Unit: Technical Assessment Unit

Public assessment report for biological products

*(*Weuphoria®*)*

Administrative information:

Trade name of the medicinal product:	Weuphoria Pre-filled Syringe
INN (or common name) of the active substance(s):	**1.** Pneumococcal polysaccharide serotype (1) 2.6 mcg/0.5ml. **2.** Pneumococcal polysaccharide serotype (14) 2.75 mcg/0.5ml. **3.** Pneumococcal polysaccharide serotype(18C) 3.25 mcg/0.5ml. **4.** Pneumococcal polysaccharide serotype (19A)2.6 mcg/0.5ml. **5.** Pneumococcal polysaccharide serotype(19F) 2.75 mcg/0.5ml. **6.** Pneumococcal polysaccharide serotype(23F) 3 mcg/0.5ml. **7.** Pneumococcal polysaccharide serotype (3) 2.5 mcg/0.5ml. **8.** Pneumococcal polysaccharide serotype (4) 3 mcg/0.5ml. **9.** Pneumococcal polysaccharide serotype (5)2.5 mcg/0.5m. **10.** Pneumococcal polysaccharide serotype(6A)2.5 mcg/0.5ml. **11.** Pneumococcal polysaccharide serotype(7F)2.85 mcg/0.5m. **12.** Pneumococcal polysaccharide serotype(9V)2.5 mcg/0.5ml. **13.** Pneumococcal polysaccharide serotype(6B)6.0 mcg/0.5ml. Bulk Purified Tetanus Toxoid 41-150 mcg/0.5ml.
Manufacturer of the finished product	Yuxi Walvax Biotechnology co. Ltd. No. 83 South Dongfeng Road, High and New Technology Industries Development Zone, Yuxi city, Yunnan Province – CHINA;
Marketing Authorization holder	Yuxi Walvax Biotechnology co. Ltd. No. 83 South Dongfeng Road, High and New Technology Industries Development Zone, Yuxi city, Yunnan Province - CHINA;
Applied Indication(s):	**Active immunization for the prevention of invasive diseases caused by 13 serotypes** (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F) of Streptococcus pneumoniae in infants and children 6 weeks through 5 years of age (before 6th birthday). The use of PCV 13-TI should be determined on the basis of official recommendations taking into consideration the risk of invasive disease and pneumonia in different age groups, underlying comorbidities as well as the variability of serotype epidemiology in different

	geographical areas.
Pharmaceutical form(s) and strength(s):	- Suspension for IM injection - Pneumococcal polysaccharide serotype (1)2.6 mcg/0.5ml ;Pneumococcal polysaccharide serotype(14)2.75 mcg/0.5ml ;Pneumococcal polysaccharide serotype(18C) 3.25 mcg/0.5ml ; Pneumococcal polysaccharide serotype(19A)2.6 mcg/0.5ml ;Pneumococcal polysaccharide serotype(19F) 2.75 mcg/0.5ml ;Pneumococcal polysaccharide serotype(23F) 3 mcg/0.5ml ; Pneumococcal polysaccharide serotype(3) 2.5 mcg/0.5ml ;Pneumococcal polysaccharide serotype(4) 3 mcg/0.5ml ;Pneumococcal polysaccharide serotype(5)2.5 mcg/0.5m; Pneumococcal polysaccharide serotype(6A)2.5 mcg/0.5ml;Pneumococcal polysaccharide serotype(7F)2.85 mcg/0.5ml;Pneumococcal polysaccharide serotype(9V)2.5 mcg/0.5ml; Pneumococcal polysaccharide serotype(6B)6.0 mcg/0.5ml and Bulk Purified Tetanus Toxoid 41-150 mcg/0.5ml
Route of administration	I.M injection
Type of registration (EMA/FDA – Local)	Imported

List of abbreviations

AE	Adverse events
GMC	Geometric Mean Concentration
GMT	geometric mean titer
IgG	Immunoglobulin G
IM	Intramuscular
OPA	Opsonophagocytic Assay
PCV13-TT	13-valent Pneumococcal Polysaccharide Tetanus Toxoid Conjugate Vaccine-Weuphoria
PCV7	7-valent Pneumococcal Polysaccharide Conjugate Vaccine (Prevenar7)
PD	Pharmacodynamics
PFS	Pre-filled syringe
PK	Pharmacokinetic

SAEs	Serious Adverse events
TRS	Technical report series
WHO	World Health Organization

