Unit: Technical Assessment Unit

Public assessment report for biological products

(BETD vacine)

Administrative information:

Trade name of the medicinal product:	BETD vacsine
INN (or common name) of the active substance(s):	Diphtheria Toxoid and Tetanus toxoid
Manufacturer of the finished product	Biological E. Limited, Plot No. 1, S.P. Biotechnology Park, Phase-II, Kolthur Village, Shameerpet ,Mandal Medchal-Malkajgiri District 500 078, Telangana - India
Marketing Authorization holder	Biological E. Limited. Plot No. 1, S.P., Biotechnology Park, Phase-11, Kolthur Village, Shameerpet , Ranga Reddy District-500 078, Telangana, India
Applied Indication(s):	Active immunization of children 7 years of age or older, and adults, against tetanus and diphtheria
Pharmaceutical form(s) and strength(s):	0.5 ml. for intramuscular injection (Vial of 10 doses)
Route of administration	Intramuscular
Type of registration (EMA/FDA – Local)	Imported

List of abbreviations

BETD vaccine: Biological E.'s Diphtheria and Tetanus Vaccine (Adsorbed)
BE: Biological E. limited
Td: Diphtheria, Tetanus
No:Number
LF : Limit of Flocculation
IU: International unit
B.No: Batch No
IPCs:In process controls
WHO:World Health Organization
DTwP-rHepB-Hib: Diphtheria, Tetanus, Pertussis (whole cell), Hepatitis B, Haemophilus influenzae type 'b' vaccine
IgG: Immunoglobulin G
NOAEL: No observable adverse effect level
SHD: Single Human Dose equivalent
WHO: World Health Organization

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1. **Quality aspects:**

1.2.1 Introduction

1. Introduction

-Diphtheria and Tetanus Vaccine (Adsorbed. Reduced Antigen(S) Content) BP Vaccine contains bulk purified diphtheria toxoid and bulk purified tetanus toxoid as active substances (bulk antigens), which are formulated with adjuvant (aluminum phosphate) and thiomersal (preservative).

The final product appears as a whitish, turbid liquid in which the mineral carrier tends to settle down slowly on holding.

Diphtheria and Tetanus Vaccine (Adsorbed. Reduced Antigen(S) Content) BP is indicated for active immunization of children 7 years of age or older and adults against tetanus and diphtheria

1.2.2 Drug Substance (Active ingredient)

- **General information**

General Properties

-Bulk Purified Diphtheria Toxoid is a sterile, pale yellow to dark brown color clear solution with antigenic purity of not less than 1500 Lf/mg PN2.

-Bulk puritied tetanus Toxoid is a sterile, fight to dark brown coloured, clear liquid with antigenic purity of not less than 1000 Lf/mgPN2. The Tetanus toxoid is prepared from the toxin produced

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

- Manufacturing Site Address.

-Biological E. Limited, 7-4-114, Gaganpahad, Rajendra Nagar Mandal, Medchal-Malkajgiri District,Andhra Pradesh 501323-India.(manufacturer of bulk purified tetanus toxoid)

-Biological E.limited plot No. 1, Biotech Park, Phase II, Kolthur village, shameerpet, Mandal, Medchal-Malkajgiri (district) 50078, Telangana - india (manufacturer of bulk purified diphtheria toxoid)

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

The detailed manufacturing process is mentioned in the MA file along with flow diagram highlighting the process steps with their IPCs.

- **Control of Materials.**
- All materials used in the manufacturing process listed in the submitted CTD file.

- Information regarding the used cell line & cell banking is mentioned in detail in the MA fil**e.**
- Biologically-sourced materials (their suitability for intended use including clearance or control of adventitious agents), Their specific use in the process and TSE/BSE risk evaluation are described in the dossier

- **Controls of Critical Steps and Intermediates**.
- -Critical process steps and critical process parameters are mentioned in the manufacturing process .
- -The process controls selected for each critical manufacturing step and the acceptance criteria are provided in the MA file .

- **2.2.5 Process Validation and/or Evaluation.**

- The process validation activities were carried out at various stages of the bulk purified diphtheria toxoid and Tetanus Toxoid manufacture were submitted in the CTD

- **Manufacturing Process Development.**
  - **Characterization**

-Characterization tests are fully described in the MA file.
-The manufacturer presented clearance data for several identified impurities.
-The applied methods for detection of impurities have been described and full validations of these methods have been presented in the dossier.

