e., alum, oil-in-water emulsion, delta, and CAF01).

Mr. Chen followed with a discussion on IPV potency reagents and assays. There is currently no standard potency assay or reagent for Sabin IPV and those for Salk IPV are all based on capture ELISA to quantify the D-antigen. Some use a pair of polyclonal antibodies while others use polyclonal-monoclonal antibody pair. Potency reagents for Salk might be appropriate for Sabin, but there may be a need for optimization and there is a strong suggestion to use polyclonal antibodies. The potency reference standards for Salk (EU reference standard, USFDA reference calibrated against EU, possible international) are compared with unknown standards for Sabin IPV.

Mr. Chen then laid out the project workflow and timeline for these studies, indicating that they are now in the reagent preparation and testing phase. Slides 20 – 23 detail the characterization of Rabbit Sera and binding antibody titres for each IPV type (1-3), showing where cross reactivity occurs. These studies continue as well as do the preparation of reagents and assay protocol. Pilot experiments of preparing assay reagents have been completed (with specificity acceptable for type 1 and type 2 IPV, but low for type 3 IPV). The next step is to prepare reagent stock and develop the assay protocol.

Gabriella Rolli, Program Director, Crucell

Progress Toward A Low Cogs PER.C6 Based IPV

Dr. Rolli began by describing Crucell’s aim to developing and delivering an affordable IPV vaccine. Using Crucell PER.C6® cell line (no serum, so no animal products; immortalized by adenovirus E1) and Process Intensification (PIN process developed by Crucell), Crucell is targeting high production capacity, full dosage, low cost of goods, adjuvant-free vaccine, IM administration, comparable immunogenic and safety profile to that of the current marketed IPV.
The PER.C6® cell line is a human cell line immortalized by adenovirus E1 that grows serum free as suspension cells and is stable without antibiotic selection pressure. It is compliant with regulatory guidelines and endorsed as a cell substrate for vaccine manufacture by the FDA. Using this cell line with PIN technology shows growth to cell densities of greater than 100 million cells/mL. This process increases production capacity while decreasing production volume, increasing the number of active ingredients (cells) in the bioreactor to increase the output per bioreactor. By adapting these processes for IPV manufacture and achieving a 2.5 fold higher poliovirus productivity per cell in PER.C6®, Crucell claims a greater than 10 fold increase in polio virus productivity compared to VERO cells. In additional studies of poliovirus production, this process has shown to be constant and robust at different production scales, resulting in high yields for all 3 poliovirus serotypes. (Publication accepted by Vaccine should be published soon.)

GMP production is planned for 2013 and downstream process optimization needs to be validated to guarantee the good yields observed in the upstream process. Characterization of the polio strains produced on this cell substrate by the PIN process is in progress and will be documented later on.

In summary, Crucell has demonstrated a way to manufacture IPV with PER.C6® cells and PIN Technology that, compared to current VERO cell IPV, has a 12 fold increase in the number of cells/mL and a 2.5 fold increase in poliovirus productivity/cell resulting in a 30 fold increase in overall poliovirus productivity. Overall, Crucell’s technology shows the potentiality for producing with one single 500L bioreactor, approximately 200 million doses/year of high quality and low cost IPV to support the WHO Polio Eradication Program.

Darin Zehrung, Senior Technical Officer Vaccine Delivery, PATH

Needle Free Devices: Latest Developments

Mr Zehrung began by detailing the FDA’s new requirement for the relabeling of a vaccine for use by ‘jet injection’ based on the experience in October 2011 for influenza vaccine delivery. A FDA/DSJI Manufacturers Meeting was held in January 2012 and since that time the agency has clarified FDA requirements for research to allow for vaccines to be relabeled for jet injection delivery. CBER requires non-inferiority based clinical studies to relabel vaccines. Jet injectors as devices are still cleared through CDRH, which will meet the definition of “jet injection” per the FDA. Vaccine relabeling may indicate delivery by jet injection as a class of devices, which would enable any cleared DSJI to be used; or, it can identify one specific jet injector. Mr Zehrung then described the PharmaJet Stratis study, which is the first study to test such a device with the influenza vaccine to allow for relabeling (slide 6).

Concerning the prequalification by WHO of DSJI, Mr Zehrung detailed the Stratis technology and its path through the prequalification process. Requirements are based on ISO standards for jet injectors (ISO+) and the device must be cleared through a globally recognized NRA.

