Unit: Technical Assessment Unit

Public assessment report for biological products

Tripvac

Administrative information:

Trade name of the medicinal product:	Tripvac
INN (or common name) of the active substance(s):	**Each dose 0.5 ml contains:** • Diphtheria toxoid: 25 Lf (≥ 30 IU) • Tetanus toxoid: 5.5 Lf (≥ 60 IU) • B. Pertussis 16 IOU (≥ 4.0IU) • Adsorbed on Aluminum phosphate (AlPO4) ≥ 1.5 mg.
Manufacturer of the finished product	Biological E. Limited, Plot No. 1, Biotech Park, Phase-II, Kolthur Village, Shameerpet Mandal, Medchal-Malkajgiri District-500 078, Telangana – India.
Marketing Authorization holder	• **Diphtheria toxoid and whole cell pertussis:** Biological E. limited, Plot No.1, S.P. Biotechnology Park, Phase-II, Kolthur Village, Shameerpet Mandal, Medchal-Malkajgiri District-500 078, Telangana-India. • **Tetanus Toxoid:** Biological E. limited,7-4-114, Gaganpahad, Rajendra Nagar Mandal, Ranga Reddy District, Telangana 501 323-India.
Applied Indication(s):	Indicated for active immunization against tetanus, diphtheria and pertussis in infants from 6 weeks of age.
Pharmaceutical form(s) and strength(s):	Suspension for injection
Route of administration	Intramuscular Injection (IM)
Type of registration (EMA/FDA – Local)	Imported

List of abbreviations

1. AI – Active Ingredient

2. $AlPO_4$ – Aluminium Phosphate
3. BDT – Bulk Diphtheria Toxoid
4. BDPT – Bulk purified Diphtheria Toxoid
5. B. pertussis – Bordetella pertussis
6. BE – Biological E. Limited
7. BPTT – Bulk Purified Tetanus Toxoid
8. CDL – Central Drugs Laboratory
9. CoA / CoAs – Certificate(s) of Analysis
10. DTwP – Diphtheria, Tetanus and whole-cell Pertussis vaccine
11. IPC / IPCs – In-Process Control(s)
12. IOU – International Opacity Unit
13. IU – International Unit
14. Lf – Limes flocculation unit
15. MA file – Marketing Authorization file
16. NIBSC – National Institute for Biological Standards and Control
17. NRA – National Regulatory Authority
18. PP – Polypropylene
19. SDS-PAGE – Sodium Dodecyl Sulfate–Polyacrylamide Gel Electrophoresis
20. SE-HPLC – Size-Exclusion High Performance Liquid Chromatography
21. SOP – Standard Operating Procedure
22. TRS – Technical Report Series (WHO)
23. USP – United States Pharmacopeia
24. wPAB – Whole-cell Pertussis Antigen Bulk
25. WCB – Working Cell Bank
26. WHO – World Health Organization
27. BE DTwP: (Biological E. Limited) Diphtheria, Tetanus & pertussis Vaccine {Adsorbed).
28. GMTs: Geometric Mean Titres

Table of contents

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

Tripvac is a combined vaccine used for the active immunization of infants from 6 weeks of age against diphtheria, tetanus, and pertussis. It is supplied as a sterile suspension for intramuscular injection in multi-dose vials.

Each dose (0.5 mL) of Diphtheria, Tetanus and Pertussis Vaccine (Adsorbed) contains purified diphtheria, tetanus toxoids and inactivated whooping cough organisms. The vaccine is adsorbed onto Aluminium Phosphate as adjuvant and thiomersal is used as a preservative. The vaccine has the appearance of a whitish turbid suspension.

The vaccine complies with the recommendations of the World Health Organization (WHO TRS 980) and the Indian Pharmacopoeia. It has been WHO-prequalified since July 2014.

2. Quality aspects:

2.2.1 Introduction.

Mentioned above in the general information.

2.2.2 Drug Substance (Active ingredient):

Diphtheria toxoid, Tetanus toxoid, and B. Pertussis.

- **General information**
  - **Diphtheria toxoid**

    Bulk purified diphtheria toxoid is a sterile, pale-yellow to yellowish clear liquid. It has an antigenic purity of not less than 1000 Lf/mgPN_2.

    International nonproprietary Name: Purified Diphtheria Toxoid European
  - **Tetanus toxoid**

    Bulk purified tetanus toxoid is a sterile, light to dark brown clear liquid. It is prepared from the tetanus toxin produced by Clostridium tetani grown in Mueller & Miller medium. The antigenic purity is not less than 1500 Lf/mgPN_2.

    International nonproprietary name: Bulk Purified Tetanus Toxoid
  - **Bordetella pertussis (whole-cell antigen)**

    The whole-cell pertussis antigen is a light to dark brown liquid containing inactivated cells. The bulk pertussis antigen is prepared from a mixture of inactivated cultures of Bordetella pertussis strains 134 and 509.

