Unit: Technical Assessment Unit

Public assessment report for biological products

Poliomyelitis vaccine inactivated 1 & 10 dose

Administrative information:

Trade name of the medicinal product:	Poliomyelitis vaccine inactivated 1 & 10 dose
INN (or common name) of the active substance(s):	Inactivated Poliomyelitis virus type 1 (40 D Antigen Units); Inactivated Poliomyelitis virus type 2 (8 D Antigen Units); Inactivated Poliomyelitis virus type 3 (32 D Antigen Units)
Manufacturer of the finished product	Bilthoven Biologicals B.V. Antonie van Leeuwenhoeklaan 9-13 3721 MA Bilthoven The Netherlands
Marketing Authorization holder	Bilthoven Biologicals B.V. Antonie van Leeuwenhoeklaan 9-13 3721 MA Bilthoven The Netherlands
Applied Indication(s):	Active immunization against poliomyelitis
Pharmaceutical form(s) and strength(s):	Suspension for injection
Route of administration	Intra muscular (I.M) \ Subcutaneous (S.C)
Type of registration (EMA/FDA – Local)	Imported

List of abbreviations

IPV Inactivated Poliovirus Vaccine
SAE Serious Adverse Event
AE Adverse Event
CAPA Central Administration of Pharmaceutical Affairs
PSUR Periodic Safety Update Report

DU D-Antigen Units

Table of contents

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

IPV contains monovalent pools of inactivated poliovirus types 1, 2 and 3 as drug substance. The capsid of the inactivated poliovirus consists of virus proteins. After vaccination with IPV, the epitopes of these virus proteins are responsible for an immunological protective response that results in active immunization against poliomyelitis.

Quality aspects:

- **Introduction**

As mentioned in the aforementioned section.

- **Drug Substance (Active ingredient)**

- **General information**

- **Nonproprietary Name:** Poliomyelitis virus type 1, type 2 and type 3, inactivated
- **Structure:** The poliovirus is a small RNA virus. The virus particle consists of a single-stranded, positive-sense RNA genome about 7.500 nucleotides long encapsulated in a thin protein shell. The capsid of the poliovirus consists of 60 copies of four virus proteins, VP1 through VP4, which form a highly structured shell.
- The drug substance is a clear, orange-red blend of polio inactivated monovalent harvests type 1, 2 and 3 in dilution medium.

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

➢ **Manufacturer**:
Bilthoven Biologicals B.V. Antonie van Leeuwenhoeklaan 9-13 3721 MA Bilthoven The Netherlands

➢ **Description of Manufacturing Process and Process Controls**

The manufacturing process consists of the following steps:
- Production of polio inactivated monovalent harvests type 1,2 and 3.
- Production of polio trivalent bulk (400-80-320 DU/ml)

The production process includes culture and harvesting, concentration, purification and inactivation.

➢ **Control of Materials**

- The cell bank used for multiplication of the seed virus is the World Health Organization (WHO) Vero cell bank obtained from the European Collection of Animal Cell Cultures (ECACC lot 10-87, 134th passage) in 1990. This lot is considered as the cell seed for manufacturing of the Master and Working Cell Bank.
- Batch analysis data are included in MA dossier.
- The quality of the components of animal origin (trypsin and donor bovine serum) is covered by specifications, certificates of origin, veterinary certificates and TSE certificates of suitability.

➢ **Controls of Critical Steps and Intermediates**

- The critical controls during the manufacturing of the polio trivalent bulk as well as the polio inactivated monovalent harvests are described in the MA dossier and are complying with the requirements described in Ph. Eur. Monograph Poliomyelitis virus (inactivated).

➢ **Process Validation**

- Validation studies are included in the MA dossier to demonstrate that the drug substance manufacturing process is well under control and leads consistently to a high quality poliomyelitis trivalent bulk (400-80-320 DU/ml) that meets the registered specifications.

➢ **Manufacturing Process Development**

- The production process at the manufacturing site in Bilthoven was based on the process described by Salk. However, the process was later on reconsidered and modified in order to reduce the required number of monkeys and introduce homogenous culture systems for monkey kidney cells (MKC) and polioviruses on microcarriers. The cell substrate for manufacture of IPV then changed from MKC to the Vero cell line established by the WHO.
- Some changes were proposed to the composition of the media used for cell and virus culture and stabilization of the drug substance. Antibiotics were removed from the formulations of all media used in the drug substance manufacturing process.

