Roadmap for assessment of nOPV2 manufactured by PT Biofarma under the EUL procedure

A. Introduction

Background

The Polio Eradication & Endgame Strategic Plan 2013-2018 was the result of the request of the World Health Assembly (WHA) 2012 to develop and finalize a comprehensive polio end-game strategy. The Plan inter alia highlighted the elimination of wild poliovirus type 2 (wPV2) since 1999.

On 5th May 2014, the Director-General of World Health Organization (WHO) declared the international spread of poliovirus a Public Health Emergency of International Concern (PHEIC) under the International Health Regulations (IHR 2005). The Director-General also issued temporary recommendations to reduce this spread and requested a reassessment of this situation by the Emergency Committee in three months.

In May 2015, the WHA adopted a resolution urging Member States to prepare for the withdrawal of the serotype 2 component of oral polio vaccine (OPV) from routine immunization programs worldwide through the replacement of trivalent oral poliovirus vaccine with the bivalent oral poliovirus vaccine. Three activities were required to schedule this switch at a global level:

- Implementation of at least one dose of inactivated polio vaccine (IPV) into routine immunization programs in all countries by the end of 2015;
- Securing a stockpile of type 2 monovalent OPV (mOPV2);
- Availability of a licensed bivalent OPV (bOPV).

The criteria used to fix the date for withdrawal was evidence of absence for at least six months of all "persistent" serotype 2 circulating vaccine-derived polioviruses serotype 2 (cVDPV2s), representing over 90% of the global cVDPVs.

WHO and the United Nations International Children's Emergency Fund (UNICEF) have a memorandum of understanding in place for the establishment of a mOPV2 bulk and finished product stockpile. The purpose of this stockpile is to ensure rapid access to mOPV2 vaccine and response capacity for emergency vaccination in case of epidemics and outbreaks caused by cVDPV2 or circulation of wPV2, accidentally or intentionally released by facilities handling the virus.

nOPV2 project

To address more efficiently the outbreaks of polio resulting from mutations in mOPV2, a novel OPV2 (nOPV2) vaccine has been developed and designed to be less likely to mutate into a form that can cause cVDPVs and vaccine-associated paralytic polio (VAPP). The goal of the nOPV2 project is to develop an oral polio vaccine that is more genetically stable than the current mOPV2 and to replace mOPV2 as the stockpile vaccine. This initiative is the result of a partnership between:

- The Program for Appropriate Technology in Health (PATH): program management and coordination;
- The Bill & Melinda Gates Foundation (BMGF): mainly funding;
- PT Biofarma: manufacturer of the vaccine;
- Stony Brook University, University of California - San Francisco (UCSF), the UK National Institute for Biological Standards and Control (NIBSC), the US Center for Disease Control and Prevention (US CDC), and the US Food and Drug Administration (US FDA): technical development of the vaccine.

Two nOPV2 candidates have been developed and tested in clinical trials, under the supervision of the University of Antwerp (for phase 1 trials) and the Fighting Infectious Diseases in Emerging Countries (for phase 2 trial).

Facilitation of access for nOPV2

As the international spread of poliovirus is a PHEIC and there have been outbreaks of cVDPVs mainly in Africa (Democratic Republic of Congo, Nigeria, Mozambique, Niger) , WHO and nOPV2 project partners met in November 2018 to discuss possible approaches to pre-licensure use of nOPV2 and listing under the Emergency Use Listing (EUL) procedure, which was under development at that time.

WHO and partners agreed that in light of the global public health emergency and the evolving serotype 2 epidemiology, WHO and the Indonesian National Regulatory Authority (Badan POM) will focus on potential pre-licensure use of nOPV2 vaccine (candidate 1) following a possible EUL of the vaccine. EUL assessment could be undertaken once sufficient data from studies through phase 2- M5 (data in young children and infants) are available. WHO and Badan POM will also work together to minimize assessment timelines.

Badan POM confirmed that their emergency licensure pathway (including for nOPV2) is not limited to health emergencies in Indonesia and can be applied for products that could be used by other countries in an emergency situation.

A pre-submission meeting took place on May 29th, 2019. PATH and PT Biofarma presented an update on their clinical development plan and the production plan for clinical lots for phase II and phase III as well as the scaling up for commercial production. They also presented a list of questions to WHO and Badan POM including chemistry, manufacturing and control (CMC), non-clinical and clinical aspects of the submission as well as the assessment pathway.

