



RECOMMENDATION FOR AN EMERGENCY USE LISTING (EUL) OF NOVEL ORAL POLIO VACCINE TYPE 2 (nOPV2) SUBMITTED BY PT BIOFARMA (PERSERO)

Abstract

Novel Oral Poliomyelitis Vaccine type 2 (nOPV2) has been granted time limited use under Emergency Use Listing procedure by WHO, on 13 November 2020. This decision is subject to commitments by the manufacturer, which are listed in the section "Recommendation". This document details the assessment process and the outcome.

1 Introduction

1.1 Background

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). In May 2015, noting that poliovirus type 2 had not been detected since 1999, the WHA adopted a resolution urging Member States to prepare for the withdrawal of this component of oral polio vaccine (OPV) from routine immunization programs worldwide through the replacement of trivalent OPV with the bivalent OPV (bOPV). Three key activities were pre-requisites for 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 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.

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 type 2 wild poliovirus, WHO and the United Nations International Children's Emergency Fund (UNICEF) established an mOPV2 (bulk and finished product) stockpile. However, given the propensity of mOPV2 to revert to a neurovirulent phenotype by introduction of mutations during replication in the human gut, cVDPV2s are, in rare instances, generated while responding to outbreaks with this vaccine.

1.2 nOPV2 project

To more efficiently address cVDPV2 outbreaks, a novel OPV2 vaccine (nOPV2) 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 nOPV2 is to provide a vaccine that is genetically more stable than the current mOPV2 and for it to eventually replace mOPV2 as the stockpile vaccine. As part of a global scientific consortium, University of California - San Francisco (UCSF), the UK National Institute for Biological Standards and Control (NIBSC), US Centers for Disease Control and Prevention (US CDC) and the US Food and Drug Administration (US FDA) participated to the development of 2 vaccine candidates.

The clinical development of nOPV2 is the result of a partnership among several partners including:

- PT Biofarma (Persero): manufacturer (referred after as Biofarma);
- The Bill & Melinda Gates Foundation (BMGF): technical guidance on development strategy and funding;
- University of Antwerp: phase I / II study sponsor;
- Fighting Infectious Diseases in Emerging Countries (FIDEC): phase II study sponsor;
- US CDC: primary laboratory partner for studies;
- PATH: program management and coordination;

1.3 EUL

WHO and nOPV2 project partners gathered in November 2018 to discuss possible approaches for emergency use authorisation by the relevant National Regulatory Authority (NRA) and Emergency Use Listing (EUL) of nOPV2 by WHO.

EUL is time limited risk-benefit assessment for emergency use of vaccines, medicines and in vitro diagnostics during PHEIC when limited data are available and the products are not yet ready for application for WHO prequalification. It is a revision of the Emergency Use Assessment and Listing (EUAL), developed in 2015 during the Ebola crisis by inclusion of a preparedness phase and is not equivalent or an alternative to prequalification¹. As the EUL is time-limited in nature, the manufacturer is still expected to complete the development of the product and submit for licensure and prequalification.

The issuance of an EUL for a product reflects WHO's recommendation for its use following a thorough scientific risk benefit assessment. However, it is the sole prerogative of each WHO Member States to allow or not the emergency use of a product under EUL - including nOPV2 - in their country.

2 Assessment process

A pre-submission meeting involving Biofarma, PATH, BMGF, WHO Polio Eradication Programme, Indonesian National Agency of Drug and Food Control (referred after as Badan POM) and WHO Vaccines & Immunization Devices Assessment team (WHO PQT/VAX) took place on May 29th, 2019. PATH and 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. WHO and Badan POM committed to focus on potential emergency use authorisation of nOPV2 vaccine followed by a possible EUL. Moreover, Badan POM confirmed that their emergency licensure pathway is not limited to health emergencies in Indonesia and can be applied for products that could be used by other countries in a situation of health emergency.

A specific roadmap was developed to outline the steps to follow for the listing of the essential information required, the submission and assessment of nOPV2 under EUL as well as a proposed pathway for the collaboration between WHO and Badan POM. It was published in January 2020².

