

Unit: Technical Assessment Unit

Public assessment report for biological products

*(Poliomyelitis vaccine (Vero cell), Inactivated,
Sabin Strain)*

Administrative information:

Trade name of the medicinal product:	Poliomyelitis vaccine (Vero cell), Inactivated, Sabin Strain
INN (or common name) of the active substance(s):	Poliovirus (Inactivated) Type I (Sabin) 15 DU; Poliovirus (Inactivated) Type II (Sabin) 45 DU; Poliovirus (Inactivated) Type III (Sabin) 45DU;
Manufacturer of the finished product	Beijing Institute of Biological Products Co., Ltd. China.
Marketing Authorization holder	Beijing Institute of Biological Products Co., Ltd., No.6,9 Bo'xing 2nd Road, Economic- Technological Development Area, Beijing-P.R.CHINA.;
Applied Indication(s):	The product is indicated the prevention poliomyelitis caused by type I, type II and type III poliovirus in 2 months and older infants and toddlers
Pharmaceutical form(s) and strength(s):	-Suspension for injection Type I (Sabin) 15 DU Type II (Sabin) 45 DU) Type III (Sabin) 45DU;
Route of administration	Intramuscular
Type of registration (EMA/FDA – Local)	Imported

List of abbreviations

AEs: adverse events
BIBP: Beijing Institute of Biological Products Co., Ltd.
CI: Confidence Interval
D-Ab: Diphtheria-antibody
DTaP: Diphtheria, Tetanus and Acellular Pertussis
FAH-Ab: Filamentous Hemagglutinin Antibody

GLP: Good Laboratory Practice
GMC: geometric mean concentration
GMT: geometric mean titer
ICR mice: Institute of Cancer Research mice (It is a strain of albino mice)
IM: Intramuscular
IPV: inactivated poliovirus vaccine
NAb : Neutralizing Antibody
OPV: Oral poliovirus vaccine
PT-Ab: Pertussis Antibody
SAEs: serious adverse events
sIPV: IPV vaccine with Sabin strain as virus seed
T-Ab: Tetanus Antibody
WHO: World Health Organization
wIPV: IPV vaccine with wild strain as virus seed
BIBP : Beijing institute of biological products
WHO : World Health Organization
DU : D-Antigen Units
sIPV : Sabin inactivated poliovirus vaccine
mL : milliliter

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1. General introduction about the product including brief description of the AI, its mode of action and indications.

- Poliomyelitis is a highly infectious viral disease that is caused when a person is infected by the poliovirus that invades the nervous system. Poliomyelitis can cause paralysis and even death, there is no cure for polio, it can only be prevented by immunization. Humanity is on the verge of one of the greatest public health achievements in history – eradicating polio. However, polio remains endemic in two countries Afghanistan and Pakistan. Until poliovirus transmission is interrupted in these countries; all countries remain at risk of importation of polio, especially vulnerable countries with weak public health and immunization services and

travel or trade links to endemic countries.

2. **Quality aspects:**

2.2.1 Introduction

As mentioned above in the general introduction.

2.2.2 Drug Substance (Active ingredient)

• General information

General Properties:

- -For Poliovirus Seeds

The components of poliovirus seeds are poliovirus (Type I, II, III), magnesium chloride and cell maintenance solution. The appearance of poliovirus seeds is homogeneous, clear, with orange-red colour, no layer divided and no sediment. Stored at - 60 °C.

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

Manufacturer:

Site	Responsibility
Beijing Economic and Technological Development Area, Boxing 2 Road No.6,9. Beijing, P.R. China 100176	Production: The preparation of the final bulk product comprises blending of the active substances, Poliomyelitis (Live) Vaccine Type I Type III (Human Diploid Cell), Oral with the excipients to achieve a homogeneous blend prior to filling into vials. The processing steps include: cell expansion, virus multiplication, harvesting, formulation, filling and packaging

- **Description of Manufacturing Process and Process Controls.**

The manufacturing process for a certain batch of the bulk production is a single continuous process consisting of six stages: cell preparation, virus inoculation & culture and single harvests, ultrafiltration & concentration, purification, inactivation, secondary ultrafiltration & sterilization filtration.

