Unit: Technical Assessment Unit

Public assessment report for biological products

Polio Sabin' One and Three (oral)

Administrative information:

Trade name of the medicinal product:	Polio Sabin' One and Three (oral)
INN (or common name) of the active substance(s):	Live attenuated poliovirus Type 1 or 3, oral
Manufacturer of the finished product	GlaxoSmithKline Biologicals SA
Marketing Authorization holder	GlaxoSmithKline Biologicals SA
Applied Indication(s):	Active immunization in all age groups against infection caused by poliomyelitis viruses of Type 1 and 3.
Pharmaceutical form(s) and strength(s):	Virus Polio Type 1, strain LSc, 2ab >10 6 $CCID_{50}$ Virus Polio Type 3, strain Leon 12a, lb >10 5'8 $CCID_{50}$
Route of administration	oral
Type of registration (EMA/FDA – Local)	Imported

List of abbreviations

OPV	Oral Poliomyelitis Virus
MA	Marketing authorization
TSE	Transmissible spongiform encephalopathies
Ph. Eur.	European pharmacopeia
WHO	World Health Organization
HDPE	high-density polyethylene
bOPV	Bivalent Oral Poliomyelitis Vaccine Type 1 and Type 3
CCID50	cell culture infectious dose 50%
cGMP	Current Good Manufacturing Practices
QC	Quality control
AE	adverse event
CI	confidence interval
ATP	according to protocol
GLP	Good Laboratory Practice
ITT	intent to treatment
MOPV	Monovalent Oral Poliomyelitis Vaccine
SAE	serious adverse event

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1. **General introduction about the product including brief description of the AI, its mode of action and indications:**
   -Polio SabinTM One and Three (oral) is a bivalent, live attenuated poliomyelitis virus vaccine of the Sabin strains. The vaccine is presented as a clear liquid, yellowish-to pink suspension for oral administration. Polio SabinTM One and Three (oral) is indicated for active immunization in all age groups against infection caused by poliomyelitis viruses of Type 1 and 3.

2. **Quality aspects:**

2.2.1 Introduction

As mentioned in the aforementioned section.

2.2.2 Drug Substance (Active ingredient)

- **General information**

-The polioviruses are members of the Enterovirus genus and belong to the family of Picornaviridae. Picornavirus virions are non-enveloped ("naked"), have icosahedral symmetry and are 28-30 nm in diameter.
-The poliovirus Type 1 monovalent bulk drug substance is a clarified viral suspension of Type 1 live attenuated poliovirus.
- The poliovirus type 3 monovalent bulk drug substance is a clarified viral suspension of type 3 live attenuated poliovirus.

- **Nomenclature**:

-Common name: Live attenuated poliovirus Type 1 or 3, oral.
- Company name: OPV monovalent bulk Type lor 3.

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

Manufacturer:
GlaxoSmithKline Biologicals SA Parc de la Noire Epine Avenue Fleming, 20 1300 Wavre Belgium is responsible for manufacturing of Drug Substance and QC testing.
GlaxoSmithKline Biologicals SA Rue de l'Institut, 89 1330 Rixensart Belgium is responsible for QC testing Drug Substance.

- **Description of Manufacturing Process and Process Controls.**
  OPV monovalent bulks are produced using the currently approved poliovirus working seed (either Type 1, Type 2 or Type 3).
  The production process of each monovalent virus bulk, along with the in-process control tests, is well represented in the MA file.
  Control of Materials.
  The constituents of media and solutions that were used to prepare OPV are listed in MA file.

All starting materials used to prepare the attenuated poliovirus antigen are compliant with the current TSE note for guidance (EMEA/410/01).

- **Controls of Critical Steps and Intermediates.**
  In-process controls are carried out during the following stages of the OPV monovalent bulk manufacturing process: cell culture preparation, virus inoculation and propagation and clarification of virus pool.
- **Process Validation**
  Validation of the process is demonstrated by the consistency of the potency results measured during production of poliovirus monovalent bulk batches.
- **Manufacturing Process Development.**
  Regarding the OPV primary manufacturing process, in order to increase its manufacturing capacity, the Company implemented a scaled-up process.
  The batch release data demonstrated that the scaled-up process did not affect the quality, the safety and the virus yield of the OPV harvested virus.
    - **Characterization.**

Neurovirulence testing have been performed on poliovirus Type 1 monovalent bulks and Type 3 monovalent bulks, both tests are detailed in the M.A. file.
The potential impurities that could be found in OPV monovalent bulk batches originate from the media and solutions used during bulk production. Regarding the cell debris, these are eliminated by clarification.

