Unit: Technical Assessment Unit

Public assessment report for biological products

(Bivalent Oral Poliomyelitis Vaccine Types 1 and 3)

Administrative information:

Trade name of the medicinal product:	***Bivalent Oral Poliomyelitis Vaccine Types 1 and 3***
INN (or common name) of the active substance(s):	live attenuated poliovirus type 1 and 3 Sabin Strain
Manufacturer of the finished product	PT Bio Farma (Persero) Jalan Pasteur 28 Bandung 40161, Indonesia
Marketing Authorization holder	PT Bio Farma(Persero) (as per the 1st page of the TAR)
Applied Indication(s):	Active immunization of all age groups against poliomyelitis caused by poliovirus types 1 and 3
Pharmaceutical form(s) and strength(s):	Each 0.1 ml dose (2 drops) contains: Live attenuated polio virus of Sabin Strain:(Active ingredient) -Type 1 :106 CCID 50 -Type 3:105.8 CCID 50
Route of administration	Oral
Type of registration (EMA/FDA – Local)	Imported

List of abbreviations

HO: World health organization
Mcg: Micro gram
TRS: Technical Report Series
BoPV: bivalent oral poliovirus vaccine.
CCID: 50% Cell Culture Infectious Dose
mOPV: monovalent oral poliovirus vaccine.
SAE: Serious adverse event
tOPV: trivalent oral poliovirus vaccine

Table of contents

1. General introduction about the product including brief description of the API, its mode of action and indications……....3
2. Quality aspects……..……3
2.1 Introduction…….....3
2.2 Drug Substance (Active ingredient) …….....3
2.3 Drug product……..5
3. Non-clinical aspects…….....7
4. Clinical aspect……7
5. General Conclusion and Recommendations if any……...8

Quality aspects:

Introduction

Bivalent oral poliomyelitis vaccine type 1 & 3 drops is a life-attenuated poliovirus (Sabin Strain) For immunization activities in children from 0 to 5 years of age to intercept types 1 & 3 poliovirus transmission in the remaining polio endemic area
The bivalent oral suspension contains in each 0.1 ml (2 drops); live attenuated Sabin Strain type 1 Not less than 106 CCID 50 type 3 Not less than 105.8 CCID 50
Each dose also contains the following excipient (erythromycin ≤ 2 mcg, kanamycin ≤ 10 mcg & sucrose 35% v/v)

3.2.S Drug Substance (Active ingredient)

- **General information**

Nomenclature: Type 1 & 3 attenuated poliomyelitis virus (Sabin Strain)

Structure: The amino acid sequence of human polio virus consists of 2209 amino acids

General properties: Monovalent bulk of poliomyelitis types 1 & 3 contains Not Less Than 7.5 log 10 CCID 50 /ml of polio virus titer

- **Manufacture, process controls and characterization:**

- Description of Manufacturing Process and Process Controls.

The drug substance is manufactured using a cell culture-based process for the propagation of poliovirus. A flow chart of the manufacturing process and associated quality control steps is provided in MA file

The DS is manufactured through the following steps:

- Cell Culture Preparation
- Cell Expansion
- Virus Inoculation
- Incubation and Monitoring
- Single Harvest Collection
- Quality Control of Single Harvest
- Pooling and Clarification
- Monovalent Bulk Preparation

The steps of each process are described in details in MA file

Control of Materials.

Raw Materials and biological starting materials are listed clearly in the MA File, stating which of them meet the compendial specifications and which meet the in-house specifications

-Controls of Critical Steps and Intermediates.

-Critical process steps and critical process parameters are mentioned in the manufacturing process

-The process controls selected for each critical manufacturing step and the acceptance criteria are provided in the MA file

--They are listed with reference to WHO TRS 904

Process Validation

Process validation has been completed prior to the manufacture of the finished product intended for sale (prospective validation). Where this is not possible, Bio Farma will be validating the processes during routine production (concurrent validation). Bio Farma will also validate some processes in-use for some time (retrospective validation). Validation of the aseptic filling process is periodically performed every six months. The media fill should simulate/mimic the regular production process from formulation, filtration, filling, stoppering, and sealing/capping

Characterization.

-Characterization tests are fully described in the MA file.

-Elucidation of structure and Impurities were fully described in the MA file

Specification

-Clearly stated in MA file and referred to WHO TRS 904

Analytical Procedures.

- Clearly stated in MA file with their detailed SOPs

- Validation reports for all analytical procedures are submitted

Batch analysis

-3 summary protocols for monovalent bulks of poliomylities Type 1 production & testing & 3 summary protocols for monovalent bulks of poliomylities Type 3 production & testing are submitted in MA file**,** The results of all release tests comply with the specifications.

Reference Standards or Materials

- Reference materials used in testing together with supportive information on their standardization to international references are provided in the dossier.

Container closure system

Primary packaging:

-Illustration with inner and outer dimensions are provided in the MA file

Secondary packaging:
- details about inner dimensions, weights, and other characteristics are mentioned in the MA file

Stability of drug substance

--Both real-time and accelerated stability studies for monovalent bulk types 1 and 3 are attached, and hence the shelf life for the drug substance is suggested to be 10 years at -60°C and 3 years at -20°C

-Post-approval stability protocol and stability commitment are also submitted.

