Unit: Technical Assessment Unit

Public assessment report for biological products

Easyfive-TT (10 doses)
Easyfive-TT (Single dose)

Administrative information:

Trade name of the medicinal product:	Easyfive-TT (10 doses) Easyfive-TT (Single dose)
INN (or common name) of the active substance(s):	Each dose of 0.5ml contains: Diphtheria Toxoid 20LF (30 IU) Tetanus Toxoid 7.5LF (60 IU) Inactivated w *B. Pertussis* 12 IOU (4IU) r-HBsAg 10 µg Hib polyssacharide conjugated to Tetanus Toxoid (PRP-TT) 10µg Al+++ (as Aluminium Phosphate Gel) 0.25mg Preservative: Thiomersal 0.025 mg
Manufacturer of the finished product	Panacea Biotec LTD. (vaccine division), Village Malpur, Baddi, Dist. Solan (HP), 173205 - India
Marketing Authorization holder	Panacea Biotec LTD. (vaccine division), Village Malpur, Baddi, Dist. Solan (HP), 173205 - India
Applied Indication(s):	Easyfive-TT vaccine is indicated for primary active immunization against Diphtheria, Tetanus, Pertussis, Hepatitis B and Haemophilus influenzae type b in infants from 6 weeks onwards.
Pharmaceutical form(s) and strength(s):	Suspension for intramuscular injection
Route of administration	I,M
Approved Pack	Carton box containing clear (type I) colorless transparent glass vial, each contains 0.5ml (single dose) or 5ml (10 doses) suspension for injection closed with grey bromobutyl rubber stopper and sealed with flip off aluminum seal.
Registration track	Normal Pathway
Type of registration (EMA/FDA – Local)	Imported

List of abbreviations:

DS	Drug Substance
IPCs	In-Process Controls
CQA	Critical Quality Attributes
DP	Drug Product

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Dossier initial submission and evaluation process:

The file evaluated according to normal track pathway & the company submitted data which are the Quality module-3 from the CTD file.

1. Introduction

- Easyfuve-TT vaccine is a sterile and uniform suspension of DTP, HepB, Hib adsorbed on aluminium phosphate (as adjuvant) and suspension in isotonic sodium chloride solution, thiomersal is added as a preservative
- the final product appears as whitish turbid suspension in which the adjuvant tends to settle down on keeping.

- the product is supplied in two presentations as single dose vial (0.5ml liquid vaccine) and 10 doses vial (5ml liquid vaccine).

- **Quality aspects:**

- General information:

a) Bulk Purified Diphtheria Toxoid: sterile, pale yellow to dark brown color clear liquid with antigenic purityof not less than 1500 Lf/mgPN_2 with shelf life 24 months stored at 2-8^{O}C
b) Bulk Purified Tetanus Toxoid: sterile, light to dark brown color clear liquid with antigenic purityof not less than 1000 Lf/mgPN_2 with shelf life 24 months stored at 2-8^{O}C
c) Whole cell Pertussis Antigen Bulk: Light to dark brown liquid with inactivated cells present in it. the shelf life is 12 months stored at 2-8^{O}C.
d) Hepatits B purified Bulk: Clear Colorless solution with shelf life 24 months stored at 2-8^{O}C
e)Haemophilus Influenza type b Vaccine Bulk Conjugate: Sterile liquid with the PRP-Protein

Manufacture, process controls and characterization:

- **Manufacturer:**

- PT Bio Farma (Persero), Jalan Pasteur 28, Bandung-40161 - Indonesia (Diphtheria, Pertussis and Tetanus)
- PanEra Biotec., Pvt., Ltd., Ambala Chandigarh Highway, Lalru Dist., Ajitgarh (Mohali) of Lunjab state - India (r-HBsAg and Haemophilus influenza type b)

* the manufacturer has been inspected and conforms to the cGMP requirements of the certifying authority.

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

a) Bulk Purified Diphtheria Toxoid:
- the production steps with the WCB (preparation of pre-seed and seed culture), Fermentation, Harvesting, concatenation of toxin and sterile filtration. Then detoxification with formaldehyde. After that purification and addition of amonium sulphate during pericipatation. Finally the filteration and concentrated and purified diphtheria toxoid.

b) Bulk Purified Tetanus Toxoid:
Tetanus Toxoid is manufactured through the fermentation of C. tetani, the toxin being harvested and then detoxified by formaldehyde. The resulting Crude Tetanus Toxoid is further purified through a selective precipitation by ammonium sulphate leading to the Purified Tetanus Toxoid.

c) Whole cell Pertussis Antigen Bulk:
- the production steps are as follows: pre-seed culture - seed culture - fermentation - harvesting - inactivation of pertussis culture - pooling of pertussis bulk antigen

d) Hepatits B purified Bulk:
- the production steps are as follows: pre-seed culture - seed culture - fermentation - harvesting - cell lysis - purification - concentration and filtration

e)Haemophilus Influenza type b Vaccine Bulk Conjugate:
- the production steps are as follows: Production and purification of Crude PRP - Conjugation of PRP-TT
* IPCs for the intermediates of the DS include tests with specified acceptance criteria and tests to monitor the process. All IPCs applied are in compliance with the international pharmacopieans, and with WHO giudelines.
* IPCs during the production process are well defined in the process schemes

- **Control of Materials**

-Sufficient information on seed bank system used in the DS manufacturing process has been submitted.
-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 pre master, master, working seed bank and it's validation are included in details.