2.1 Scientific Review

Oral polio vaccines have been manufactured for over 50 years using the same methodology. The nOPV2 development project was focused on using virus strains that are genetically more stable than the current OPVs (made from Sabin strains) while production process would remain the same.

¹ <https://www.who.int/teams/regulation-prequalification/eul>

² <https://www.who.int/news/item/09-01-2020-emergency-use-listing-procedure-and-roadmap-health-emergencies?ua=1>

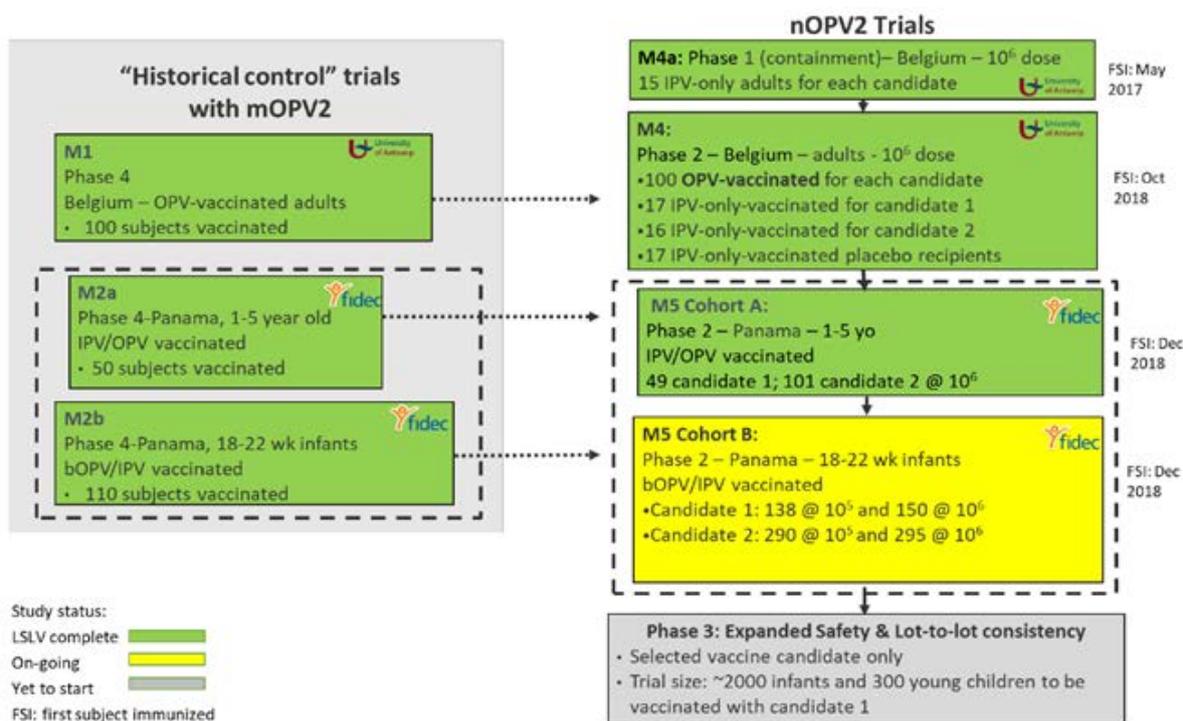
In accordance with the roadmap, an evaluation group was established by WHO with quality and clinical experts and members from Badan POM. Experts of several NRAs - Ethiopia, Ghana, Malaysia, Nigeria and Pakistan - were invited to participate in the review of the data. Unfortunately, due to the Covid-19 pandemic, only the Malaysian NRA representative was able to be part of this review.

The first task was to discuss the essential data requirements. In accordance with the EUL procedure, the assessment file was sent on “rolling submission” basis: the manufacturer submitted data sets following agreed timelines with WHO PQT/VAX and BADAN-POM. Consequently, the nOPV2 data was submitted between 28/02/2020 and 25/08/2020.

Clinical overview

BioFarma developed two nOPV2 vaccine formulations, candidate 1 and candidate 2, that were studied in non-clinical studies and in phase I and II clinical trials. The first candidate was finally selected and submitted for EUL assessment. The available non-clinical studies were considered to provide sufficient evidence to allow the initiation/conduct of nOPV2 clinical trials.