- **Specification**

- Specifications of Bulk Purified Diphtheria Toxoid and Tetanus Toxoid comply with Pharmacopoeical and WHO TRS

- **Analytical procedures**

-The detailed analytical procedures submitted n the CTD file

- **Batch analysis.**

- Summary of batch results for three consecutive batches of Bulk Purified Diphtheria and Tetanus toxoids Toxoid submitted in the CTD file.

- **Reference Standards or Materials**.

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-Working Standard of "Diphtheria Antitoxin for Flocculation Test is used for estimation of Lf in Bulk Purified Diphtheria Toxoid. This working standard is having daigned unitage of 100 Lf/ml

-Working Standard of "Tetanus Antitoxin for Flocculation Test is used for estimation of Lf in Bulk Purified Tetanus Toxoid (BPTT). This working standard is having an assigned unitage of 100 LI/ml.

-The Certificate of Working Standard is enclosed in the CTD file.

- **Container closure system**

-Bulk Purified Diphtheria Toxoid is stored in 20 L borosilicate glass bottles with blue polypropylene (PP) screw cap closures.

- **Stability of drug substance**

-Three batches of Bulk Purified Tetanus Toxoid manufactured at commercial production scale were charged for stability at accelerated (21-25°C) for 6 months and real time conditions (2-8°C) for 36months.

- Three Bulk Purified Diphtheria Toxoid batches were placed on stability at 2-8°C (real time) for 36months and 21-25°C (accelerated) for 6 months.

-The full stability study data were submitted in the CTD

2.2.3 Drug product:

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

Diphtheria and Tetanus Vaccine (Adsorbed, Reduced Antigen(s) Content) contains
Bulk Purified Diphtheria Toxoid and Bulk Purified Tetanus Toxoid (Bulk Antigens), which are formulated with Adjuvant (Aluminum Phosphate) and Thiomersal **(Preservative) as** Excipients in the final product. The final product appears as a whitish turbid liquid in which the mineral carrier tends to settle down slowly upon keeping.
-Composition of the drug product:

Each 0.5 ml dose contains:

Each dose of 0.5 mL	:	
contains: Diphtheria Toxoid		2 Lf (≥ 2 IU)
Tetanus Toxoid	:	8.8 Lf (≥ 20 IU)
Adsorbed on Aluminium Phosphate (AlPO4)	:	≥ 1.5 mg
Preservative: Thiomersal BP	:	0.005% w/v

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

- Drug substance: The drug substances used for formulation of Diphtheria and Tetanus Vaccine (Adsorbed, Reduced Antigen(S) Content) consist of Bulk Purified Diphtheria Toxoid and Bulk Purified Tetanus Toxoid, complying with WHO/Pharmacopoeial requirements.

- Excipients

The vaccine is formulated with adjuvant (aluminum phosphate) and Thiomersal (preservative) as Excipients. Aluminium phosphate has been historically used as immune potentiators for vaccines. Thiomersal has been one of the most widely used preservatives in vaccines. The content of thiomersal meets the requirements and is able to prevent the growth of the challenge fungi .

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

MANUFACTURE ADDRESS: M/S Biological E. Limited Plot No. 1, Biotech Park, Phase II, Kolthur Village, Shameerpet, Medchal-Malkajgiri (District), Telangana State, INDIA – 500078

-The detailed manufacturing process is mentioned in the MA file along with flow diagram highlighting the process steps with their IPCs.

- Control of critical steps and intermediates

Critical process steps and critical process parameters are mentioned in the manufacturing process .

The process controls selected for each critical manufacturing step and the acceptance criteria are provided in the MA file .

- Process validation and / or evaluation.

Process and cleaning validation was carried out in three manufacturing consistency batches and the study reports enclosed.

- **Product specification:**
  - **Description of the product specifications (state the reference whether compendial or in-house) and the excipients (mention excipient specifications) as well.**

  - The vaccine meets Pharmacopoeial and WHO the requirements except for potency test of tetanus which states that the tetanus potency should not be less than 20 IU per single human dose while in the TRS it should not be less than 40 IU per single human dose and the company stated that Id vaccine is not intended for primary immunization so a reduced tetanus content was used.
  - All the excipients are pharmacopoeial grade and comply with the respective pharmacopoeia.
  - Highlight whether human or animal origin are present and novel excipients as well.