- **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.

- **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 pharmacopiean, WHO and ICH guidelines.
Analytical Procedures
All analytical procedures either pharmacopeia or in house developed were described. The analytical procedures that need validation are clearly mentioned and well described.
Validation of analytical procedures
Analytical procedures are validated by demonstrating that the performance characteristics of the method meet the requirements of the intended analytical applications. The validity of an analytical method is established by laboratory studies. Validation reports are fully described in the submitted dossier.
Batch analysis

The company submitted the summary protocol for the batches under analysis and the submitted data shows production consistency.

- **Container Closure System**

Primary closure system is described together with its specification

- **Stability of DS**

- The results of stability studies for three production batches of each DS component support the claimed shelf-life when stored in its proper container.

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

- The DP is presented as whitish turbid suspension in which the adjuvant tends to settle down on keeping.
- the product is filled into clear (type I) colorless transparent glass vial, each contains 0.5ml (single dose) or 5ml (10 doses) suspension for injection closed with grey bromobutyl rubber stopper and sealed with flip off aluminum seal. The product is supplied in two presentations: single dose 0.5ml vial or 10 doses 5ml vial

  - **Manufacture of drug product**

- The Finished product is manufactured at Panacea Biotec LTD. (vaccine division), Village Malpur, Baddi, Dist. Solan (HP), 173205 - India
- 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**

- manufacturing process is simply divided into two processes: formulation or blending process and filling of the vial process.

- **Control of critical steps and intermediates**

There is only one intermediate in the manufacturing process before filling, which is the blended bulk
The critical steps of the DP manufacturing process along with the associated in-process tests and acceptance criteria are listed in the dossier.

- **Process validation and / or evaluation**

- process and cleaning validation: carried out in three manufacturing consistency batches and the study reports enclosed
- Media fill simulation study: the aseptic media fill simulation study report for blending and filling process are enclosed

- **Control of excipients**

- excipients and their use during the DP manufacturing are mentioned. All excipients comply with BP/IP except aluminium phosphate gel and Thiomersal are in-house.
- no excipient of human or animal origin are used during DP manufacture. No novel excipients were used

- **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.
- the analytical procedures, principles and validity criteria used for control testing of the vaccine were provided.

- **Container closure system**

- the product is filled into clear (type I) colorless transparent glass vial, each contains 0.5ml (single dose) or 5ml (10 doses) suspension for injection closed with grey bromobutyl rubber stopper and sealed with flip off aluminum seal. The product is supplied in two presentations: single dose 0.5ml vial or 10 doses 5ml vial
- Identity of materials of construction together with their specifications are described

- **Stability**

-Approved shelf life for the Finished product: 3 years
-Approved Storage Conditions:
- Store at temperature 2-8ºC,
- after opening: store at temperature 2-8 ºC for 28 days
- don't freeze and discard if the vaccine has been frozen
- shake well before use

- **Non –Clinical aspect & Clinical aspect:**
  - **Non –clinical aspect:**

Easyfive TT vaccine showed immunological response to all five antigens (DTwP- HePB- HIB-TT) in both sexes on day 28, 50 and 64 when given to mice at 20 µg/ml.
HIB-TT conjugate and Easyfive TT Vaccines were well tolerated after either single or repeated administration in mice and rabbits up to the dose-Level of 0.5 mL/rabbit and 0.1mL/mice.

  - **Clinical aspect:**

Clinical Efficacy:

A Phase III, "Panbio/CR/0932004/CT" demonstrated that the Easy five vaccine was either non-inferior or superior to DTwP-HepB/Hib across all evaluated antigens. Easyfive achieved higher seroprotection rates for hepatitis B (97.3% vs. 93.7%) and diphtheria (97.7% vs. 94.9%), and comparable rates for tetanus (99% vs. 99.3%), confirming non-inferiority. Although the pertussis IgG response rate was slightly lower for Easyfive (30.7% vs. 35.2%), the post-vaccination geometric mean titers (GMTs) were similar, supporting non-inferiority. For anti-PT, Easyfive showed a higher response rate (35% vs. 32.1%). GMT analysis further confirmed Easyfive's superiority for hepatitis B, diphtheria, and tetanus, and non-inferiority for pertussis and PRP antigens. Overall, the study supports Easyfive as a safe and effective alternative to DTwP-HepB/Hib.

Clinical Safety:

The safety profile of Easyfive was generally comparable to that of DTwP-HepB/Hib, with similar rates of both solicited and unsolicited adverse events (AEs). Local symptoms such as redness and hardness were slightly more frequent in the DTwP-HepB/Hib group after the first dose, while swelling was more common in the Easy five group after the second dose. Swelling was the most frequent local AE in both groups.

General symptoms, including "warm to touch," occurred at similar rates with no significant differences. One serious local AE (bleeding at the injection site) occurred in the DTwP-HepB/Hib group, but no general symptoms were classified as serious. Most AEs were mild and considered related to the vaccines. Unsolicited AEs were rare and similar between groups, with injection site swelling being the most common. Four unsolicited serious AEs were reported, one in the Easyfive group and three in the DTwP-HepB/Hib group, all with doubtful relation to the vaccine. No deaths occurred, and all affected participants recovered fully without study withdrawal.

Overall conclusion:

Finally, the submitted data supports Easyfive as a safe and effective alternative to DTwP-HepB/Hib.

General Conclusion and Recommendations if any:

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