Unit: Technical Assessment Unit

Public assessment report for biological products

Synflorix vaccine (4 doses)

Administrative information:

Trade name of the medicinal product:	Synflorix vaccine (4 doses)
INN (or common name) of the active substance(s):	Each one dose 0.5 ml contains: Pneumococcal polysaccharide serotypes 1 (1µg), 4 (3µg), 5(1µg), 6B (1µg), 7F (1µg), 9V (1µg), 14 (1µg), 18C (3µg), 19F (3µg), 23F (1µg) * adsorbed on aluminum phosphate 0.5 mg, conjugated to protein D (derived from non-typeable Haemophilus infleunzae) carrier protein 9-16 µg, conjugated to tetanus toxoid carrier protein 5-10 µg, conjugated to diphtheria toxoid carrier protein 3-6 µg
Manufacturer of the finished product	GlaxoSmithKline Biologicals S.A., Rue des Aulnois 637, 59230 Saint-Amand-Les-Eaux - France.
Marketing Authorization holder	GlaxoSmithKline Biologicals s.a., Rue de l ' Institut 89, B-1330 Rixensart-Belgium
Applied Indication(s):	1-Active immunization of infants & children from 6 weeks to 2 years of age against disease caused by streptococcus pneumonia serotypes l, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F (including sepsis, meningitis, pneumonia, bacteraemia & acute otitis media) 2-Against acute otitis media caused by non-typeable Haemophilus influenza
Pharmaceutical form(s) and strength(s):	Suspension for injection in vial
Route of administration	I,M
Type of registration (EMA/FDA – Local)	Imported

List of abbreviations:

10Pn-PD-DiT	10-Valent Pneumococcal Protein D Conjugate Vaccine
GMC	Geometric Mean Concentration
CI	Confidence Interval
DTwP-HBV/Hib	Diphtheria-Tetanus-whole-cell Pertussis, Hepatitis B Virus, Haemophilus influenzae type b vaccine
EMA	European Medicines Agency

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

-The applicant introduced the Synflorix vaccine for marketing authorization purpose for the following indication:

1-Active immunization of infants & children from 6 weeks to 2 years of age against disease caused by streptococcus pneumonia serotypes l,4,5,6B,7F,9V,14,18C,19F and 23F (including sepsis, meningitis, pneumonia, bacteraemia & acute otitis media).

2-Against acute otitis media caused by non- typeable Haemophilus influenza

2. Quality aspects:

- Manufacture, process controls and characterization:

- **Manufacturer:**

Serotypes and PD bulk

GlaxoSmithKline Biologicals S.A., Parc de la Noire Epine, Rue Fleming 20, B-1300 Wavre - Belgium.

Serotypes-PD conjugate bulk, serotypes-TT conjugate bulk and serotypes-DT conjugate bulk

GlaxoSmithKline Biologicals S.A., 89, rue de l'Institut, BE-1330 Rixensart - Belgium.

Serotypes, PD bulk, serotypes-PD conjugate bulk, serotypes-TT conjugate bulk and serotypes-DT conjugate bulk

GlaxoSmithKline Biologicals, 10, Tuas South Avenue 8, Singapore 637421 - Singapore.

TT bulk + DT bulk

GlaxoSmithKine Biologicals Kft., Homoki Nagy István utca 1., 2100 Gödöllö - Hungary.

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

-PROTEIN-D

- The purified protein D bulk manufacturing process is divided into 2 stages: fermentation and purification.
- Purification is achieved by two chromatographic steps and one diafiltration step.
-The purified protein D is then sterilized by filtration.
- Production of master and working seed lot and their corresponding in-process control (identity, plasmid retention, microbial purity, antigen identity) and specifications are adequately described in the M.A. dossier.

-Purified diphtheria toxoid:

The manufacturing process of the purified diphtheria toxoid consists of 3 main stages: fermentation, detoxification and purification

Satisfactory description of history of the master and working seeds.

In-process control of master and working seeds (Microbiological purity, Colony morphology, Haemolysis, Purity by microscopic control) *and their corresponding specifications are adequately described.*
In-process tests during the fermentation and detoxification of DT, methods of analysis and acceptance criteria are described satisfactory

-Purified tetanus toxoid
The manufacturing process of the purified tetanus toxoid consists of three main stages: fermentation, detoxification and purification.
Satisfactory description of history of the master and working seeds
Production of master and working seed lot and their corresponding in-process control(identity, plasmid retention, microbial purity, antigen identity) and specifications are adequately described.
In-process tests during the fermentation and detoxification of TT, methods of analysis and acceptance criteria are described satisfactory.

