Unit: Technical Assessment Unit

Public assessment report for biological products

Pneumovax 23

Administrative information:

Trade name of the medicinal product:	Pneumovax 23 (Pneumococcal Vaccine Polyvalent)
INN (or common name) of the active substance(s):	Mixture of purified capsular polysaccharides from 23 serotypes of Streptococcus pneumoniae (Serotypes: 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, 33F)
Manufacturer of the finished product	Merck Sharp & Dohme Corp., 770 Sumneytown Pike, West Point, PA 19486 - USA
Marketing Authorization holder	Merck Sharp & Dohme Corp., P.O. Box 4, West Point, PA 19486 - USA
Applied Indication(s):	Active immunization for the prevention of pneumococcal disease caused by the 23 serotypes contained in the vaccine
Pharmaceutical form(s) and strength(s):	Solution for injection in pre-filled syringe Each 0.5ml dose of vaccines contains 25 mcg of each Pneumococcal polysaccharide serotype
Route of administration	Intra muscular (I.M) \ Subcutaneous (S.C)
Type of registration (EMA/FDA – Local)	Imported

List of abbreviations

V110: Pneumovax 23
IgG: Immunoglobulin G

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

Pneumovax 23 is a mixture of purified capsular polysaccharides from Streptococcus Pneumonia serotypes 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, 33F. It's found as a clear colorless sterile solution for injection in a prefilled syringe, each of 0.5 ml single dose.

2. Quality aspects:

- **Introduction**

As mentioned in the aforementioned section.

- **Drug Substance (Active ingredient)**

- **General information**

- **Nomenclature:** Vaccinum Pneumococcale Polysaccharidicum (Eur. Ph.)
- **Structure:** The active substances in Pneomococcal Vaccine Polyvalent are the purified capsular polysaccharides from the 23 most prevalent or invasive serotypes of Streptococcus pneumoniae. Each of the capsular polysaccharide types has a unique monomeric repeat unit structure, the repeated units are fully described in the submitted MA dossier.
- The chemical structure and composition of the repeat unit and the polymeric nature of the polysaccharides combine to produce antigenic epitopes.
- Endogenous impurities include residual protein, nucleic acid, and C-polysaccharide. Process impurities include salts and organic solvents. The polysaccharide content of powders is determined using the Quantitative NMR assay.

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

➢ **Manufacturer**:

Merck Sharp & Dohme Corp.,P.O. Box 100, Whitehouse Station, New Jersey, 08889-0100.

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

The manufacturing process consists of the following steps:
- Fermentation
- Inactivation
- Purification (Clarification – Membrane Ultrafiltration – Polishing – Product Recovery)

Full details are described in the submitted MA file.

➢ **Control of Materials**

- A list of raw materials, culture media and buffers used for the manufacture of the 23 serotypes of pneumococcal polysaccharide is provided in the MA file.
- No animal-derived materials are used in the manufacturing process for the master seeds, working seeds, or throughout the fermentation and purification processes.

➢ **Controls of Critical Steps and Intermediates**

- In-process controls were identified for the fermentation process.
- There are no in-process controls upon which purification decisions are based.

➢ **Process Validation**

- Validation studies are included in the MA dossier to demonstrate that the manufacture of all 23 polysaccharide serotypes in the current facility is consistent and well controlled. The validation lots satisfied the acceptance criteria and therefore the process has been validated.

➢ **Manufacturing Process Development**

- Fermentation and purification processes were developed for the manufacture of pneumococcal polysaccharides.
- The manufacturing process provides process consistency and pneumococcal bulk polysaccharide powders have been successfully manufactured by the current process for approximately five years in several markets.

- **Characterization**
  - Structure and schematic structures of each of the pneumococcal polysaccharides are clearly described in the MA file.
  - Availability of the molecular structure of the repeat unit for each serotype also provides information regarding physical properties.
  - Analytical characterization was performed on each of the process validation lots (39 lots) to assess the molecular structure and composition of the repeat unit.
  - Process-related impurities are clearly identified and controlled.