- **Specification**

The specifications pertaining to the release testing of OPV monovalent bulk Type 1 and monovalent bulk Type 3 are presented in the MA file and aligned on the current Ph. Eur. Monograph applicable to OPV vaccines.

- **Analytical Procedures.**

Details of the test methods are provided.
Validation data for the tests developed in-house are provided as well as information on the qualification of the Company in-house Quality Control (QC) laboratory for the implementation of the neurovirulence test according to WHO standard operating procedure and Eur.Ph. requirements for this test.

- **Batch analysis.**

The submitted batch analysis results confirm consistency & uniformity of the product and indicate that the process is under control.
Specifications applied to oral poliovirus monovalent bulk comply with the current European Pharmacopoeia monograph 0215 for Poliomyelitis Vaccine (Oral), and with current WHO requirements.

- **Reference Standards or Materials.**

The reference material used for identity testing is a commercial OPV Type 1 monovalent bulk lot released according to the specifications in force at the time of its production.

- **Container closure system**

OPV single harvests and monovalent bulks are stored in polyethylene containers (HDPE) as used for the other bulk vaccines manufactured by the Company.
The compatibility between bulk vaccine and primary container/closure materials is demonstrated through real-time stability studies

- **Stability of drug substance**

Based on WHO plan for OPV bulk stockpiling, a real-time stability study supporting a shelf-life of up to 20-year at -45°C has been initiated.
Regarding the oral poliovirus Type land Type 3 single harvest, the currently approved storage period is of up to 5 years at -45°C.
Complete real-time data are presented in MA file.

2.2.3 Drug product:

- **Description and Composition of the Drug Product:**

Bivalent Oral Poliomyelitis Vaccine (bOPV) is a clear liquid, yellowish-pink suspension for oral administration. The vaccine is presented as 10 or 20-dose preparations, each filled in 3 ml glass vials, stoppered with rubber closures and closed with tear-off aluminum caps.

- Pharmaceutical Development including brief description on Components of drug product.

Bivalent Oral Poliomyelitis Vaccine Type 1 and Type 3 (bOPV), is a stabilized preparation of live, attenuated poliomyelitis viruses of Type 1 and Type 3 derived from the Sabin original strains of poliovirus Type 1 and Type 3.

- Formulation Development

The formulated final bulk vaccine is composed of:
• OPV Type 1 and Type 3 clarified virus pools (monovalent bulks)
• Magnesium chloride / L-Arginine
• Polysorbate 80
• Water for injection

- Overages

An overage of 0.1 log10CCID50 in each poliovirus Type is applied during formulation.

- **Physicochemical and Biological Properties**

Bivalent oral poliomyelitis vaccine (bOPV) is indicated for active immunization in all age groups against infection caused by poliomyelitis viruses of Type 1 and Type 3.
The vaccine will elicit the immune memory and induce the production of antibodies against polioviruses of Type 1 and Type 3.

- Manufacturing Process Development.

The final bulk vaccine is aseptically filled into washed, siliconized, sterile multidose glass vials.
The sterilization methods used for equipment/containers/stoppers are routinely used for the current range of OPV vaccines and for other vaccines produced by the Company.

- Container closure system and their compatibility.
The vaccine is presented in 3 ml glass vials which are sealed with rubber stoppers and aluminium tear-off caps. The aluminium tear-off caps are colored, in order to visually differentiate the products along the production line. The container closure system is identical to that used for other vaccines manufactured by the Company. The dropper to be used to deliver each vaccine dose (2 drops per dose) is provided separately.
The compatibility with the vaccine is supported by the stability studies.
- **Microbiological Attributes.**
Each product in the current OPV vaccines range is a sterile preservative-free vaccine manufactured according to the cGMP rules.
- Compatibility.
Excipients and container/closure systems that are used during manufacture of the vaccine have been shown to be compatible with the oral poliovirus antigens through the stability studies completed with the vaccine.

- **Manufacture of the drug product:**
- Description of manufacturing process and process controls along with manufacturers and responsibilities
Manufacturer:
GlaxoSrnithiKline Biologicals SA Rue de I'Instilut,, 8,Mi 1330 Rixensart 'Belgium is responsible for formulation, filling, QC testing and batch release.
GlaxoSrnithiKline Biologicals SA Parc de la Noire Epine Avenue Fleming, 20 1300 wavre 'Belgium is responsible for formulation, labelling and packaging and QC testing.
- Control of critical steps and intermediates
The manufacturing process is controlled through critical process parameters, in process testing and release testing.
A summary of the critical process parameters and tests for the finished product is provided in the dossier.
- Process validation and / or evaluation.
Compliance with the product specifications retrospectively validates production runs. Batch analysis results are presented in MA file, all the requirements were met, therefore confirming consistency of production.