-Purified PS bulk

Fermentation of S. *pneumoniae* bacterial strain of the specific serotype, followed by Inactivation of the broth by phenol, extraction then purification to have purified polysaccharide bulk

Purification of the polysaccharide bulk go through the following steps:
1-One impurities complexation step aimed at eliminating cell debris, nucleic acid and proteins
2-One ultrafiltration step aimed at eliminating small nucleic acids and phenol, concentrating the product
3-One anion exchange chromatography aimed at eliminating CPS (C-polysaccharide)
4-One alcohol precipitation step to precipitate any remaining proteins.
5-One final alcohol precipitation step to precipitate the polysaccharide followed by filtration of the polysaccharide in order to recover the polysaccharide as a pellet and finally vacuum drying.

-Purified PS-carrier protein conjugate bulks
The production process of this PS-PD orPS-TT orPS-DT conjugate done through the following steps:
- Fermentation of *S. pneumoniae* bacterial strain of the specific serotype, followed by Inactivation of the broth by phenol, extraction then purification to have purified polysaccharide bulk
- Fermentation of *E. coli* for the production of recombinant Protein D, followed by purification.
- Fermentation of *Clostridium tetani* for the production of the tetanus toxin followed by detoxification, and then purification of the tetanus toxoid (TT).
- Fermentation of *Corynebacterium diphtheriae* for the production of diphtheria toxoid (DT), followed by DT purification
- Coupling of *S. pneumoniae* polysaccharide serotype I, 4, 5, 6B, 7F, 9V, 14, and 23F to PD
- Serotype 19F is coupled to DT.
-Serotype 18C is coupled to TT.

- Purification and sterile filtration of the conjugate

* Identification of critical steps and intermediates is illustrated in the dossier through the enclosed flow charts

- **Control of Materials**

-Sufficient information on seed bank system used in the DS manufacturing process has been submitted.
-the master and working seed banks were prepared without the use of biologically derived material
-Materials used in the manufacture of DS are tested internally and accepted on the basis of relevant pharmacopeia testing methods & Supplier's Certificate of Analysis with reference to internal specifications.
- IPCs applied during production of bacterial pre master, master, working seed bank and it's validation are included in details.
- Name, production step, analytical reference, method of analysis and specifications which concern the Raw materials used in the preparation of PS bulks, carrier protein bulks and conjugate bulks are adequately illustrated in the dossier.

- **Controls of Critical Steps and Intermediates**

Process parameter and the Critical quality attribute for the manufacturing process stages had been identified. Information on the quality control of the intermediate had been submitted with description of the acceptance criteria of tests and process parameter.

- **Process Validation**

-The DS manufacturing process has been validated adequately. All process parameters were maintained and all CQA were achieved.
- Tests results of critical quality attribute and results for critical parameter attribute in each stage of DS manufacturing had been demonstrated, aligned with the pre-determined acceptance criteria and show production process consistency.
- Satisfactory validation of DS production steps are enclosed in the dossier.
- The validation of the production process is achieved through the demonstration of process consistency for at least 3 consecutive batches show compliance with the pre-established QC standards

- **Control of Drug substance:**

Specification

The release specification for the DS comprises tests for physical characters, identity, purity and impurities, potency, quantity, microbiological attributes and general attributes. The specification has been prepared in line with the requirements of requirements of USP and ICH guidelines.

PD purified bulks

Identity, sterility, protein content, antigenic purity, purity protein D and endotoxin content are the routine QC- release tests.

Proposed specifications have been established based on batch analysis data obtained from the 18 lots that have been produced to date. They are in line with the testing proposed for the control of carrier proteins in the relevant guidelinesز (WHO guideline .Recommendations for production and control of S. *pneumoniae* conjugate vaccines (TRS 927, 2005); and Ph. Eur. guideline. Adsorbed pneumococcal conjugate vaccine}. Satisfactory description and validation of method of analysis.

-Purified diphtheria toxoid

Appearance, identity, sterility, antigen content, antigenic purity, free formaldehyde ,PH, absence of toxin, irreversibility of toxoid, NaCl content are the routine QC-release tests.
The company plans to replace the in-vivo tests for absence of toxin and irreversibility oftoxoid by the in vitro test on Vero cells.
Satisfactory description and validation of the methods of analysis
specification& justification of specification:

Specification are in line with those proposed in the relevant guidelines for the requirements on bulk Diphtheria Toxoid, {WHO (TRS n° 800) and Ph. Eur. (Ph. Eur. 0443)} .