- **Specification**
  The routine tests and specifications for the fermentation broths and pneumococcal polysaccharide bulk powders are provided.

- **Analytical Procedures**
  - Detailed analytical procedures and validation reports are provided in MA file.

- **Batch analysis**
  Batch analyses are provided for the pilot-scale batches used in the manufacture of the “8+15” clinical lot and for each commercial scale validation lot.

- **Reference Standards or Materials**
  - The pneumococcal polysaccharide powder is tested for serological identity using standards that are monovalent solutions produced from 23 process pneumococcal polysaccharides types. The reference standards are qualified prior to use.

- **Container closure system**
  - For long term storage, the pneumococcal final powder is stored as non-sterile material at temperature -70 ± 10ºC in single use centrifuge bottles with polypropylene caps.
  - The final formulated drug product is sterile filtered subsequent to powder manufacture & storage. Sterilized bottles are used for the storage of the final powder.

- **Stability of drug substance**

Based on available stability data**:**

✓ **Approved Shelf Life:** Up to 15 years
✓ **Approved Storage Conditions:** -70 ± 10ºC

Drug product:

- **Description and Composition of the Drug Product:**
  - Pneomococcal Vaccine Polyvalent is a sterile, liquid vaccine for intramuscular or subcutaneous injection.
  - The pneumococcal polyvalent bulk contains a mixture of purified pneumococcal capsular polysaccharides.
  - The vaccine is used directly as supplied. No dilution or reconstitution is necessary.
  - The vaccine is a colorless clear liquid.

- **Pharmaceutical Development**

Components of drug product

- The drug substances in Pneomococcal Vaccine Polyvalent are the purified capsular polysaccharides from the 23 most prevalent or invasive serotypes of Streptococcus pneumoniae.
- The excipients are sodium chloride, liquified phenol and water for injection.

Formulation Development

In order to meet customer demand for Pneumococcal Vaccine Polyvalent in a pre-filled syringe image, a capital project was completed and modifications were made to allow for pre-filled syringe filling of Pneumococcal Vaccine Polyvalent. Following the capital project, the new pre-filled syringe filling process was qualified.

Manufacturing Process Development

- An overview of the manufacturing process development is provided including formulation and filling manufacturing processes and a comparison of the process and equipment used for the pre-filled syringe image.
- The current formulation transfer and storage for the new pre-filled syringe is provided in the MA file.
- Critical Process Parameters (CPP), Critical Quality Attribute (CQA), Key Operating Parameter (KOP), Key Process Attribute (KPA) are well identified.

Microbiological Attributes
- Suitability of the container closure system is demonstrated by compendial testing of the components, leachable and extractable studies and drug product stability studies.

Compatibility
NA

- **Manufacture of the drug product:**
  Description of manufacturing process and process controls along with manufacturers and responsibilities.
  Manufacturer:
  Merck Sharp & Dohme Corp. 770 Sumneytown Pike West Point, Pennsylvania, 19486 USA.

  - Description of drug product manufacturing process:
  The formulation and filling processes are well described and flow diagrams are provided.

  Control of critical steps and intermediates
  - The pre-filled syringe filling process was designed to be robust and has been validated.
  - Process controls for pre-filled syringe filling process are mentioned.

  Process validation and / or evaluation
  - Process performance qualification study is submitted and it was found to meet all pre-determined criteria.
  - The container closure integrity was verified and indicate that the pre-filled syringe to be used provides an adequate barrier for preventing microbial ingress.

- **Product specification**
  - Specifications of excipients used in the drug product manufacturing process are according to USP/Ph. Eur.
  - Analytical procedures for excipients are performed according to the respective pharmacopoeia.
  - Pneumococcal Vaccine Polyvalent release tests and specifications for pre-filled syringe are attached in the MA file.
  - Analytical procedures are described in details in the MA file together with their reference.

- Validation reports are attached in the MA dossier and all the validation methods fulfill the acceptance criteria for linearity, precision accuracy, specificity, reproducibility and LOD.