Overall, the clinical program included a small phase 1 study in adults under containment, a Phase 2 study in cohorts of adults with OPV or exclusively IPV vaccination histories, and then a larger Phase 2 study in young children and infants as indicated in the Figure 1 (nOPV2 Clinical Development Plan at the time of the submission of the first data set) below:



Notes: As of today, the M5 Cohort B has been completed

The data analysis is not carried out by direct comparisons of nOPV2 with mOPV2 recipients but rather using mOPV2 as historical control. Randomized study comparing nOPV2 versus mOPV2 was not feasible due to i) the non-availability of nOPV2 before 2016 when the switch between tOPV and bOPV was implemented and ii) the unpredictability of outbreaks which are the only circumstance where mOPV2 can currently be used. More than 400 million doses of mOPV2 were produced by BioFarma have been distributed through the global stockpile. The study design was based on the principle that acceptability is fulfilled since prior to global cessation of routine Sabin-2 use in 2016 and prior to the availability of nOPV2 candidate vaccine for clinical trials, Phase 4 clinical trials (Belgium, Panama) were conducted with mOPV2 to provide data for comparison with nOPV2, evaluated in later trials as nOPV2 clinical trial

materials were not available before the global switch. In order to maximize comparability of safety, immunogenicity, and genetic stability data, the manufacturer designed the mOPV2 phase 4 trials in a way to parallel the design of the phase 1 and 2 nOPV2 studies with respect to overall design, endpoints, location, and study populations and employed the same laboratories for the polio serologic, viral shedding, and mouse neurovirulence assays (TgmNVT). mOPV2 serology and TgmNVT samples from these studies were held to run in a blinded manner with samples from the analogous nOPV2 trials.

Particular attention was given to the assessment of the nOPV2 specific points:

1. **Genetic stability:** the primary reason for nOPV2 development is the risk of genetic reversion of mOPV2 and possible cVDPV occurrence, including development of neurotropic events (i.e. acute flaccid paralysis, aseptic meningitis, encephalitis).
2. **Genetic safety:** nOPV2 is genetically modified and thus a thorough environmental risk assessment was conducted. Monitoring of shedding of nOPV2 into the environment is of primary importance, particularly in a context where mOPV2 was used and/or OPV1 and OPV3 with potential risk potential of recombination (see also point 8).
3. **Safety:** OPV vaccination is associated with rare cases of Vaccine Associated Paralytic Polio (VAPP) in vaccinated individuals or their contacts, or the emergence of vaccine-derived polioviruses ((c)VDPV). Although nOPV2 is reported to have lower neurovirulence, it is unclear whether this translates into no or lower risk of VAPP or other non-paralytic polio associated neurotropic events (e.g. aseptic meningitis, encephalitis). Available evidence indicates that OPV is non-teratogenic and safe to administer to pregnant women. Whether this also applies to nOPV2, being genetically modified, still needs to be established.
4. **Immunogenicity:** In emergency settings where mOPV2 is used, responses to other OPVs appear to vary, possibly as a result from complex interactions between the host (e.g. levels of maternal antibody, poor intestinal immunity in malnourished children, diarrhoea at the time of vaccination, and household exposure to other OPV recipients), the vaccine and its delivery, and the environment (e.g. prevalence of other enteric infectious agents). In these settings, type 2 vaccine virus was shown to interfere with immunological responses to vaccine virus types 1 and 3. For the purpose of the EUL assessment the relative seroprotection rate of nOPV2 compared to mOPV2 is important, particularly at lower virus neutralisation titres.
5. **Vaccination schedule:** A dose of OPV administered at birth, or as soon as possible after birth, can significantly improve the seroconversion rates for the types of polioviruses contained in the vaccine after subsequent doses in some settings, and induce mucosal protection before other enteric pathogens can interfere with the immune response. Theoretically, giving the first dose of any OPV at a time when the infant is still protected by maternally-derived antibodies may also prevent VAPP. The effectiveness of nOPV2 in naïve infants at birth should be substantiated.
6. **Co-administration:** OPV is usually administered concurrently with other vaccines including BCG, DPT, hepatitis B, measles, *H. influenzae* type b (Hib), pneumococcal conjugate and/or rotavirus vaccines. No interference regarding effectiveness or increased incidence of adverse events have been observed when tOPV was administered with these vaccines. Co-administration with rotavirus vaccine or oral cholera vaccine did not affect the response to the poliovirus types. Although no data are available for nOPV2, it is assumed that, as for mOPV2 or tOPV, no interference would occur with other routinely administered vaccines, as far as it will be of relevance in the emergency setting.
7. **Duration of protection:** There is no evidence that protective immunity against paralytic disease wanes over time. After induction of active immunity either by vaccination or exposure to poliovirus, usually measured by circulating antibody titre, protection is life-long. As antibody titres decline over time and may fall below detectable levels, seroprevalence may not reflect the true immune status of a given population. There is no evidence that loss of detectable antibody puts immunocompetent