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

- The Applicant has developed the 13-valent Pneumococcal Polysaccharide Conjugate Vaccine (PCV13-TT), for use in infants and young children to prevent pneumococcal disease, caused by the 13 pneumococcal serotypes contained in the vaccine.
- PCV13-TT is a sterile liquid suspension of pneumococcal capsular polysaccharides of serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F, individually conjugated to tetanus toxoid. Phosphate-buffered Saline is also included in the PCV13-TT to improve process control and to provide further pH control following the addition of aluminum phosphate.
- Route of administration: The vaccine should be shaken well immediately prior to use, and be given intramuscularly. The preferred sites for injection are the anterolateral aspect of the thigh in infants and the deltoid muscle of the upper arm in toddlers and children. Each dose (0.5 mL) is to be injected. The vaccine should not be injected in and/or near the areas where there may be a nerve trunk and/or blood vessel.

2. **Quality aspects:**

2.2.1 Introduction

- The Applicant has developed the 13-valent Pneumococcal Polysaccharide Conjugate Vaccine (PCV13-TT), for use in infants and young children to prevent pneumococcal disease, caused by the 13 pneumococcal serotypes contained in the vaccine.
- The individual polysaccharides are extracted from the cultures of Streptococcus pneumoniae, and purified through centrifugation, precipitation, and ultrafiltration.

2.2.2 Drug Substance (Active ingredient)

- **General information**

-The drug substances of 13-valent Pneumococcal Polysaccharide Conjugate Vaccine (PCV13-TT) are capsular polysaccharide antigen of Streptococcus pneumoniae serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F, individually conjugated to tetanus toxoid carrier protein.

- Information on the nomenclature of the drug substance is provided including the name of drug substance, number of serotypes, with reference to the product name, and the carrier protein.

- Detailed description of The Structural Formula of all Pneumococcal Polysaccharide Serotypes is provided. In addition to the Molecular size specification and control parameters for each serotype.

- Physicochemical properties: Each serotype of the bulk conjugate is a sterile, clear, transparent liquid or slightly white floccule after shaking.

- Biological properties: Each serotype of the bulk conjugate can form the obvious precipitation line with the corresponding pneumococcal specific antiserum and tetanus toxoid immune serum.

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

- **Manufacturer Of the active substance**:

Yuxi Walvax Biotechnology co. Ltd. No. 83 South Dongfeng Road, High and New Technology Industries Development Zone, Yuxi city, Yunnan Province - CHINA;

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

- An overview of the manufacturing process of PCV13-TT with a general identification of the key stages of the manufacturing process which are polysaccharide production, bulk conjugates production, and final product production, followed by a detailed explanation of each individual stage. In addition to a clarification of the variations between the different stage classifications.
- Flow Charts for manufacturing process different steps are properly provided, for example; Pneumococcal Strain Recovery, Crude Polysaccharide Preparation, Monovalent Bulk Conjugate…etc.
- Detailed description of each flow chart with adequate information are provided, for example; processing steps, control tests, number of generations and the used reagent.
- Batch and Scale Definition: Definition of Batch Number for seed lot, intermediate products and finished products is provided in tabular form to ensure the traceability of product information.

- **Control of Materials.**

- The materials used in the manufacture of the drug substances were presented in tabular format. These included details related to the production strains—namely, pneumococcal serotypes and Clostridium tetani—such as the source of the strain, its role, the seed bank system, relevant references, suppliers, and storage conditions.
- Flowcharts illustrating the seed bank levels of each strain were provided.
- Culture media preparations, control parameters for the strains, specifications, and test results were

documented.

- Material and Supplier List of 13 Serotypes of Pneumococcal Polysaccharide Bulk Conjugate and Tetanus Toxoid were provided.
- Materials including animal derived substances were identified in MA file.
- Safety certification (TSE free) for animal derived materials was provided.

- **Controls of Critical Steps and Intermediates.**

- Critical Manufacture Steps of all Serotypes of Pneumococcal Polysaccharide and Bulk Conjugate and Purified Liquid of Tetanus Toxoid were identified and listed in a tabular form including process step, related critical steps and Critical Process Parameters with justification of selection of the critical process parameters.
- Intermediates were identified and listed in tabular form including Storage conditions, validity period, Test Items and Specification of Pneumococcal Polysaccharide, Polysaccharide Derivative, Bulk Tetanus Toxoid, Purified Liquid of Tetanus Toxoid, and Monovalent Bulk Conjugate. Moreover, Stability Information of Intermediates were provided including Batch No., Storage condition, Stability storage period, Results, and stability summary showing that all the test results can meet the requirements.