It was agreed that a roadmap would be developed to outline the steps to follow for the submission and assessment of nOPV2 for Emergency Use Listing as well as a proposed pathway for the collaboration between WHO and Badan POM.

The submission and assessment of nOPV2 candidate vaccine will be in accordance and subject to the terms of the EUL procedure (https://www.who.int/medicines/publications/EULprocedure.pdf). This document provides an overview of the process to ensure expedited access of this vaccine.

B. Steps, activities and timelines of assessment

As a PHE for polio is currently in progress the pre-emergency activities specified in the EUL procedure will be implemented during the emergency phase.

1) Receipt of preliminary information prior to submission (Q4/2019)

a) Upon request by WHO/PQT/VXA, PT Biofarma will provide Badan POM and the WHO vaccine assessment team (WHO/PQT/VXA) preliminary supporting information and literature prior to the formal submission for Emergency Use Listing. This information will be assessed by the aforementioned organisations with the help of experts with expertise in relevant areas to understand the data gaps ahead of the submission.

b) PT Biofarma will provide WHO with adequate advanced notice of the planned date of submission to ensure that the review process with relevant experts is appropriately planned ahead of the time of submission.

c) During the pre-submission period, WHO may organize ad hoc face-to-face (F2F) meetings as well as tele-/videoconferences of the *ad hoc* product evaluation committee (PEC) referred to below, so as to ensure that the PEC will be able to adequately fulfil its responsibilities at the time of submission.

2) Establishment of the product evaluation committee (Q4/2019)

a) Establishment by WHO of the PEC with members from a roster of experts including:
   - experts in CMC and clinical, including manufacturing changes during clinical development and evaluation of genetic stability of modified strains;
   - Experts in polio epidemiology;
   - Experts in polio emergency response.

   WHO will serve as the secretariat for the meetings of the PEC.
   Badan POM and members of regulatory fora or initiatives of regions, where cVPDV2s are still present, will be invited to participate as observers in the meetings of the PEC.

   Members of the PEC (experts) will be assessed for conflicts of interest and be required to enter into a Memorandum of Agreement with WHO, including an adequate Confidentiality Undertaking.

b) Role and responsibilities of the different bodies involved:

   I. Secretariat - WHO/PQT/VXA

      - acting as focal point for submission of data (prior to-/at/post submission) and transmission of this data to the PEC and/or relevant regulatory experts;
      - screening (jointly with Badan POM) of submission for completeness of the information required;
      - organisation of ad hoc F2F meetings, tele-/videoconferences of the PEC prior to/at/post submission, including a joint evaluation meeting at submission of all data packages;
      - facilitation of the activities of the PEC;

   II. Product evaluation committee (PEC)

      - preparation of a refined list of the essential data requirements for the submission for emergency use (including post listing surveillance commitments and lot release program) and sharing of the list with PT Biofarma (prior to submission);
      - development of a set of guidelines and identification of scientific literature that will be used for the assessment and recommendation (prior to submission);
      - evaluation of the quality, clinical and performance data to be submitted at times agreed with manufacturer. Programmatic aspects will be reviewed concomitantly;

- drafting of the evaluation report(s);
- issuance of recommendation (acceptance or non-acceptance) for emergency use listing of the evaluated product;

III. Badan POM (outside PEC roles and responsibilities)

- evaluation of preliminary information (prior to submission);

IV. WHO/POL

- provision of programmatic and technical guidance to help the evaluation process of the PEC;

V. WHO/TSN/NSB

- assistance to the PEC for the development of a set of guidelines and identification of relevant scientific literature to support the evaluation by the PEC.

3) Preparations for the assessment upon submission of the application (Q1/2020)

a) Badan POM and WHO/PQT/VXA will jointly screen the application for acceptance or request of additional information within 5 working days after receipt of the submission. The manufacturer is to respond to potential requests for additional information within the transmitted timeframes;

b) The WHO secretariat will provide the final version of the submission file to the PEC.