- **Control of Materials.**

The materials used for manufacturing the bulk include the Vero cells and raw materials. The original Vero cell line was obtained from WHO, and the original cell bank, master cell bank, and working cell bank were established by BIBP.

Controls of Critical Steps and Intermediates.

Purified Monovalent Pools:

Three types of the purified monovalent pools were prepared respectively by ultrafiltration & concentration on single harvests of corresponding type of virus Specifications: The specifications of the purified monovalent pools of each type are established according to WHO TRS993, "Recommendation to Assure the Quality, Safety and Efficacy of Poliomyelitis Vaccines (inactivated)" and current Chinese Pharmacopoeia (ChP)

- **Characterization.**

- 1-Elucidation of structure and other characteristics:**

- Structure of poliovirus and study on the stability of poliovirus seed passage, as well as the physical and biological characteristics of bulk is fully described in the file

- Specification**

The specifications of the inactivated purified monovalent bulks of each type virus are established according to WHO TRS993, "Recommendation to Assure the Quality, Safety and Efficacy of Poliomyelitis Vaccines (inactivated)" and current Chinese Pharmacopoeia (ChP)

- **Analytical Procedures.**

The test methods in the specification for the inactivated purified monovalent bulks are either derived from WHO TRS or current Chinese Pharmacopoeia (ChP) or developed in-house by BIBP, and approved by National Medical Products Administration (NMPA). All detailed test procedure can be found in the file

- **Batch analysis.**

-Batch Analysis description of the two Monovalent Bulk and Monovalent Final Bulk are provided and found to be complied with the predefined acceptance criteria.

- **Reference Standards or Materials.**

The information regarding name, lot number, source and related tests, etc. of reference standards for the intermediates and the bulk are shown in quality module

- **Container closure system**

The manufacturing process for a certain batch of the bulk production is a single continuous process consisting of six stages: cell preparation, virus inoculation & culture and single harvests, ultrafiltration & concentration, purification, inactivation, secondary ultrafiltration & sterilization filtration.

- **Stability of drug substance**

Required Shelf Life:

Active substance:

1-For Inactivated Purified monovalent bulks: 12 months after inactivation.

2-For Trivalent final bulk: not more than 72 hours

Suggested Storage Conditions:

Active substance:

For Inactivated Purified monovalent bulks: Store at 2-8°C

2.2.3 Drug product:

- Physicochemical and Biological Properties**

- The appearance: Clear, transparent, object-free and colorless liquid.

- Filling amount: 0.5mL/dose;

- D-antigen content: Type I: 15 DU/dose; Type II: 45 DU/dose; Type III: 45 DU/dose

- pH: 6.8~7.5;

Sterile Products

- **Manufacturing Process Development.**

The final product manufacturing process is consisted of 2 stages: trivalent final bulk formulation and filling/packaging. Main technical parameters in each manufacturing process above were explored and optimized in the study process, and the study results of main technical parameters in each step of process are summarized in the MA file.

- **Container closure system and their compatibility.**

The container closure system for the final product includes primary packaging materials and secondary packaging materials. The primary packaging materials contain 2-mL film-coated middle-borosilicate glass vials, film-coated rubber stoppers and aluminium foil caps. The secondary packaging materials contain vial label, VVM7 label, carbon box, leaflet, and outer paper box. Whether the vaccine product is labeled with VVM7 depends on the specific

- **Control of critical steps and intermediates**

Before filling and packaging, three types of inactivated purified monovalent bulks is mixed with 199 solutions at the determined ratio. The final mixture is the trivalent final bulk, which is the critical intermediate for the final product.

-No excipient of human and animal origin hasn't been included in the final product.

- **Characterization of impurities.**

Sodium hydroxide and 199 solutions are newly additions during the drug product manufacturing process. The table below is to display all potential impurities may exist in final product, including those carried from bulk production stage which is already described in 3.2.S.3.2. The impurities are all under control at different stages of the production, and all meet the specifications. So, the impurities will not affect the product quality.

• **Reference Standards or Materials.**

The information regarding name, lot number, source and related tests, etc. of reference standards for the final bulk and final product are shown in quality Module.

• **Container closure system.**

The container closure system includes primary packaging materials and secondary packaging materials.

The primary packaging materials contain 2-mL film-coated middle-borosilicate glass vials, film-coated rubber stoppers and aluminium foil caps. The secondary packaging materials contain vial label, VVM7, carbon box, leaflet and outer paper box.