individuals at risk for paralytic disease. There is no experience with nOPV2 in this respect. In the context of its projected use, it is unlikely that relevant long-term clinical data will ever be generated.

8. **Immunocompromised persons as special risk groups:** Very few people with primary immunodeficiency diseases may chronically excrete VDPVs following OPV immunization (iVDPV); with iVDPVs that show regained neurovirulence, as demonstrated by genetic sequencing. The true incidence of chronic iVDPV infections remains uncertain, because only some infections lead to acute flaccid paralysis (AFP). There is presently no evidence that acquired (secondary) immunodeficiency syndromes (e.g. HIV), lead to prolonged poliovirus excretion after OPV vaccination, but such data are not available for nOPV2. Data on duration of shedding from the healthy population studied might provide some insight into different kinetics in duration shedding between mOPV2 and nOPV2.

The clinical development of this vaccine is still not complete, and phase II and III clinical trials are planned, respectively in Bangladesh and Gambia, in order to assess clinical lot-to-lot consistency and use in naïve neonates (at birth).

Quality overview

The **initial submission** consisted in the information related to the development, production and control of drug substance (DS) and drug product (DP) of the 20 doses presentation of nOPV2. This presentation was manufactured in the pilot scale building, where phase 1 and 2 clinical batches were produced, at an intermediate production scale between pilot and commercial of 32 L for DS and 20 L for DP. The review process was conducted and highlighted the following positive aspects:

- the low environmental risk of nOPV2 as a genetically modified product;
- the adequacy of the non-clinical studies;
- the satisfactorily production outline of DS and DP;
- the adequate framework for process validation;
- the commitment of the manufacturer to generate homologous references for quality control of nOPV2.

Several issues were identified during the review, which were resolved over the various rounds of questions and responses with BioFarma. Those that were not resolved at the time of this initial submission were transferred for follow up during the next assessment and were as follows:

- Vaccine Vial Monitor type 2 (VVM2) request could not initially be granted due to non-compliance of potency stability results with specifications for at least 2 temperatures according to VVM2 requirements³. Discussions with manufacturer and polio eradication program were initiated to come up with a suitable outcome;
- viral safety on working seed lot (WSL) in use was not adequately addressed as the risk assessment provided should be strengthened with data on each of the materials used to prepare the WSL;
- establishment of specifications for monitoring by Massive Parallel Sequencing (MPS) of identified and characterised genetic modifications outside the nOPV2 specific regions (see below) was not addressed satisfactorily as it was based on a very limited clinical data set;
- the proposed identity determination by combination of seroneutralisation (for serotype setting) and multiplex real time PCR (for mOPV2 vs. nOPV2 discrimination) identifies the presence of nOPV2 without confirming the absence of Sabin-2;
- stability of finished product was not adequately documented to grant the claimed shelf life.