- **Product specification:**
  - **Description of the product specifications (state the reference whether compendial or in-house) and the excipients (mention excipient specifications) as well.**
    Specifications for testing of the vaccine are based on current WHO and Ph. Eur. requirements for oral poliomyelitis vaccines.
    The excipients present in the vaccine all are compendial (described in the Ph. Eur).
  - **Justify the specification if needed.**
  - **Mention the product excipients, role of each.**

- The excipients present in the vaccine are: magnesium chloride as virus stabilizer, L-arginine as pH stabilizer, polysorbate 80 and water for injection as solvent and all are compendial.
- **Highlight whether human or animal origin are present and novel excipients as well.**
- There is no excipient of human or animal origin in the vaccine.
- **Characterization of impurities**.
  The origin of potential impurities present in the vaccine cannot be attributed to the manufacturing process of the final product. Potential impurities are at the level of the Drug Substance.
  - **Reference Standards or Materials.**

  Reference materials used in Bopv identity and potency tests are described in the M.A. file.
  - **Container closure system.**

  For each packaging component (Glass vial 3 ml, Vial stoppers 13 mm bulk for liquid formulations, Tear-off caps, Vial droppers and Hoods for droppers) the description, tests and acceptance criteria are provided in the M.A. file.
  - **Stability of the drug product.**

  -Based on available stability data,
  approved Shelf Life: 24 months
  approved Storage Conditions: -20°.
  - **Adventitious agents:**

  -**Non-viral adventitious agents**: Detailed information regarding the control of adventitious agents including bacteria, mycoplasma and fungi is provided.
  Materials of ruminant origin used in the manufacture of Drug Product are listed.
  A full risk assessment was carried out and included the traceability of the FBS used.
  -**Viral adventitious agents**: Viral clearance validation studies conducted to support the commercial manufacture.
  These studies include the validation of the scaled-down model and demonstrate the removal and inactivation of relevant and model viruses throughout the process.

3. Non –clinical aspect:

For the Candidate bOPV vaccine, the antigens (Polio type 1 and 3) and the excipients used for the production and formulation process are the same as that used for the trivalent Polio Sabin™ (OPV). Accordingly, the safety and reactogenicity profile of the candidate bOPV vaccine is expected to be the same as that for the trivalent Polio Sabin™ (OPV).
Therefore, it is accepted that no additional nonclinical pharmacology/ immunology or GLP toxicity studies in animals are to be performed.

4. Clinical aspect:

➢ **<u>Clinical Efficacy Conclusion</u>**

The study enrolled 1,000 children, with high completion rates across both the ITT (92.7%) and ATP (90.0%) cohorts. The primary objective demonstrating non-inferiority of immunogenicity of three doses of bOPV compared to monovalent OPV1 (mOPV1) was successfully met for Type 1 poliovirus across both 2-week and 4-week dosing intervals. Seroconversion rates remained above the predefined non-inferiority margin of -10%, confirming comparable immune responses. Additionally, bOPV administered on a 2-week schedule was non-inferior to the 4-week schedule, and similar results were observed for mOPV1 across both intervals. These findings support the immunogenic equivalence of bOPV to mOPV1 under varied dosing schedules.

- **Clinical Safety Conclusion**

  A total of 104 adverse events (AEs) were reported among 100 subjects, including 36 serious adverse events (SAEs). The most frequent mild-to-moderate AEs were acute respiratory infections (65%), while pneumonia accounted for the majority of SAEs (89%). One death occurred, but none of the SAEs were deemed vaccine-related by the Principal Investigator. Overall, the safety profile was acceptable, with no direct safety concerns attributed to the bOPV.

- **Overall Conclusion**

  GSK's bOPV (Sabin Type 1 & 3) demonstrates strong immunogenicity and meets non-inferiority criteria compared to mOPV1 across different dosing schedules. The vaccine is well tolerated, with no vaccine-related serious safety concerns identified. These results support the use of bOPV as a safe and effective option for poliovirus immunization in pediatric populations.

5. General Conclusion and Recommendations if any:

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