• **Stability of the drug product.**

Required Shelf Life:

Finished product: 24 months.

Suggested Storage Conditions:

Finished product:

For Trivalent final bulk: Store at 2-8°C.

For Final Product: Store at 2-8 °C, Protect from Light, don't freeze

3. Non –clinical aspect:

Poliomyelitis Vaccine (Vero Cell) is Inactivated, Sabin Strains of Poliovirus (inactivated): Type I (Sabin): 15DU; Type II (Sabin): 45DU; Type III (Sabin): 45DU 0.5mL/dose/vial for IM Injection. The vaccine produces antibodies in the blood ('humoral' or serum immunity) to type I, II and III poliovirus, and in the event of infection, this protects the individual against polio paralysis by preventing the spread of poliovirus to the nervous system. WHO prequalified it for use on 15/02/2022.

Human is the only host for the poliomyelitis virus. So, the preclinical program produced supportive data and the reliable efficacy and safety will be withdrawn from clinical data. Toxicological safety considerations were conducted in compliance with Good Laboratory Practice (GLP) regulations as claimed by the applicant.

➤ **Pharmacology:**

Immunogenicity data were driven at the level of preclinical, pre-marketing and post-marketing studies. The inactivated monovalent bulk of type I, II and III showed good immunogenicity after immunization of Wistar rats, at pre-clinical stage of sIPV immunogenicity study. At the stage of pre-marketing, there was no significant difference between the results after immunization with sIPV manufactured by BIBP or marketed sIPV in Wistar rats.

The results of post-marketing study showed that the seroconversion of antibody in ICR mice reached 100% after being immunized with sIPV-containing or non-containing phenol red and preservative, and there was no significant difference in NAb GMT against type I, II and III poliovirus after full immunization, which indicated that sIPV had good immunogenicity with or without phenol red and preservative.

Pharmacokinetic studies are normally not required for vaccines.

➤ **Toxicology:**

After single injection of sIPV produced in either the original site, after scaled-up production or in the new site to ICR mice, no toxicity reactions were observed. The maximum tolerated dose was greater than 0.5 mL/dose/animal. Data was consistent with the test results of in-situ control article from original site. Meanwhile, after repeated (once every 3 weeks for 12 weeks, 5 times in total) IM injection of Macaca Fascicularis, no toxicity reaction related to the test article in all groups of animals were observed. The safety dose was 5 doses/animal, which was equivalent to 75 folds of the proposed clinical dose (based on mg/kg body weight). Additionally, there were no irritation changes related

to test articles that were observed at the injection site in both Macaca Fascicularis and New Zealand rabbits. The pathological changes of muscle tissues at all injection sites were considered to be mechanical injuries which recovered on 3 days after the administration. Moreover, active systemic anaphylaxis was negative in guinea pigs. This was consistent with the results of in-situ control article manufactured from the original site.

- **Overall conclusion:** Based on the pharmacology and the toxicology data, sIPV is considered acceptable from the preclinical point of view.

4. Clinical aspect:

BIBP developed an inactivated poliomyelitis vaccine (sIPV), using the polioviruses strains (Sabin strains) with OPV, for which BIBP conducted Phase 1, Phase 2, and Phase 3 in China during 2015 to 2017. After confirming its safety in adult group, 4 years old group and 2 months old group (sIPV01), BIBP had adopted different dosage with low, middle, high to assess the safety and immunogenicity of the vaccine in comparison to the wIPV (Sanofi Pasture) and sIPV (Kunming Institute) (sIPV02). A Phase III clinical trial was conducted by BIBP to assess the safety and immunogenicity in comparison to wIPV (Sanofi Pasture, sIPV03).

A Phase IV clinical study (sIPV04) was initiated by BIBP to assess the safety, immunogenicity and lot-to-lot consistency of sIPV in comparison to a WHO prequalified comparator wIPV (Sanofi Pasture).