- **Process Validation**

- Brief description of the validation process, purposes and its impact on commercial manufacturing is provided.
- Flowchart of process validation strategy of the Company is provided demonstrating process design, process qualification.
- Detailed description of the concept of validation protocols, including number of consecutive batches, time of completion of the processes including monovalent bulk polysaccharide production, monovalent bulk conjugate production as well as final product production (pre-filled syringe) are provided.
- The provided results successfully demonstrated the effectiveness, consistency, and product and process control of the DS

- **Specification**

- The specifications of all intermediates including pneumococcal polysaccharide, polysaccharide derivatives, bulk tetanus toxoid, purified liquid of tetanus toxoid and monovalent bulk conjugate are provided in tabular form.
- COAs for drug substances including polysaccharide, polysaccharide derivatives, bulk tetanus toxoid, bulk purified tetanus toxoid and bulk conjugate were provided.
- Justification for the drug substance specification were provided in tabular form providing depending on Ph. Eur. 11.0 and WHO TRS 977 Annex 3.

- **Analytical Procedures.**

- All analytical procedures for Polysaccharide Test, derivatives, bulk tetanus toxoid, Purified Liquid of Tetanus Toxoid, Monovalent Bulk Conjugate, were provided involving essential parameters for testing, ensuring validity and test method references.

- Analytical validation information, including experimental data for the analytical procedures used for testing the drug substance were provided.

- **Batch analysis.**

- Description of batches and results of batch analyses for DS were provided. All results were complied with the acceptance criteria.

- **Reference Standards or Materials.**

- List of Reference Standards or Materials Used in Intermediate and Tetanus Toxoid including Manufacturer, unit and storage conditions were provided. COAs for each one was provided.

- **Container closure system**

- Description of containers used for Polysaccharide Bulk Conjugate and Tetanus Toxoid including type, container material and supplier are provided in tabular form. In addition to that, specifications and control testing were provided in the COAs for each type.

- **Stability of drug substance**

Approved Shelf Life:

-13 Serotypes of Pneumococcal Polysaccharide: 36 months

- 13 Serotypes of Pneumococcal Polysaccharide Derivatives: not more than 4 days

- Bulk Tetanus Toxoid: not more than 38 months

- Purified Liquid of Tetanus Toxoid: 4 months

- 13 Serotypes of Bulk Conjugated: 9months

Approved Storage Conditions:

-13 Serotypes of Pneumococcal Polysaccharide: Below -20°C

- 13 Serotypes of Pneumococcal Polysaccharide Derivatives: 2-8°C

- Bulk Tetanus Toxoid: 2-8°C

- Purified Liquid of Tetanus Toxoid: 2-8°C

- 13 Serotypes of Bulk Conjugated: 2-8°C

2.2.3 Drug product:

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

- 13-valent Pneumococcal Polysaccharide Conjugate Vaccine (PCV13-TT) is a sterile liquid suspension of capsular polysaccharide antigens of Streptococcus pneumoniae serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F, with each polysaccharide individually conjugated to Tetanus Toxoid protein. Each 1 mL syringe contains a single 0.5 mL dose of vaccine for intramuscular administration, with no preservative. The vaccine is a homogeneous milky suspension. During storage, a white deposit and clear supernatant might be observed due to adjuvant precipitation. Composition The vaccine contains 2.6 µg/dose of serotype 1 and 19A, 2.5 µg/dose of serotype 3, 5, 6A, 9V, 3.0 µg/dose of serotype 4 and 23F, 6 µg/dose of serotype 6B, 2.85 µg/dose of serotype 7F, 2.75 µg/dose of serotype 14 and 19F, 3.25 µg/dose of serotype

18C. The vaccine is formulated in Phosphate-buffered Saline containing 4.25 mg/dose sodium chloride (NaCl), 44.35 µg/dose sodium dihydrogen phosphate monohydrate ($NaH_2PO_4•H_2O$), 19.0 µg/dose disodium hydrogen phosphate dodecahydrate ($Na_2HPO_4•12H_2O$), and contains 0.5 mg/dose of aluminum phosphate ($AlPO_4$) as an adjuvant.