-Purified tetanus toxoid-

-the purified PS bulks tested for Identity S. *pneumoniae* polysaccharide of the specific serotype by ELISA, Molecular size distribution by, Protein content, Nucleic acid content, Phosphorus content, Nitrogen content, acetyl identity, Methylpentose content, uronic acid content, Water content, Alcohol content, Endotoxin content, Core polysaccharide content by P-NMR
Specification, method of analysis, validity criteria of these tests are adequately described in the M.A. file.
-The test results and specifications are calculated with reference to the dry weight of the polysaccharide (% w/w)
-For the quantification of functional group (e.g.methyl pentose, hexosamine, uronic acid), traditional chemical assays with spectrophotometric read-out and according to Ph. Eur. 966 have been used for the QC release of batches from the clinical and the first commercial campaigns.
Justification of specifications: the specification applied to underlined tests are in line with WHOTRS927,EUR Ph966 and EUR Ph monograph2 l 50 For the other tests, release limits have been established based on batch analysis data obtained from development and clinical lots.

TT purified bulk

Appearance, identity, sterility, antigen content, antigenic purity, free formaldehyde ,PH, absence of toxin, irreversibility of toxoid, NaCl content are the routine Q.C.release.
Satisfactory description and validation of the methods of analysis

Specification are in line with those proposed in the relevant guidelines for the requirements on bulk Diphtheria Toxoid, WHO (TRS n° 800) and Ph. Eur. (Ph. Eur. 0443).
Specifications for antigenic content, pH and NaCl content are based on manufacturing experience and are within physiological range (for pH and NaCl content).

-*Purified PS bulk*

The QC-release tests will remain the same with the exception of the S. *pneumoniae* serotype PS identity by ELISA and the functional groups content (uronic acid, hexosamine, methylpentose and O-acetyl) which were done by traditional colorimetric method As of the second commercial campaign and onwards, the Company proposes to use a more direct method by proton nuclear magnetic resonance (H1-NMR for functional groups) for these tests

-*Purified PS-carrier protein conjugate bulks*

the *S.pneumoniae* conjugate bulks are tested for Identity *S.pneumoniae* polysaccharide, Sterility, Protein content, Endotoxin content, PS content, PS to protein ratio, Free PS content, Free carrier content, Molecular size distribution.

Analytical Procedures
All analytical procedures either pharmacopeia or in house developed were described.
Batch analysis
Compliance of all results to the predetermined specification indicates production consistency

- **Container Closure System**

Primary closure system is described together with its specification

- **Stability of DS**

- The stability studies have been completed to support the shelf-life.

- **Drug product**
  - **Description and composition of DP**

- Pneumococcal polysaccharide and *Haemophilus influenzae* proteinD, conjugate vaccine, adsorbed, Synflorix., is composed of 10 active ingredients: the *S. pneumoniae* polysaccharide serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F, each conjugated to a carrier protein (protein D, tetanus toxoid (TT) or diphtheria toxoid (DT)). The vaccine.s code name is IOPn-PD-DiT.the product is a preservative-free liquid vaccine, adjuvanted with aluminium phosphate, and presented as a monodose in a prefilled syringe ready for intramuscular injection. The volume per nominal dose is 0.5ml.
- Pharmaceutical form: suspension for injection
Presentations:
Monodose: 0.5 ml of suspension in a pre-filled syringe
4-doses: 2 ml of suspension in a vial

Storage conditions: at +2°C/+8°C

- **Manufacture of drug product**

- The Finished product is manufactured at

Secondary Packaging & Labeling:
GlaxoSmithKline Biologicals s.a., Parc de la Noire Epine Rue Fleming 20 1300 Wavre – Belgium
GlaxoSmithKline Biologicals s.a., Rue des Aulnois 637, 59730 SAINT-AMAND-LES-EAUX France.

Manufacturer of finished product, Batch control testing & Batch releaser in EU:
Adsorption, Formulation step & batch releaser
GlaxoSmithKline Biologicals s.a., Rue de l ' Institut 89, B-1330 Rixensart-Belgium
Filling step & batch control testing
GlaxoSmithKline Biologicals s.a., Parc de la Noire Epine Rue Fleming, 20 1300 Wavre – Belgium
- All manufacturing steps and release of DP is conducted at this site. Besides the filling and packaging of DP final container vaccine is done their too.