- **Characterization**
  - Poliovirus is a well-known and well-characterized compound. Results of biochemical and immunochemical testing of monovalent harvests of poliovirus produced on MKC and Vero cells from 1992-2003 are provided.
  - Potential impurities related to the manufacturing process of the drug substance are residual host cell DNA, protein impurities from host cells or the cell culture medium and alive poliovirus. Data has demonstrated that the drug substance manufacturing process is capable of consistently reducing DNA to very low levels and the DNA testing was therefore discontinued.

- **Specification**
  The drug substance is analyzed as per In-house and Ph. Eur. specifications.

- **Analytical Procedures**
  - Detailed analytical procedures are provided in MA file.
  - Validation reports for the D-antigen content and bovine serum albumin test methods are provided in MA file.

- **Batch analysis**
  Analysis results of three representative batches of polio trivalent bulk (400-80-320 DU/ml) are presented. Data demonstrating the production consistency of the monovalent pools of poliovirus used in the three trivalent bulk batches are provided.

- **Reference Standards or Materials**
  - The standard polio reference for D-antigen content determination is polio reference trivalent bulk. The standard preparation is prepared by the Netherlands Vaccine Institute (NVI), the predecessor of Bilthoven Biologicals B.V.

- **Container closure system**
  - Polio trivalent bulk (400-80-320 DU/ml) is packed in 10 L or 20 L hydrolytic type I glass bottles, covered with stainless steel coupling plates and stored until release and further processing.

- **Stability of drug substance**

Based on available stability data**:**

<u>For polio inactivated monovalent harvest:</u>

✓ **Approved Shelf Life:** 36 months (This can be extended with 12 months if the D-antigen content still complies with the release specification).
✓ **Approved Storage Conditions:** 2-8 °C

<u>For polio trivalent bulk:</u>

✓ **Approved Shelf Life:** 36 months
✓ **Approved Storage Conditions:** 2-8 °C

Drug product:

- **Description and Composition of the Drug Product:**
  - Inactivated polio vaccine (IPV) is a sterile suspension for injection, containing inactivated poliovirus type 1, 2 and 3.
  - A monodose vial is filled with 0.6 to 0.7 ml IPV.
  - A multidose vial is filled with 3.1-3.2 ml IPV and contains 5 human doses.

- **Pharmaceutical Development**

  Components of drug product
  - The drug substance of inactivated polio vaccine is a clear, orange-red blend of polio inactivated monovalent harvests type 1, 2 and 3 in dilution medium.
  - Polio trivalent bulk complies with the Ph. Eur. Monograph Poliomyelitis vaccine (inactivated).
  - The excipients are 2-phenoxyethanol, formaldehyde, concentrated dilution fluid, 0.1 M sodium phosphate buffer pH 7 and water for injection.

  Formulation Development

  Polio trivalent bulk has been used for incorporation in Diphtheria-Tetanus-Polio vaccine which is included in the National Immunization Program since 1962. Plain inactivated polio vaccine as drug product has consistently been produced since 1982.

Manufacturing Process Development
- The IPV finished product manufacturing process consists of formulation of the final bulk followed by filling of the final lot into containers under aseptic conditions. Standard pharmaceutical techniques are used during the manufacturing process.

Microbiological Attributes
- 2-Phenoxyethanol and formaldehyde are used as preservatives in the formulation of inactivated polio vaccine (IPV).
- Container closure integrity tests were performed to demonstrate that the vial stopper combination maintains sterility of the vial content under worst case test conditions.

Compatibility
Inactivated polio vaccine (IPV) is a ready-to-use suspension for injection. Compatibility with reconstitution diluents is not applicable.

- **Manufacture of the drug product:**
  Description of manufacturing process and process controls along with manufacturers and responsibilities.
  Manufacturer:
  Bilthoven Biologicals B.V. Antonie van Leeuwenhoeklaan 9-13 3721 MA Bilthoven The Netherlands

  - Description of drug product manufacturing process:
  Polio trivalent bulk (400-80-320 DU/ml) is used as drug substance in the formulation of the final bulk of inactivated polio vaccine (IPV). Multiple trivalent bulk batches may be combined in a single batch of final bulk IPV. The final bulk production process is presented in the MA dossier.
  Final lot production consists of aseptic filling of final bulk in vials followed by labelling and packaging.

  Control of critical steps and intermediates
  - Critical steps are determined according to manufacturing process development of inactivated polio vaccine (IPV). Control of critical steps is stated for production of final bulk IPV, final lot IPV monodose and multidose along with validation reports of the used analytical methods.
  - There is only one process step during drug product manufacture at which intermediate material is tested: storage of final bulk IPV.