International nonproprietary name: Whole cell Pertussis antigen bulk

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

The active substances (diphtheria toxoid, tetanus toxoid, and Bordetella pertussis) are manufactured by Biological E. Limited, Plot No. 1, Biotech Park, Phase II, Kolthur Village, Shameerpet Mandal, Medchal-Malkajgiri District, Telangana, India.

- **Diphtheria Toxoid**

Manufacturing process:

Production steps involve seed preparation, fermentation, harvesting, detoxification, purification, and formulation, with in-process controls at each critical step. Full details are available in the MA file.

- **Tetanus Toxoid**

Manufacturing process:

The process includes seed inoculation, subculture, fermentation, detoxification, purification, diafiltration, sterile filtration, and release of purified bulk tetanus toxoid, with in-process controls at each critical step. Full details are available in the MA file.

- **Bordetella pertussis (Whole-cell Antigen)**

Manufacturing process:

Production starts with WCB and seed preparation, followed by fermentation, harvesting, collection of cell biomass, inactivation, pooling), with in-process controls at each critical step. Full details are available in the MA file.

All starting materials used in the production of DT, TT, and B, pertussis is controlled according to relevant pharmacopeial standards to make sure they are safe and effective. Acceptance criteria for each critical step and intermediate such as step are proposed and justified.

Validation was conducted on three consecutive batches for DT, TT, and B, pertussis. All results met the acceptance criteria Full validation protocol and reports are available in the MA file.

The manufacturing process of DT, TT, and B, pertussis was developed and optimized. The development history is fully described in the MA file. The history of process development is fully described in the MA file. All the process changes were approved by the National regulatory authority of India and WHO.

- **Characterization.**
  - **Diphtheria toxoid**

The toxin is detoxified by formaldehyde treatment. Bulk toxoid is characterized using physicochemical and biological tests, confirming identity, safety, and stability in line with WHO requirements.

- **Tetanus toxoid**

  The toxin is detoxified by formaldehyde to yield a non-toxic but immunogenic toxoid. Characterization confirms purity, consistency, and compliance with WHO standards.

- **Bordetella pertussis (whole-cell antigen)**

  Produced from inactivated cultures of strains 134 and 509 to ensure the presence of agglutinogens 1, 2, and 3. Characterization includes physicochemical analysis and biological testing, confirming immunogenicity and safety.

- **Specification**
  - **Diphtheria toxoid**

    The release specifications include description, sterility, specific toxicity, irreversibility, antigenic purity, and Lf determination. All requirements comply with WHO TRS (Annex 4).

    Tetanus toxoid

    Specifications include description, sterility, specific toxicity, irreversibility, antigenic purity, and Lf determination. All requirements comply with British Pharmacopoeia and WHO TRS 980.
  - **Bordetella pertussis (whole-cell antigen)**

    Specifications include description, sterility, specific toxicity, potency, agglutinogen content, opacity, and pH. Requirements are consistent with WHO TRS 941.

- **Analytical Procedures.**

  Full validated analytical procedures for testing diphtheria toxoid, tetanus toxoid, and Bordetella pertussis are provided in the MA file to ensure their quality and compliance with specifications.

- **Batch analysis.**

  Three consecutive batches of diphtheria toxoid, tetanus toxoid, and pertussis antigen were analyzed. All quality control results complied with the release specifications, confirming consistency and reproducibility of the manufacturing process.

- **Reference Standards or Materials.**
  - For **diphtheria** and **tetanus toxoids**, in-house working standards of antitoxins are established, qualified against national or international reference standards, and used for Lf estimation.
  - For **pertussis**, the reference standard for potency and opacity is provided by the National Testing Laboratory of India (CDL – Kasauli).

- **Container closure system**

- **Diphtheria toxoid:** Stored in borosilicate glass bottles with polypropylene closures.
- **Tetanus toxoid:** Stored in polypropylene bottles at 2–8 °C.
- **Pertussis antigen:** Stored in stainless steel vessels or borosilicate glass bottles with polypropylene closures.

All container closure components are compliant and described in the MA file.

- **Stability of drug substance**
  - For **diphtheria** and **tetanus toxoids**, shelf life is 36 months.
  - For **pertussis**, shelf life is 18 months.

2.2.3 Drug product:

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

The Diphtheria, Tetanus and Pertussis Vaccine (Adsorbed) is a sterile whitish, turbid suspension containing purified diphtheria and tetanus toxoids, together with inactivated Bordetella pertussis organisms. The antigens are adsorbed onto aluminium phosphate as an adjuvant, and thiomersal (0.01% w/v) is included as a preservative. The vaccine complies with WHO requirements.

It is supplied in 5 mL multi-dose glass vials, each containing ten (10) doses for intramuscular administration.

- **Compatibility:** No separate compatibility studies were performed, but compatibility with excipients and the container closure system was confirmed through stability studies.

- **Manufacture of the drug product:**
  - **Description of manufacturing process and process controls along with manufacturers and responsibilities.**

    The DTwP vaccine is manufactured, packaged, and released by Biological E. Limited, Plot No. 1, Biotech Park, Phase-II, Kolthur Village, Shameerpet Mandal, Medchal-Malkajgiri District-500 078, Telangana – India

    Full details and description of the process are provided in the MA file. Each step of the process is controlled through defined in-process controls (IPCs).
  - **Process validation and / or evaluation.**

    All parameters and final bulk results met the acceptance criteria.