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

- The manufacture of the lOPn-PD-DiT vaccine consists of the following unit steps:
a. preparation of the AlP04 adsorbed conjugate monobulks
b. mixing the AlP04 adsorbed conjugate monobulks with sodium chloride, water for injections and adjustment of the AJ3+ concentration up to 500ìg/vaccine dose (0.5ml)
c. filling into glass vials or glass syringes and closure with rubber stopper
d. labeling and packaging.
Production of the lOPn-PD-DiT vaccine is carried out in aseptic conditions (class 100- grade A).
- The final formulation of the lOPn-PD-DiT vaccine involves mixing of the adsorbed monobulks, which can be stored at 2-8 °C (storage period of 18 to 36 months, depending on serotype) until final formulation of the vaccine. The adsorbed monobulks are therefore considered as *intermediate products.*
Once formulated, the final bulk can be stored at 2-8°C in the formulation tank (maximum storage period of 30 days is planned) until filling
into final containers. Final containers are stored for a maximum of 36 months at 2-8°C

- **Control of critical steps and intermediates**

The critical steps of the DP manufacturing process along with the associated in-process tests and acceptance criteria are listed in the dossier.

- **Control of excipients**

- Sodium chloride and Water for injection are in line with a European pharmacopoeia monograph.
aluminum phosphate is not described in a Pharmacopoeia. Specification, method of analysis and quality controls performed on aluminum phosphate are presented in the M.A. file.
Analytical procedures for testing of the aluminum phosphate, sodium chloride, and water for injections are performed according to Pharmacopoeia requirements and therefore they are considered as validated.

Specifications for aluminum phosphate, sodium chloride, and water for injections have been set based on Pharmacopoeia monographs.
- There is no excipient of human or animal origin in the IOPn-PD-DiT vaccine
- No novel excipient is included in the lOPn-PD-DiT vaccine.

- **Control of drug product**

-The specifications include physical characters, general tests, tests for identity, tests for purity, activity, quantity, tests for contaminants.
- Justification of the DP specifications at the release and during stability studies are provided.

- **Container closure system**

- primary packaging: Unit dose meets specification of EP
- Identity of materials of construction together with their specifications are described

3. Stability

-Approved shelf life for the Finished product: 3 years
-Approved Storage Conditions: Store in a refrigerator (2° - 8°C), Do not freeze & store in the original package in order to protect from light.

3. Non –Clinical aspect & Clinical aspect:

1. Non –clinical aspect:

No new Preclinical studies were needed for registering Synflorix 4-doses as the studies evaluated previously for Synflorix single-dose are sufficient.

4. Clinical aspect:

- **Clinical Efficacy Including Immunogenicity**

The 4-dose schedule of Synflorix (10Pn-PD-DiT) demonstrated non-inferiority compared to the 1-dose presentation in terms of immune response. The antibody geometric mean concentration (GMC) ratios between the 10Pn 4-dose and 10Pn 1-dose groups were the upper limit of the 95% confidence interval of the GMC ratios remained below 2 for each of the 10 pneumococcal serotypes. The first secondary confirmatory objective, assessing the vaccine-related serotype 19A, also confirmed non-inferiority with GMC ratios below 2. The vaccine elicited a strong immune response against all 10 pneumococcal serotypes, related serotypes 6A and 19A, and protein D. The 4-dose presentation was given as a 3-dose primary series (co-administered with DTwP-HBV/Hib at doses 1 and 2) followed by a booster dose.
Pharmacokinetic studies were not applicable, as antigen kinetics do not determine vaccine dosing. Such studies are only required when novel adjuvants or delivery systems are used, in accordance with EMA guidance.

Immune interference evaluation is not required for Synflorix since it contains only one antigen, and cross-reactive immune responses are not expected except in post-marketing safety evaluations.

- **Clinical Safety**

The 4-dose presentation containing preservative was well-tolerated in healthy infants when administered as a 3-dose primary vaccination schedule followed by a booster. Co-administration with DTwP-HBV/Hib did not raise any safety concerns. Adverse events were consistent with the known safety profile of Synflorix.

- **Overall Conclusion**

The 10Pn-PD-DiT (Synflorix) 4-dose presentation with preservative met all primary and secondary objectives. It demonstrated non-inferior immunogenicity compared with the 1-dose formulation, was immunogenic for all targeted serotypes, and was well-tolerated in infants. The formulation did not raise safety concerns and is suitable for routine use as part of a 3-dose primary schedule plus booster, co-administered with DTwP-HBV/Hib.

5. General Conclusion and Recommendations if any:

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