The **second submission** of CMC data was the information related to the development, production and control of drug substance and drug product of the 50 doses presentation. This is produced at the commercial scale of 200L for DS and 400 L DP in an existing building for DS and a new building for DP. The latest was authorised for commercial scale production by Indonesian NRA in October 2020, following

³ WHO/PQS/E006/IN05.4: "Vaccine Vial Monitor Performance Specification"

a dedicated inspection. The review of this set of data was focused on the parts of the dossier that were amended in comparison with the 20 doses presentation file. 3 out of 5 issues transferred from assessment of the 20 doses presentation could be solved. The resolved issues are as follows:

- VVM2 claim could be granted as the manufacturer decided, upon discussions initiated as stated above, to increase the target formulation titre. As a consequence, for 2 temperatures, potency stability results were in compliance with specifications according to VVM2 requirements. Compliance for the 3rd temperature was achieved by extrapolation;
- the manufacturer committed to refine, with production data, MPS specifications for the genetic modifications outside the nOPV2 specific regions (see next paragraph) on an agreed frequency and to communicate the updates to WHO;
- given the lack of available commercial stability data and the 20 doses batches not being suitable to support the claimed shelf life of 36 months (see next paragraph), this claim was reduced to 12 months. Additionally, the storage period at 2-8°C was fixed to 3 months, due to lack of appropriate data. These two periods will be reviewed upon provision of additional supportive stability data.

The most important critical quality parameter of this live attenuated viral vaccine is the stability of its genome. As highlighted in the introduction, conventional OPVs tend to revert, while replicating in the human gut, to a virulent phenotype by substitution mutations at positions that are well described in the literature⁴. This new generation OPV was engineered to have higher genetic stability by reducing the likelihood of reversion mutations and recombination events with other vaccinal strains while replicating. However, since there is little experience with this new type of OPV and since the WSL will be replicating during production, a close control of the genetic steadiness is required. The quality experts from the evaluation group highlighted that MPS was the method of choice to monitor closely any change in the sequence of the drug substance in comparison to the nOPV2 S2/cre5/S15domV/rec1/hifi3 reference sequence and recommended it to be implemented as a release test. The company agreed and consequently established specifications that were addressing 2 aspects.

- the genetic constancy of the nOPV2 specific regions;
- the monitoring of the abundance of 3 particular variants, outside the nOPV2 sequences, with effect on safety and efficacy that were discovered during development of the product. As the specifications related to nOPV2 modifications are of quantal nature, the other ones had to be determined based on data coming from DS used for the formulation of clinical batches. Given the reduced data set, the quality experts recommended to widen it to production data. The manufacturer again agreed with the proposition.

Additionally, during the assessment of the 50 doses presentation data, it was noted that production processes of drug substance between pilot scale (used for the manufacturing of 20 doses presentation) and commercial scale buildings were slightly different. Moreover, the abundance of 2 of the 3 variants was significantly different between drug substances produced in the pilot and commercial scale buildings, suggesting the genetic composition of DS is influenced by the manufacturing process. Therefore, the experts concluded that finished products formulated with bulks produced in those 2 buildings could not be considered comparable and batches manufactured in the pilot scale building could not be used to establish the shelf life of the commercial finished product.

⁴ Ren et al.; J. Virol. 1991; 65(3): 1377-82 / Rezapkin et al.; Virology 1999; 258: 152-60

2.2 Outcome of review

Clinical

This clinical assessment raised a series of queries on different aspects of the submitted evidence. There were two main issues that were critical to resolve as part of the decision-making for granting an EUL to nOPV2: evidence of genetic stability of the vaccine and ability of BioFarma and WHO/GPEI to gather reliable post-deployment surveillance data. **Upon request for further clarification and information, Biofarma satisfactorily addressed all the issues raised during the assessment, including the main ones previously mentioned.**

One of the key elements of the review was the Risk Management Plan which details the risks of nOPV2 use and outlines the proposed risk minimization measures. It describes how the vaccine will be deployed in the field, including the preparedness phase of the affected countries. The submitted plan outlines how the vaccine will be deployed progressively, including that GPEI will oversee and confirm readiness to meet the requirement for the initial countries using the vaccine—that they are able to monitor the performance of the vaccine by detecting and collecting the data which will allow to confirm the safety profile and the effectiveness of the nOPV2 vaccine - e.g. acute flaccid paralysis (AFP) cases are expected to be captured by AFP surveillance. Close collaboration of GPEI with Biofarma in this regard was deemed essential.