  Process validation and / or evaluation
  - Production experience based on the successful manufacture of numerous batches and supported by analytical batch data demonstrate that the drug product manufacturing process is

well under control and leads consistently to a high quality inactivated polio vaccine (IPV) that meets the registered specifications.
- Validation study for waiving of the in vivo rat potency assay was provided.

- **Product specification**
- Specifications of compendial as well as non-compendial excipients used in the drug product manufacturing process are described in MA dossier.
- Analytical procedures for compendial excipients are performed according to the respective pharmacopoeia. Test methods for Phenol Red testing are provided in MA file.
- No novel excipients or excipients of human or animal origin are used.
- Specifications of inactivated polio vaccine (IPV) comply with the Ph. Eur. Monograph Poliomyelitis virus (inactivated).
- Analytical procedures are illustrated in the MA file. Appearance and D-antigen content/identity tests are done according to in-house methods presented in the MA file.
- Validation report for the D-antigen content/identity test method is provided in MA dossier.

- **Reference Standards or Materials**
- The standard polio reference for D-antigen content determination is polio reference trivalent bulk, prepared by the Netherlands Vaccine Institute (NVI), the predecessor of Bilthoven Biologicals B.V.
- **Container closure system**
- Inactivated polio vaccine (IPV) is filled in either 2 ml (monodose) or 4 ml (multidose) vials of colorless siliconized neutral hydrolytic type I glass, closed with a latex-free siliconized bromobutyl rubber stopper and aluminum crimp cap with polypropylene flip-off cap. The color of the caps are red for the monodose and dark blue for the multidose.

- **Stability of the drug product**
Based on available stability data:
<u>For inactivated polio vaccine (IPV) final bulk:</u>
Approved Shelf Life: 12 months
Approved Storage Conditions: 2-8°C

<u>For inactivated polio vaccine (IPV) final lot monodose:</u>
Approved Shelf Life: 36 months
Approved Storage Conditions: 2-8°C

<u>For inactivated polio vaccine (IPV) final lot multidose (5-dose):</u>
Approved Shelf Life: 18 months
Approved Storage Conditions: 2-8°C

3. **Non-clinical aspect:**
The current formulation contains concentrations of 40, 8, 32 DU for Polio type 1, 2, 3 respectively. As human is the only host for the poliomyelitis virus. So, the preclinical program produced supportive data and the reliable efficacy and safety will be concluded from clinical data. Toxicological safety was performed in a repeated dose toxicity study where injection site side effects were only observed, with no generalized systemic effects. No studies have been included regarding reproductive toxicity, embryo-, foetal or neonatal toxicity, mutagenic nor carcinogenic toxicity. However, no adverse events were recorded regarding these toxicities over 50 years of use of IPV. Additionally, Pyrogenicity and endotoxins were never reported, due to strict quality control of every batch.

4. **Clinical aspect:**

- **Clinical Efficacy including Immunogenicity**

The IPV formulation (Salk strains in a 40:8:32 ratio for Types 1, 2, and 3) demonstrated high efficacy when administered as a three-dose primary series followed by a booster. Clinical trials, primarily conducted in pediatric populations, confirmed strong seroconversion rates and protective antibody levels consistent with previously licensed IPV products. Immunogenicity was also observed in newborns vaccinated within 24 hours of birth, indicating effectiveness even in early infancy. Although no specific subpopulation studies were conducted, no differences in seroconversion rates or overall immune response are expected among various demographic or clinical groups that showed from extensive post-marketing data over 15 years in the Netherlands support consistent immune responses across demographic groups.

- **Clinical Safety**

The safety profile of the IPV Vero cell vaccine is well established and favorable. Most adverse events were mild, transient, and localized such as injection-site redness, swelling, and tenderness. Systemic reactions like fever and rash were infrequent and resolved within three days. Serious adverse events (SAEs) were rare, with no vaccine-related SAEs or deaths reported. Booster doses were associated with fewer adverse events than primary doses. Literature suggests mild side effects may be slightly more frequent post-booster. While not all trial-observed reactions were captured in the submission, post-marketing surveillance revealed no new safety concerns. The vaccine is compatible with co-administration and does not impair daily activities.

- **Overall Conclusion**

Bilthoven Biologicals' IPV (Vero cell, Salk strain 40:8:32) demonstrates robust immunogenicity and high clinical efficacy, supported by both trial data and long-term real-world use. Its excellent

safety record, low incidence of adverse events, and suitability for use in pediatric vaccination programs affirm its value in routine immunization. No dose-related toxicity or increased risk in specific populations has been identified, reinforcing its reliability and public health utility.

5. General Conclusion and Recommendations if any:

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