Clinical Efficacy: (Clinical Immunogenicity analysis)

- The seropositive rate of neutralizing antibodies against Type I, II and III poliovirus with a titer of $\geq 1:8$ in the low-dosage, middle-dosage and high-dosage groups of the trial vaccine and the wIPV control group was 100%. In the sIPV control group, the seropositive rate of Type I and III neutralizing antibodies was also 100%, while the seropositive rate of Type II antibodies was 98.99%. There was no significant difference between the middle-dose study vaccine group and the wIPV control group. In conclusion, selection of the middle dose as the final vaccine dose.
- Results from immunogenicity showed that primary immunization led to raised GMTs and seropositive rates for all three poliovirus types. Comparison of study group (BIBP-sIPV) and control group (wIPV) matching pairs showed that the BIBP-sIPV performed statistically better than the control in terms of GMTs. Following the primary immunization, the seropositive rates ($>1:8$) for both study and control vaccines were 100% for all three antigen types.
- Before booster immunization at 18 months of age, the neutralizing antibody seropositive rates in the study group and the control group before booster immunization were maintained at a high level of more than 90%, but the antibody GMT significantly decreased to varying degrees.

- After booster immunization at 18 months of age, the neutralizing antibody seropositive rates in the study group and the control group reached 100%, and the antibody GMT in the study group was higher than that in the control group, which was significantly increased comparing that before booster immunization and also much higher than the test results 1 month after primary immunization. The antibody GMT before booster immunization in the study group was higher than that in the control group, resulting in differences between groups in the fold increase.
- The BIBP sIPV has a good lot-to-lot consistency. After the primary immunization, the GMT ratios (95% CI) of type 1, 2, and 3 poliovirus antibodies of any two sIPV batches were between (2/3, 3/2), meeting the requirements of lot-to-lot consistency hypothesis.
- The sIPV-sIPV-bOPV sequential immunization showed superiority compared to sIPV-bOPV- bOPV and IPV-IPV-IPV, and the GMT was the highest for types I and III and the seroconversion rate for type II was close to that of the 3-dose sIPV group (reaching up to 94%).
- The positive rate, seroconversion rate, GMT and increase factor of neutralizing antibodies against poliomyelitis Types I, II and III after immunization showed no statistically significant differences between the Coadministration group and the sIPV administration group; in addition, the seroconversion rate of neutralizing antibodies against poliomyelitis Types I, II and III was non-inferior to that in the sIPV administration group. There were no statistically significant differences in the positive rate and GMC of D-Ab, PT-Ab, FHA-Ab and T-Ab after immunization, the seroconversion rate of D-Ab, FHA-Ab and T-Ab, and the increase factor of D-Ab between the Coadministration group and the DTaP administration group; in addition, the seroconversion rate of D-Ab, FHA-Ab, T-Ab and PT-Ab was non-inferior to that in the DTaP administration group.

Clinical Safety:

- In the primary immunization stage of Phase 3 study, there was no significant difference in the total incidence of AEs between the study group and the control group; the incidence of systemic adverse reactions relevant to trial vaccines in the study group were higher than that in the control group. the most common symptom of adverse reactions was fever.
- The incidence of grade 2 fever in the study group was higher than in the control group (similar to the clinical test results of similar vaccines commercially available in China and the results of the Phase II clinical trial of BIBP-sIPV. However, in the study group the main symptom was transient fever lasting for 1

day; the duration of fever for more than 2 days at grade 2 was significantly lower than that in the control group.

- Local reaction symptoms were mainly tenderness and redness. The incidence of local redness in the study group was higher than in the control group, while the incidence of other adverse reaction symptoms showed difference between groups.
- There was no difference in the incidence of adverse reactions at grade 3 severity between groups; incidence of SAEs also showed no difference between groups. These were irrelevant to trial.

Benefit/ Risk discussion:

BIBP-sIPV has an excellent safety profile, similar to that for the standard reference Sanofi Pasteur Imovax Polio wIPV. There is an excellent immune response to BIBP-sIPV following completion of the primary immunization, similar to that for the standard reference Sanofi Pasteur IMOVAX® Polio IPV. The BIBP-sIPV has a good lot-to-lot consistency for both immunogenicity and safety. Also, could coadministration with DTaP in infants.

In conclusion, the overall benefit/risk of Poliomyelitis Vaccine (Vero Cell), Inactivated, Sabin Strains 0.5 mL is favorable in Active immunization of infants, children and adolescents for the prevention of poliomyelitis caused by poliovirus Types I, II, and III.

5. General Conclusion and Recommendations if any:

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