After discussion, the proposed way to monitor the genetic stability was considered acceptable.

Finally, given the public health need for nOPV2, it was found acceptable that WHO receives the immunogenicity and safety results in the naive neonates population at a later stage as post-EUL commitment. Biofarma was also requested to follow up the pregnant women indirectly exposed to the nOPV2. This will be done by an ad-hoc observational study.

Pharmacovigilance (PV) plan included in the RMP contains the following ongoing or planned activities:

Activities	Objectives	Safety Concerns Addressed	Status
Enhanced AEFI surveillance	To identify AEFI cases	Anaphylactic reaction Aseptic meningitis/ encephalitis Acute disseminated encephalomyelitis Guillain-Barre syndrome Transverse myelitis	Preparation phase
Enhanced AFP surveillance	To identify VAPP and VDPV cases and VDPV circulation	VAPP, VDPV	Preparation phase
Enhanced environmental surveillance	To identify VDPV	VDPV	Preparation phase
iVDPV registry	To assess safety in immunocompromised	Immunocompromised individuals	Planned
PID active surveillance	To assess safety in immunocompromised	Immunocompromised individuals	Planned
Pregnancy registry (if target population 15 years of age and under)	To assess safety in pregnant women	Pregnant and lactating women	Planned
Ad hoc observational study of the safety of nOPV2 among pregnant women exposed via shedding	To assess safety in pregnant women	Pregnant and lactating women	Planned
Clinical trial to generate data on truly polio vaccine-naïve infants in Bangladesh	To assess safety in naïve populations	Naïve population	Ongoing
Clinical trial to generate additional data on the immunogenicity of the final dose in children 1-5 years old.	To assess immunogenicity of the final selected dose in children 1-5 years old	Children 1-5 years old	Planned

Quality

The critical quality issues were satisfactorily resolved. The few remaining issues are considered to have minor impact on the quality of the product, and thus it was decided that these could be solved post recommendation. **Therefore, the overall quality of the nOPV2 50 doses was considered acceptable for use under emergency listing.**

3 Technical considerations

3.1 Vaccine characteristics

Novel Oral Poliomyelitis Vaccine Type 2 (nOPV2) 50 doses is a clear sterile suspension of live attenuated Poliomyelitis virus type 2 of modified Sabin strain prepared in Vero cells derived from African green monkey kidney. The nOPV2 strain S2/cre5/S15domV/rec1/hifi3 is an attenuated serotype 2 poliovirus derived from a modified Sabin-2 infectious cDNA clone. Increased genetic stability and decreased recombination rate are achieved with five modifications in the parental genome affecting domain V, cre element and RNA dependent RNA polymerase.

The vaccine is a clear liquid with slightly yellow to light red color due to presence of phenol red used as pH indicator. Each dose of 2 drops (0.1 ml) contains the following composition:

Components	Quantity/dose (2drops/0.1 mL)
Poliovirus Type 2 (S2/cre5/S15domV/rec1/hifi3)	Not less than $10^{5.0}$ CCID ₅₀
Sucrose	35% (w/v)
Acetic acid	Quantity sufficient to pH 6.5-7.2
NAHCO ₃	Quantity sufficient to pH 6.5-7.2
Basal Medium Eagle (BME)	Quantity sufficient to bring to volume

The oral vaccine is available in USP type 1 borosilicate vials with grey rubber stopper and green lacerated side tear down aluminium seals. Each vial contains the volume necessary to deliver 50 doses (≥ 100 drops; 1 dose = 2 drops = 0.1 ml).

The vaccine is supplied with a dropper made of natural Low-Density Polyethylene. Droppers are blistered individually and packed in separate boxes.

Novel Polio Two vaccine 50 doses (oral) bears a VVM2 affixed on the label of the vaccine vial.

3.2 Special precautions for storage and handling

The assigned shelf life of novel Polio Two vaccine 50 doses (oral) is currently **12 months when stored at minus 20°C**. It can also be stored for up to **3 months between +2° C and +8° C**. These storage periods can be revised upon provision of additional supportive stability data.