- **Product specification:**

Release specifications for the Finished Product comply with USP, I.P, B.P, and WHO TRS specifications. Detailed SOPs, validation protocols, and reports for in-house methods are available in the MA file and CoAs confirm compliance with the stated specifications.

All excipients are Pharmacopoeial grade and comply with the respective pharmacopoeia. No excipients are of human or animal origin, and no novel excipients are included.in the formulation of Diphtheria, Tetanus and Pertussis Vaccine (Adsorbed).

- **Reference Standards or Materials.**
  In-house reference standards for diphtheria and tetanus toxoids are established and calibrated against the NIBSC standards.
  The current reference standard for pertussis potency testing is provided by the National Testing Laboratory of India (CDL – Kasauli).

- **Container closure system.**
  The DTwP vaccine is filled in USP Type I glass vials, sealed with bromobutyl rubber stoppers, and secured with aluminium seals. Full specifications are available in the MA file.

- **Stability of the drug product.**
  - Shelf life (unopened) is 24 months.
  - Shelf life (after first opening) is 28 days, when stored at 2–8 °C.
  - Do not freeze; discard if frozen.
  - Shake well before use.
  - Protect from light.

- **Adventitious agents.** Not applicable.

3. Non – clinical aspect:

There is no pre-clinical data specific for BE DTwP Vaccine. In addition, the submitted data illustrated that there is "no single dose toxicity studies & repeat dose toxicity studies" were conducted on Diphtheria, Tetanus & pertussis Vaccine {Adsorbed} (DTwP vaccine) by the applicant, Biological E. The vaccine is not a novel vaccine and is being used in the world from many years. Moreover, Biological E. has conducted pre-clinical studies on other combination vaccines containing same antigen content of Diphtheria, Tetanus & pertussis.

4. Clinical aspect:

Overview of Efficacy:

Though there were no clinical trials conducted on the DTwP Vaccine, BE has conducted Phase-III and IV clinical trials on other combination vaccines like DTwP-rHepB-Hib Vaccine (Fully Liquid

Pentavalent Vaccine) and DTwP-rHepB+Hib Vaccine (Reconstituted Pentavalent Vaccine), which contain the same or similar contents of Diphtheria, Tetanus, and Pertussis components.These two fully liquid and reconstituted pentavalent vaccines are licensed in India and are pre-qualified by WHO also.

Apart from this, millions of doses of these two vaccines are being supplied within India and outside India, which proved the safety and efficacy of the vaccine. Moreover, the DTwP Vaccine licensed and distributed in India for several years has also proved safety and efficacy of the vaccine.

-Immunogenicity:

Pentavalent DTwP-rHepB-HIB vaccine consistently demonstrated immunogenicity comparable and non-inferior to licensed comparator vaccines, including those from Shantha and GSK, across multiple Phase III and Phase IV studies.

The vaccine elicited high seroprotection rates against all five antigens diphtheria, tetanus, pertussis, hepatitis B, and Haemophilus influenzae type b by Day 84 post-vaccination. Geometric Mean Titres (GMTs) were similar between BE's vaccine and the control groups, with some minor statistical differences observed that were not deemed clinically significant. Subjects showed significant antibody responses, including 4-fold rises in antibody titres for most antigens, while occasional differences, such as for tetanus and Hib, were attributed to maternal antibody interference rather than vaccine performance. The vaccine consistently met the primary immunogenicity non-inferiority criteria, supporting its effectiveness in inducing protective immunity in the target infant and paediatric populations.

Safety Summary

The safety profile of BE's pentavalent DTwP-rHepB-HIB vaccine was favorable and consistent across controlled clinical trials and post-licensure observational studies. Adverse event frequencies were comparable between BE's vaccine and licensed comparators, with the majority of vaccine-related events classified as mild. Importantly, no vaccine-related serious adverse events or unexpected safety concerns were reported. Both local and systemic adverse events were similar across different vaccine lots and study populations, demonstrating reproducible safety and tolerability. Monitoring of vital signs and other clinical safety parameters showed no significant issues. Overall, the vaccine was well tolerated and deemed safe for routine immunization in infants and children.

5. General Conclusion and Recommendations if any:

Compared to benefits, risk associated with DTwP Vaccination, includes local reactions such as pain at injection site, redness, warmth, oedema, induration with or without tenderness, as well as urticaria and rash possible.

Systemic reactions such as fever, restlessness, fretfulness, poor feeding, vomiting and diarrhea may appear in a few infants. Some data suggests that febrile reactions are more likely to occur in those who have experienced such responses after prior doses. Fatigue, malaise, headache, arthralgia, myalgia, urticaria and anaphylaxis have been reported in rare cases. Infants participating in the study are expected to be protected against Diphtheria, Tetanus and Pertussis diseases through this vaccination.