- **Reference Standards or Materials**
  - The polyvalent reference standard used for routine quantitative and identity testing for both the current and the replacement assay is a 23-valent lot prepared in-house. It is prepared from 23 individual monovalent standards which can be used for identity and specificity testing.
  - Monovalent and polyvalent standard solutions are fully described in the MA file. A representative certificate of analysis from the current polyvalent lot is provided.

- **Container closure system**
  - Pneumococcal Vaccine Polyvalent can be supplied in a pre-filled syringe image.
  - Suitability of the container closure systems is demonstrated by compendial testing of the components, leachable and extractable studies and drug product stability studies that are provided in the file.

- **Stability of the drug product**
  Based on available stability data:
  Approved Shelf Life: 24 months
  Approved Storage Conditions: 2-8°C

Non –clinical aspect:

Although no nonclinical pharmacology or toxicology studies were performed during the development of V110, during product development, commercial vaccine lots formulated using pneumococcal powders met the release criteria of a general safety *in vivo* release test that was performed in mice and guinea pigs. Moreover, the actual usage in humans and the review of adverse experience reporting following the distribution of millions of doses of V110 world-wide demonstrate the overall acceptable safety profile of the vaccine. V110 has proven to be well-tolerated and very safe, as demonstrated by post-marketing surveillance in millions of persons worldwide.

Clinical aspect:

- **Clinical Efficacy and Immunogenicity**

PNEUMOVAX® 23 (Pneumococcal Vaccine Polyvalent, also known as V110) is a 23-valent vaccine designed to protect against invasive and non-invasive pneumococcal diseases. Clinical trials have demonstrated that the vaccine induces strong, type-specific antibody responses against all 23 included pneumococcal serotypes. These antibodies enhance opsonization, phagocytosis, and bacterial killing by leukocytes.

Across multiple studies, PNEUMOVAX® 23 consistently demonstrated significant increases in antibody titers:
- In adults aged 22- 49 years, antibody titers increased 5.4-6.9-fold within 3 weeks of vaccination, with ≥ 2-fold increases in 88- 92% of subjects.
- Comparative trials in Japanese adults showed immunogenicity of the new formulation (V110) to be statistically similar to the current marketed Pneumovax® formulation.
- In Indian adults aged ≥ 50 years, 87- 88% of subjects achieved ≥ 2-fold IgG increases for serotypes 1 and 6B, with mean antibody titers increasing 7-9 fold post-vaccination.
- In older adults (≥ 65 years), both primary vaccination and revaccination induced robust immune responses, although antibody levels were slightly lower in those with high preexisting titers or advanced age.

Overall, PNEUMOVAX® 23 elicits durable, type-specific immune protection across diverse adult populations, confirming its strong immunogenic profile and comparable efficacy across manufacturing processes.

- **Clinical Safety**

Safety assessments across clinical and post-marketing studies confirm that PNEUMOVAX® 23 is well tolerated.
- Local reactions (pain, redness, and swelling at the injection site) were the most common, reported in approximately 60-75% of subjects, usually mild and self-limiting within 3-5 days.
- Systemic events such as headache, malaise, fatigue, and mild fever were infrequent and transient.
- No serious vaccine-related adverse events were reported in the evaluated populations.
- In revaccination studies, older adults (≥ 65 years) had higher rates of local injection-site reactions compared to primary vaccination, but reactions remained within acceptable clinical limits.
- When co-administered with ZOSTAVAX®, PNEUMOVAX® 23 maintained similar pneumococcal antibody responses and safety outcomes, with no significant increase in systemic adverse events.

Cumulative global post-marketing surveillance involving millions of doses further supports an excellent safety profile with no unexpected adverse signals.

- **Overall Conclusion**

Clinical evidence demonstrates that PNEUMOVAX® 23 is safe, immunogenic, and effective in inducing protective antibody responses against pneumococcal infections. The vaccine shows consistent efficacy across age groups and study populations, including revaccinated and high-risk individuals. Its well-established safety record is reinforced by extensive real-world use and regulatory approvals in over fifty countries.

General Conclusion and Recommendations if any:

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