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

The choice of excipients listed in MA file, their concentration and characteristics that can influence the drug product performance are discussed relative to their respective functions.
- Determination of Adjuvants based on the European Pharmacopoeia (5.0) Pneumococcal polysaccharide conjugate vaccine (adsorption), approval by US FDA for human vaccine
- Specification and dose study were based on pre-clinical study and reviewing other bioequivalence vaccines approved for marketing in the world (PCV7- PCV13 Pfizer) moreover the proposed route of administration was clearly discussed in MA file.

- Manufacturing Process Development.

According to the established formulation process of final bulk, "Yuxi Walvax" used three batches of each serotype of bulk conjugate to continuously prepare three batches of final bulk.

- Container closure system and their compatibility.

Yuxi Walvax conducted compatibility studies of pre-filled syringes manufactured by Shandong Wego Prefills Pharmaceutical Packaging Co., Ltd. and PCV13-TT to investigate the influence of packaging materials on formulation stability and potential migration, as well as safety and applicability in use. studies showed no high-risk leachable substances in PCV13-TT and no destruction to the packaging material, PCV13-TT maintained good quality and safety.

- **Manufacture of the drug product:**

- Description of manufacturing process and process controls along with manufacturers and responsibilities.

Manufacturer of finished product: Yuxi Walvax Biotechnology co. Ltd. No. 83 South Dongfeng Road, High and New Technology Industries Development Zone, Yuxi city, Yunnan Province - CHINA;

- A flow diagram is clearly presented giving the steps of the process and showing where materials enter the process. A narrative description of the manufacturing process, which represents the sequence of steps undertaken are provided.

- Control of critical steps and intermediates

The critical steps and points at which process controls was justified. CPP with justification was submitted in the MA file. Details regarding the aseptic filling of the different DP volume and concentration were presented in this MA file.

- Process validation and / or evaluation.

- The production process of 13-valent Pneumococcal Polysaccharide Conjugate Vaccine (pre-filled syringe) under pre-determined process parameters can continuously manufacture products that comply with Manufacturing and Testing Procedure of 13-valent Pneumococcal Polysaccharide Conjugate Vaccine (Pre-filled syringe), critical process parameters and critical quality attributes are well in control during manufacturing process and the process is stable.

- **Product specification:**

- The specifications and justifications for all tests conducted on the drug product are clearly defined, with appropriate analytical methods and corresponding references provided. Furthermore, all relevant Standard Operating Procedures (SOPs) are included, along with method validation reports. The batch analysis, including batch numbers and test results, is comprehensively documented.
- The excipients used in the vaccine are appropriately tested, with compendial excipients following established guidelines and non-compendial aluminum phosphate validated according to a specific SOP.
- The analytical procedures are compliant with Chinese pharmacopeia, with method validation carried out for the non-compendial aluminum phosphate.

- **Reference Standards or Materials.**

- The reference materials used in analysis of finished product along with COA(s) are provided in MA File.

- **Container closure system.**

- Description of the packaging forms for 13-valent Pneumococcal Polysaccharide Conjugate Vaccine, the packaging materials for direct contact drugs used in pre-filled syringes are pre-filled syringe rubber stoppers and pre-filled syringe tube are provided in MA file.

- **Stability of the drug product.**
  Approved Shelf Life of Finished product: 24 months
  Approved Storage Conditions of Finished product:
  - Transport and store refrigerated at 2 to 8ºC, protect from light
  - DO not freeze & Discard if the vaccine is frozen.
  - The vaccine should be shaken well to obtain a turbid white suspension prior to expelling air from the syringe.

3. Non–clinical aspect

-Weuphoria is a pneumococcal conjugate vaccine (PCV) that contains 13 distinct pneumo-coccal capsular polysaccharides (1,3,4,5,6A,6B,7F,9V,14,18C,19A,19F,23F). Each serotype is individually conjugated to tetanus toxoid (T-T) carrier protein.

-Pneumococcal polysaccharide vaccines specifically elicit a T-cell independent antibody response, which is not very effective in children under the age of two. Covalent conjugation of the pneumococcal polysaccharides to a carrier protein converts the immune response to a T-cell dependent response, which induces antibodies that enhance opsonisation, phagocytosis, and killing of pneumococci with improved immunological memory in pneumococcal vaccine-naïve children, thus priming the immune system for a future natural exposure to S. pneumoniae or a subsequent dose of vaccine.
-Compared to pneumococcal polysaccharide vaccines, pneumococcal conjugated vaccines are more effective in infants and generally elicit a stronger functional antibody response in older adults.