3.2.P Drug product:

Description and Composition of the Drug Product:

Description:

The live types 1 & 3 oral polio vaccine is a bivalent vaccine containing a suspension of types 1 & 3 attenuated poliomyelitis virus (Sabin strain) prepared in primary monkey kidney cells. Each dose (2 drops = 0.1 ml) contains not less than 10% infective units of type 1 & 10.5% of type 3.

Sucrose is used as a stabilizer, and the vaccine may contain trace amounts of not more than 2 mcg ,erythromycin & not more than 10 mcg kanamycin

Composition:

Each 0.1 ml dose (2 drops) contains:
Live attenuated polio virus of Sabin Strain:(Active ingredient) Type 1 and Type 3
Sucrose as Stabilizer
Erythromycin as Antibiotic
Kanamycin as Antibiotic

Manufacture of the drug product:

- A flow chart of the manufacturing process and process control is provided in the file , Vaccine packaging and The batch numbering system are described in detail in the MA file

Control of critical steps and intermediates

Sterility testing is performed at the final bulk level.

Process validation and / or evaluation.

Validation report of the manufacturing process to ensure the blending and filling process of the vaccine is submitted.

This validation was conducted on three consecutive batches and the results comply with predetermined specifications.

Product specification:

-The specifications for the routine release of Oral bivalent types 1&3 are descriped in the file and they are according to WHO TRS 904/2002

- Analytical procedures with detailed SOPs are submitted along with their validation reports.

-Excepients are mentioned in the dossier along with their specifications which align with USP 27&USP 27,detailed analytical procedures and their references and validation report are provided also.

Justify the specification if needed.

The specifications are according to WHO TRS904/202

- **Mention the product excipients, role of each.**

-Excipients are listed in the MA file along with the role of each of them

Highlight whether human or animal origin are present and novel excipients as well.

NA

Reference Standards or Materials

No	tests	Reference	Remarks
1	Identity Test	tOPV NR 10/1	In house reference, has been standardized to International Ref.02-306
2	Potency bOPV	tOPV NR 10/1	In house reference, has been standardized to International Ref.02-306

- **Container closure system.**

--Satisfactory details of container closure system have been provided in the MA file
- Details on the vial, rubber stopper, aluminum cap, and dropper have been submitted in detail, including the tests performed on each and its requirements.
- Details on the label with VVM, box of the 20 doses, and box of dropper with the specification of the leaflet have also been submitted

- **Stability of the drug product.**

-Stability summary and conclusion for both real-time and accelerated studies have been submitted.

-The result of the real-time stability shows that the 20-dose bivalent oral polio vaccine is stable for 3 years at -25/-20°C.

-The result of the accelerated stability shows that the 20-dose bivalent oral polio vaccine is stable at 5+ or -3°C for 6 months, 23+ or -2°C for 7 days, and 37+ or -1°C for 12 hours.

-Post-approval stability protocol and stability commitment have also been submitted.

1. **Non –clinical aspect:**

Not applicable since human is the only host for the poliomyelitis virus. Safety and efficacy of the candidate product were evidenced in clinical trials.

2. **Clinical aspect:**

- Clinical Efficacy Conclusion

-The study enrolled 900 infants, with 830 (92%) completing all study procedures. The two-dose cumulative seroconversion rates demonstrated strong immunogenicity for bOPV:

· Type 1: 86% for bOPV vs. 90% for mOPV1 and 63% for tOPV ($p < 0.001$)

· Type 3: 74% for bOPV vs. 87% for mOPV3 and 52% for tOPV ($p < 0.001$)

· Type 2: Comparable between mOPV2 (90%) and tOPV (91%) ($p > 0.05$)

Median antibody titers supported these findings, with bOPV titers significantly higher than tOPV for both Type 1 and Type 3 ($p < 0.001$), though still lower than mOPV1 and mOPV3. These results confirm that bOPV provides superior immunogenicity to tOPV for Types 1 and 3.

Clinical Safety

No serious adverse events (SAEs) were observed within 30 minutes post-vaccination. Eighteen hospitalizations occurred during the follow-up period (birth to 60 days), primarily due to common neonatal conditions such as bronchiolitis, hyperbilirubinemia, and sepsis. One death due to sudden infant death syndrome (SIDS) was reported in the tOPV group.

· Hospitalizations: 8 (mOPV1), 3 (mOPV2), 1 (mOPV3), 4 (tOPV), 1 (bOPV)

No statistically significant differences in SAE rates between groups ($p > 0.05$)

No causal link was established between any vaccine and hospitalization or death

Overall Conclusion:

Biovac's bOPV (Type 1 & 3) demonstrates strong immunogenicity, significantly outperforming tOPV for both targeted serotypes and approaching the efficacy of monovalent formulations. The vaccine was well tolerated, with no vaccine-related serious

adverse events or safety concerns identified. These findings support the use of bOPV as a safe and effective option for routine immunization against poliovirus Types 1 and 3.

3. General Conclusion and Recommendations if any:

Based on the review of CTD modules and other supplementary documents, the product is approved.