When distribution or administration is not imminent, it is advisable to store the vaccine at temperatures of minus 20°C or lower since this halts deterioration of vaccine potency. If the vaccine has been accidentally exposed to high environmental temperatures, it is recommended to be used immediately or stored ideally at minus 20°C or at +2° C and +8° C until administration under condition that the VVM allows its use.

3.3 Indication, warnings and contraindications

Indication:

Novel Oral Poliomyelitis Vaccine Type 2 (nOPV2) is indicated for active immunization in all age groups for emergency use in response to outbreaks caused by Type 2 poliomyelitis virus when and where it is required by the Global Polio Eradication Initiative (GPEI) or WHO.

Special warnings and precautions for use

Pregnancy:

nOPV2 should not be administered to pregnant women.

To date, there are no clinical data on the use of nOPV2 in infants who have not been previously immunized with poliovirus type 2.

In case of diarrhoea and/or vomiting (including gastrointestinal infection), the dose received will not be considered as administered, and it should be repeated after recovery.

Transmission:

Like Sabin-2, nOPV2 is shed in stool, and possibly saliva of vaccine recipients. Transmission of vaccine virus to close contacts is possible and is likely to be no greater and possibly less than that of Sabin-2. This vaccine should be used with caution in close contacts of persons with immune deficiency disorder. If personal contact must occur, precautions should be taken to avoid contact with stool or saliva of the vaccinated individual.

Contraindications:

Immunocompromised individuals

The vaccine is contraindicated in those with primary immune deficiency disease or suppressed immune response from medication, leukemia, lymphoma or generalized malignancy.

Although no data are available specific to the use of nOPV2 in individuals infected with human immunodeficiency virus (HIV), both asymptomatic and symptomatic, given the derivation of this vaccine from the Sabin type 2 strain, health authorities may consider adopting an approach for nOPV2 similar to that accepted for Sabin-2 in this population.

3.4 Administration

Two drops (0.1 mL containing $\geq 10^{5.0}$ CCID₅₀) are delivered directly into the mouth from the multi-dose vial by dropper or dispenser. Care should be taken not to contaminate a multidose dropper with saliva.

Multidose vials of nOPV2 from which one or more doses of vaccine have been removed during an immunization session may be used in subsequent immunization sessions for up to a maximum of 4 weeks, provided that all of the following conditions are met (as described in the WHO policy statement: Multi-dose Vial Policy (MDVP) WHO/IVB/14.07):

- The expiry date of the vaccine has not passed;
- The vaccine vial has been, and will continue to be, stored at WHO-or manufacturer-recommended temperatures; furthermore, the vaccine vial monitor (VVM), is attached and visible on the vaccine label and is not past its discard point

Concomitant administration: There is no data available yet on co-administration with another vaccine.

3.5 Reported Adverse Events following Immunization (AEFIs)

The limited data gathered to-date indicate that nOPV2 is well tolerated in adults, young children (1 to 5-year old) and infants (18 to 22-week old), with no safety concerns identified. In clinical trials, solicited events among infants and children receiving any nOPV2 vaccination included predominantly mild or moderate abnormal crying (15%), drowsiness (7%), fever (11%), irritability (15%), loss of appetite (11%), and vomiting (13%), with similar rates among mOPV2 control vaccinees. Among adults, most subjects reported mild or moderate solicited events composed predominantly of abdominal pain, diarrhea, fatigue, and headache, with severe events of headache (2.2%) and myalgia (0.8%). Severe unsolicited events assessed by investigators as related to vaccination occurring in >2% of vaccinees included diarrhea (5.3%) and upper respiratory tract infection (2.3%). The data from clinical trials indicate no meaningful imbalance associated with vaccination between the nOPV2 and mOPV2 or placebo control groups.

Although not observed in any study of nOPV2, in very rare cases (less than one case for every million children receiving their first dose, for whom rates are highest) Sabin-strain trivalent oral polio vaccines are associated with vaccine-associated paralytic poliomyelitis (VAPP) in vaccinees or susceptible contacts.

The possibility of this occurrence or other unanticipated rare or very rare events following nOPV2 administration cannot be conclusively ruled out.

4 Monitoring of performance of the vaccine in the field

Biofarma will collaborate with the partners involved to ensure that the following aspects will be monitored.