Pharmacology: the results of the studies submitted showed that the 13 types of polysaccharide conjugates had significant animal immunogenicity compared with the corresponding polysaccharides. No interference between the 13 antigens was observed**.**
-The antibody positive conversion rate and GMT level of PCV-TT were similar to those of the same kind of Prevenar 13 available in the market, noting that the GMT value of the 3-dose regimen was higher than that of the 2-dose regimen.

Pharmacokinetics: No PK studies have been conducted for PCV13-TT. This is consistent with the guidelines for vaccines (WHO TRS 927, 2005 and WHO TRS 987, 2014).

Toxicology: The results of the studies submitted showed that the dosage of PCV13-TT was within the safe range after repeated injections. However, the licensed Prevenar, aluminium phosphate adjuvant and PCV13-TT caused irritation to the muscles at the injection site of rabbits and rhesus monkeys, but the irritation could be recovered after the administration ended.
-PCV13-TT also had an aggregation effect on rabbit red blood cells, but no hemolytic reaction was observed.

Overall conclusion: The primary pharmacodynamics studies provided adequate evidence that PCV13-TT induces functional antibody activity, which is expected to protect against pneumococcal infection. Moreover, the toxicological studies demonstrate excellent safety and tolerability.

4. Clinical aspect:

Clinical Overview

- PCV13-TT was evaluated in **Phase I** (N=120; adults, children, infants) and **Phase III** (N=2,760; children 2–71 months).
- Phase I: Open-label, single-center, focused on safety and exploratory immunogenicity.
- Phase III: Randomized, blinded, vaccine-controlled, non-inferiority/superiority design comparing PCV13-TT vs Prevenar 7.

- No PK/PD assessment required per WHO vaccine guidelines.

❖ **Clinical Efficacy & Immunogenicity**

Phase I

- **IgG & OPA responses** increased substantially across all ages.
- **Adults and 2–5 years:** Near-universal IgG positivity post-vaccination (≥96–100% for most serotypes).
- **Infants (2–3 months):** High seroconversion; {IgG fold increases ≥5–10+}; OPA positive rates ≥90% in 3-month group.
- Consistency between IgG and OPA responses >90% for most serotypes.

Phase III

- **Common 7 serotypes:**

Achieved **non-inferiority** vs PCV7 in most age groups and schedules (except isolated gaps in serotype 6B during primary series).

- **Additional 6 serotypes:**

Met **superiority criteria** consistently across age groups.

- **OPA responses:**

- Positive rates >90% for most serotypes in both 2-month and 3-71-month populations.
- Additional serotypes strongly superior to PCV7.

- **Booster dose:**

Showed strong anamnestic response GMCs and seroprotection ≥ primary series → confirms **immunological memory**.

❖ **Clinical Safety**

Phase I

- No SAEs or withdrawals due to AEs.
- Overall, AE rates:

Adults: 80%
Children 2–5 yrs: 53%
Infants 2 months: 66.7%
Infants 3 months: 70%

- **Grade 3 reactions:**

Mostly local in adults (20%); ≤15% in other groups.

- **Most common AEs:** fever, pain, redness, swelling; usually grade 1; occurred mainly 0-7 days.
- No increase in AEs with subsequent doses.

Phase III

- Safety comparable to PCV7 across age groups.
- No new safety signals.
- Expected vaccine reactions (fever, irritability, injection-site reactions) dominated; largely mild/moderate.

❖ **Overall Conclusion**

- PCV13-TT demonstrated:

Strong immunogenicity across all age groups, with both IgG and OPA responses meeting non-inferiority and superiority criteria.

Effective priming and robust booster responses, indicating excellent immunological memory.

Acceptable safety profile, consistent with licensed pneumococcal conjugate vaccines.

- Immunogenicity was particularly strong for the **additional 6 serotypes**, offering broader serotype coverage than PCV7.

❖ **Benefit–Risk Evaluation**

Benefits

- Broad serotype coverage (13 serotypes).
- High seroprotection rates and OPA activity.
- Demonstrated superiority over PCV7 for additional serotypes.
- Strong booster response → long-term protection.
- Effective in infants, toddlers, and older children.

Risks

- Mostly mild-to-moderate local/systemic reactions.
- Limited grade 3 events; no SAEs related to vaccination.
- Reactogenicity comparable to existing conjugate vaccines.

Benefit–Risk Conclusion

The overall benefit-risk profile of PCV13-TT is strongly favorable, supporting its use in infants, children, and adults for prevention of pneumococcal disease.

5. General Conclusion and Recommendations if any:

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