- No Excipients of human or animal origin are used in the formulation of Diphtheria and Tetanus Vaccine (Adsorbed, Reduced Antigen(s) Content).
- No novel Excipients have been used in the formulation of Diphtheria and Tetanus Vaccine (Adsorbed. Reduced Antigen(s) Content).

- **Reference Standards or Materials.**

-Diphtheria: At Biological E. Limited, internal reference standard for Diphtheria Toxoid is established in-house and calibrated against the NIBSC standard of Diphtheria Toxoid.
-Tetanus: At Biological E. Limited, internal reference standard for Tetanus Toxoid is established in-house and calibrated against the NIBSC standard of Tetanus Toxoid.

- **Container closure system.**

- **Stability of the drug product.**

Table 16: List of Primary Packing Materials

S. No.	Component used	10 Dose Vial
1	Glass Vials	5 mL
2	Rubber Stoppers	20 mm
3	Aluminium flip-off Seals (Ash Color)	20 mm

-The proposed shelf life for Td based on data available to date is 36 months when stored at 2-8ºc

2. **Non –clinical aspect:**

- **BE Diphtheria and Tetanus Vaccine (Adsorbed)** is prepared by combining purified Diphtheria and Tetanus Toxoids. Both antigens are adsorbed onto aluminum phosphate as an adjuvant. It is indicated for active immunization of children 7 years of age or older and adults against tetanus and diphtheria. BE-Td vaccine is prequalified from WHO.
- **Toxicology:** As stated by the applicant that there is no separate "single dose toxicity studies & repeat dose toxicity studies" were conducted on BE Diphtheria and Tetanus Vaccine (Adsorbed. Reduced Antigen(s) content) as the vaccine is not a novel vaccine and is being used worldwide for many years.

  - Moreover, the applicant, Biological E., has conducted pre-clinical studies on other combination vaccines containing same antigen contents of Diphtheria and Tetanus e.g., tetravalent combination vaccine in single-dose toxicity study (DTwP-rHepB) & pentavalent vaccine in repeat-dose toxicity study (DTwP-rHepB-Hib). Based on the studies observations it can be concluded that the test DTwP-rHepB vaccine is safe in terms of toxicity related to general behavior, nervous and respiratory systems, clinical chemistry parameters as well as haematological parameters and histopathological examination and efficacious in terms of anti-body response against the vaccine antigens in mice and rabbits. Additionally, Treatment of rats with DTwP-rHepB-Hib vaccine up to the dose of double SHD/rat did not exhibit any significant treatment effects on their hematology and biochemistry parameters. The NOAEL of DTwP-rHepB-Hib vaccine in Wistar rats following repeated IM administration was found to be double that of SHD/rat.
- **Overall conclusion:** Based on the results of pre-clinical studies conducted on other combination vaccines containing same antigen contents of Diphtheria and Tetanus, BE Td vaccine is considered efficient and safe for use in the proposed patient population.

3. Clinical aspect:

- **<u>Clinical Efficacy including immunogenicity</u>**

The BE-Td® vaccine demonstrated non-inferiority in immunogenicity compared to the licensed Sii Td-Vac™ (Serum Institute of India) for both tetanus and diphtheria antigens. This was confirmed at Day 30 following a single intramuscular booster dose in healthy Indian children (≥7 years), adolescents, and adults previously primed with Td-containing vaccines. Seroprotection rates were statistically equivalent between the two groups: 100% for tetanus and approximately 99% for diphtheria in the BE-Td® group, with no significant differences observed (p-values: 1.000 for tetanus, 0.605 for diphtheria). These findings support the immunogenic equivalence of BE-Td® across age subsets.

- **Clinical Safety Conclusion**

Both BE-Td® and Sii Td-Vac™ vaccines exhibited comparable safety and tolerability profiles. No serious or unexpected adverse events related to the study vaccines were reported. The absence of significant safety concerns reinforces the suitability of BE-Td® for booster administration in the studied population.

- **Overall Conclusion**

The BE-Td® vaccine by Biological E Limited is clinically non-inferior in immunogenicity to the established Sii Td-Vac™ and demonstrates a favourable safety profile. These results support its use as a safe and effective booster dose for tetanus and diphtheria in children, adolescents, and adults who have completed primary immunization.

4. General Conclusion and Recommendations if any:

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