4.1 Vaccine efficacy/effectiveness

Additional data collection on effectiveness of the nOPV2 vaccine as an outbreak response is required to assess the impact of the vaccine under real-world conditions. Cases of suspected vaccine failure should be documented.

4.2 Safety Monitoring

Safety monitoring for nOPV2 will be done using data from adverse event following immunization (AEFI) surveillance, adverse events of special interest (AESI) surveillance along with routine data on VAPP and VDPVs collected by the polio Acute flaccid paralysis (AFP) surveillance system. Passive AEFI surveillance will be useful for detecting unanticipated or unexpected safety signals. Active AESI surveillance will be used to detect complex, serious adverse events that may be expected based on polio disease and polio vaccine.

The active AESI surveillance will continue for six weeks after each (of the proposed two) nOPV2 campaign rounds, as this is a biologically plausible risk window for identifying neurological adverse events following administration of vaccines. Monitoring of data will occur monthly for the initial use period of nOPV2 and quarterly thereafter. Any reported serious adverse event will be reported ad hoc to the manufacturer, to report to their national regulatory authority and WHO PQT/VAX within 15 days upon receipt of the case.

A dedicated nOPV2 safety sub-committee of the Global Advisory Committee on Vaccine Safety is currently being established. It is comprised of independent expert members whose primary objective is to advise the clinical safety outcomes related to the use of nOPV2 under EUL.

Genetic characterisation of nOPV2-related viruses detected through environmental surveillance (ES) and AFP surveillance will be conducted to evaluate genetic stability of the vaccine virus. The genetic stability evaluation will be conducted and overseen by a dedicated genetic characterization group.

4.3 Programmatic aspects

Use of novel oral polio type 2 vaccine (nOPV2) while under EUL will require verification that a country has met a series of readiness requirements, from securing national approvals to demonstrating adequate preparation across vaccine management, surveillance, safety, training, communications and laboratory. The verification of readiness must be issued prior to the release of nOPV2 to a given country from the global stockpile.

Further details on the requirements countries need to meet can be found in the Implementation of nOPV2 for cVDPV2 outbreak response: Technical guidance for countries and the accompanying nOPV2 Vaccine Deployment Readiness Checklist.

5 SAGE recommendations

During the 2020 October session, SAGE re-affirmed its April 2020 recommendation on the nOPV2 initial use criteria under EUL and made new recommendations related to nOPV2 assessment and safety monitoring to support decision-making for subsequent phases of nOPV2 use.

In principle, SAGE endorsed that nOPV2 becomes the vaccine of choice for response to cVDPV2 outbreaks after the recommendation for EUL is issued and after review of the initial use period is completed and all requirements for use are met.⁵

6 Regulatory oversight

The NRA of Record for this vaccine is Badan-POM in Indonesia⁶ that granted emergency use approval of nOPV2. The authority will oversee the compliance of the manufacturer's facilities to Good Manufacturing Practices and will perform the batch release of each lot supplied to be included in the stockpile.

7 Recommendation

Considering the public health need to stop as soon as possible spreading of cVDPV2, WHO has made, on 13 November 2020, a positive decision on emergency use listing of nOPV2 to allow a time-limited use of the vaccine in a public health emergency situation based on the evaluation of available data. This decision will be reviewed when new data become available.

The listing is subject to the following commitments:

- Development of the product towards prequalification, according to the EUL procedure;
- Additional quality data in accordance with the quality assessment report;
- Full implementation of the RMP which includes the monitoring of the safety, effectiveness and programmatic aspects (see table in section 2.2). The information has to be reported back to WHO;
- Lot to lot consistency study;
- Reports of quality complaints from the field for batches supplied;
- Any change that may have an impact on the quality, safety and/or efficacy of the vaccine or change the basis of the regulatory approval by the NRA. This change has to be approved by Badan POM and WHO;
- Notification of any problems/constraints in production or quality control which might affect the inclusion into the stockpile for emergency use.

⁵ https://www.who.int/news-room/events/detail/2020/10/05/default-calendar/sage_meeting_october_2020

⁶ <https://pom.go.id>