4) Assessment of first data package with quality, non-clinical and clinical data (Q1/2020)

a) WHO/PQT/VXA will organize a joint evaluation meeting after submission during which members of the PEC will review the data set and will prepare a consolidated list of questions (LoQ) and comments based on the review and discussions;

b) The consolidated LoQ will be sent to PT Biofarma with a timeframe for response;

c) PT Biofarma will submit responses to the WHO secretariat, who will forward these to the PEC along with a timeframe for review;

d) A second round of questions may be needed depending on the responses to the first LoQ that will be transmitted to the manufacturer by the WHO secretariat. Responses

to this second round will be submitted to the WHO secretariat by the manufacturer, who will forward these responses to the PEC along with a timeframe for review;

e) Depending on the outcome of the evaluation of the first data package, the PEC will provide an interim recommendation (acceptance or non-acceptance) for emergency use listing of the evaluated product or postpone its recommendation and request and evaluate additional data if necessary. The PEC will submit an interim report to WHO and (if accepted by WHO) transmitted by WHO to the manufacturer, with UNICEF in copy.

5) Assessment of second data package with clinical data (Q3-Q4/2020)

a) The interim recommendation issued pursuant to section 4.e will be re-evaluated after submission of the second data package. WHO will organize a joint evaluation process after the manufacturer's submission of the second data package. The EC will review the data set and will prepare a consolidated LoQ and comments based on the review and discussions;

b) WHO will send the consolidated LoQ to PT Biofarma with a timeframe for response;

c) PT Biofarma will submit its responses to the WHO secretariat, who will forward these responses to the PEC along with a timeframe for review;

d) Follow up questions may be needed depending on the responses to the first set of LoQ and will be transmitted to the manufacturer by the WHO secretariat. Responses to this second round will be submitted by the manufacturer to the WHO secretariat, who will forward them to the PEC along with a timeframe for review;

e) WHO may organize ad hoc tele-/videoconferences of the PEC to discuss the outcome of the evaluation process and potential final recommendation;

f) Depending on the outcome of evaluation of the second data package (including Corporate social responsibility), the PEC will revise the interim recommendation and provide a final recommendation (acceptance or non-acceptance) for emergency use listing of the evaluated product. For this purpose, the PEC will submit a final report to WHO and (if accepted by WHO) transmitted by WHO to the manufacturer with UNICEF in copy.

6) Other activities related to the assessment: Inspection and testing

a) A joint inspection of PT Bio Farma's manufacturing facilities by BADAN POM and WHO will be conducted in February 2020.
b) Badan POM will perform testing on lots produced for release and will share results with WHO.

Outcome of the inspection and testing will also be forwarded to the PEC as part of the assessment.

C. Outcome of assessment

The outcome of the assessment includes:

a) recommendation (acceptance or non-acceptance) for emergency use listing of the evaluated product;

b) supporting assessment report with i.e. executive summary, scientific review and final remarks.

D. Post recommendation activities

The final recommendation (acceptance or non-acceptance) for emergency use listing of the evaluated product can be re-evaluated after the submission by the manufacturer to the WHO secretariat of further data packages pertaining to production and/or clinical data. The WHO secretariat will transmit the data to the PEC and/or relevant regulatory experts for assessment. The outcome (if accepted by WHO) will be transmitted to the manufacturer by the WHO secretariat, with UNICEF in copy.

Monitoring performance of the vaccine deployed to countries.

Since vaccines listed under the EUL procedure have not been licensed for use in routine immunization settings, post marketing data would not be available at the time of application. Therefore, the manufacturer should provide the plans to ensure the active data collection and analysis of information on the safety and effectiveness of the product during the period when the EUL listing would be in effect and for a reasonable time following such period.

After a product has been listed, WHO will take into consideration reports on safety surveillance, efficacy/effectiveness/performance monitoring, quality complaints and other relevant data that may impact the validity of the listing status.

The sources of such information will inter alia be based on existing surveillance mechanisms in affected countries and on post-listing surveillance commitments of the manufacturer, set as conditions for the listing.

Upon making a decision whether or not to grant an emergency use listing, WHO will (without prejudice to any confidential information of the applicant/manufacturer) publish information about the product in a public report available on a dedicated portal of the WHO website. This may include negative assessment outcomes.

In addition, WHO reserves the right to share full reports with the relevant authorities of any interested Member State and interested United Nations agencies.

Post-listing changes

Any changes to the product dossier after the granting of an EUL are to be submitted to Badan POM and WHO/PQT/VXA for assessment. The outcome will be transmitted to the manufacture by the WHO secretariat.

E. Communication strategy to facilitate access in countries.

A communication strategy to facilitate the emergency use will be developed ahead of the submission and will be published as an addendum of this roadmap.