Mr Zehrung then provided an update on two device developers: Bioject and PharmaJet (slides kindly provided by both developers). Bioject’s design paradigm is to use robust materials in all critical areas of the device, and this had helped lead to the development of other technologies that include spring and CO2 powered devices for ID, SC and IM. Additionally, the new ID pen is a device you power by pulling back a lever and filling a cartridge through a vial adapter, making this product easy and reusable. Mr Zehrung finished by showing the results of a Phase I study completed with the Zetajet device comparing ID, SC, and IM delivery. Similar validation of clinical performance was also conducted for the ID pen injector. PharmaJet has developed the Tropis, an ID specific jet injector for which they will soon seek FDA clearance and which will be the technology used in clinical trials. Clinical validation of device performance has been conducted in order to assess injection quality through wheal diameter and residual moisture measurements (as was done in Bioject’s study). So far, PharmaJet’s studies have indicated that Tropis achieved delivered volume accuracy of more than 90% at least 95% of the time. The results are better than published data on Mantoux success rates of 75-85%. Additionally, Tropis has demonstrated very efficient vaccine usage, with a reduction in dead space volume of 28 times more than a conventional 3cc syringe and needle. The Tropis is moving forward with clinical trials planned in Leiden (Rabies), Cuba and China (Polio), and EU (BCG).

Mr Zehrung concluded by laying out the overview of planned ID DSJI studies, which include the following devices: ID adapter and PharmaJet Tropis (India); Bioject ID pen (South Africa); and PharmaJet Tropis, Bioject ID pen, Bioject B2000 (Cuba). Furthermore, the IPV study in Cuba has a 5 arm comparison of
immune response to full and fractional dose IPV administered via IM and ID using a number of different techniques. This will demonstrate non-inferiority of a fractional dose IPV administered intradermally with multiple needle free devices (as compared to full doses of IPV). The data generated by this clinical trial could possibly facilitate the regulatory approval for use of fractional doses of IPV.

Wilfried Bakker, Project Leader, RIVM
WHO/RIVM Sabin-IPV Development: Current Status, Technology Transfer And Future Strategies

Dr Bakker began by addressing the question of whether Sabin IPV type 2 is in fact less immunogenic than Salk IPV type 2. When considering the comparison of Sabin type 2 with Salk IPV, Salk had a steep Virus Neutralization Titres (VNT) slope up to a high VNT, while Sabin’s slope was less steep (which could be increased with adjuvant). Eventually, however, Sabin type 2 still had a high VNT (expressed in Log2 values), with an upper limit at 12 (with protection conferred once 3 Log2 cycles of VNT is established). Due to the somewhat less steep slope, these results appear to show a low relative potency, but because this is a comparison with standard Salk, the question is whether or not this is a problem. Based on results from these studies, Dr Bakker determined that although it may appear less immunogenic in comparison to the Salk IPV reference, Sabin IPV type 2 is in fact extremely immunogenic and what is required is a Sabin IPV reference standard.

Dr Bakker then continued with a review of clinical studies that address the question of whether Sabin IPV also induces neutralizing antibodies against wild-type poliovirus strains in humans. Dr Bakker provided the current update on the clinical studies’ answers to this question; including the milestones and phases of studies being conducted in Poland and Cuba (slide 15). According to advice provided by the Dutch MEB in July 2008, Sabin IPV immunogenicity and safety should be equivalent or better than that of Salk IPV. The preliminary conclusions of RIVM’s Phase I Sabin IPV in adults study shows that all three polio virus types in both Sabin groups (plain and alum adjuvanted) show a booster immune response against both Salk and Sabin strains and for each poliovirus type, the immunogenicity results were comparable with the control group (conventional IPV). In terms of safety, there were no noticeable issues in any of the groups.

In addition, RIVM focused on optimization of type 2 yield for D-antigen. Through relatively easy-to-implement improvements (i.e. use of increased cell densities for virus replication, reduction of hold-up volumes in clarification filters, and alternative concentration procedures) RIVM could bring yields to comparable levels as those known for Salk-IPV: 3mL bioreactor volume to make 1 dose of IPV (slide 35). This is sufficient yield to make manufacturers interested in making an sIPV product. Moreover, a fully optimized process results in a 1mL bioreactor volume required to make 1 dose of Sabin IPV. This is less volume than required for regular IPV. RIVM has also developed a technology transfer program of both hands-on and theoretical courses, which allows RIVM to share these developments with their partners.

Wrap Up

Dr Jafari thanked the participants for the productive discussion on the plan for the endgame of polio eradication. Collaboration between NRAs, partners and manufacturers remains essential to our collective. It is clear that the program is entering an era in which we can see an end to WPV transmission. In order to achieve this goal, the program will continuously reassess and project the demand for vaccine, always keeping manufacturers informed and engaged. Furthermore, discussions on the introduction of IPV for the endgame and the development of an affordable, long-term IPV solution – including devices and adjuvants – must continue. As always, the GPEI will continue to work closely with manufacturers to achieve our mutual goal of eradicating polio and we look forward to hearing about any and all exciting new developments that may arise.