Unit: Technical Assessment Unit

Public assessment report for biological products

(Adsorbed Tetanus Vaccine B.P. Multi Dose 5 ml & 10 ml)

Administrative information:

Trade name of the medicinal product:	Adsorbed Tetanus Vaccine B.P. Multi Dose 5 ml & 10 ml
INN (or common name) of the active substance(s):	Each dose 0.5ml contains tetanus toxoid ≥ 40 IU Adsorbed on Aluminium Phhosphate (AIPO) ≥ 1.5mg Preservative: Thiomersal 0.01%
Manufacturer of the finished product	M/s Biological E. Limited, Plot No. 1, Biotech Park, Phase II, Kolthur Village, Shameerpet Mandal, Medchal-Malkajgiri District-500 078, Telangana - INDIA
Marketing Authorization holder	M/s Biological E. Limited, Plot No. 1, Biotech Park, Phase II, Kolthur Village, Shameerpet, Medchal-Malkajgiri District – 500 078, Telangana - INDIA
Applied Indication(s):	Tetanus prophylaxis Post Exposure prophylaxis of tetanus Neonatal tetanus Prevention Tetanus prophylaxis in wound management
Pharmaceutical form(s) and strength(s):	Suspension for intramuscular injection
Route of administration	intramuscular injection
Type of registration (EMA/FDA – Local)	Imported

List of abbreviations

TT	Tetanus toxoid
BE	Biologicals E
IV	Intravenous
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……..……2
2. Quality aspects…….…….2
2.1 Introduction…….…….....2
2.2 Drug Substance (Active ingredient)…….....2
2.3 Drug product…….……...5
3. Non-clinical aspects……..…….....9
4. Clinical aspect…….……..9
5. General Conclusion and Recommendations if any…….....10

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

Adsorbed TT vaccine is bacterial vaccine used in active immunization it is injectable suspension for intramuscular use only containing Tetanus Toxoid ≥ 40 IU, The product is enclosed in Borosilicate glass vials with Bromobutyl rubber stopper and flip-off aluminum seal in a carton box. Used in Tetanus prophylaxis & Post Exposure prophylaxis of tetanus & Neonatal tetanus Prevention and Tetanus prophylaxis in wound management.

2. Quality aspects:

2.2.1 Introduction

As mentioned above

2.2.2 Drug Substance (Active ingredient)

- **General information**

Nomenclature:

Bulk Purified Tetanus Toxoid,Biological E.Limited

General Properties

Bulk purified tetanus Toxoid is a sterile, light 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 by growth of organism - Clostridium tetani in Mueller & Miller medium. The tetanus toxin is converted to a toxoid by using formaldehyde. This is further purified by ammonium sulphate precipitation and diafiltration to get the purified tetanus toxoid. This purified tetanus toxoid is sterile filtered into the glass bottled labeled as "Bulk Purified Tetanus Toxoid (BPTT)" (Drug Substance) and is sampled and tested as per the specification and is stored at 2-8°C

Manufacture, process controls and characterization:

- **Manufacture**

M/s Biological E. Limited, Plot No. 1, Biotech Park, Phase II, Kolthur Village, Shameerpet Mandal, Medchal-Malkajgiri District-500 078, Telangana - INDIA

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

Manufacturing flow diagram (Bulk Purified Tetanus Toxoid, Biological E. Limited) is provided illustrating all steps in details

- **Control of Materials.**

- List of raw materials used are attached together with their reference either USP, BP or In-house Reference
- Quality and control of the materials: Materials with Pharmacopoeial reference are tested as per the specifications following the test procedures of the respective pharmacopoeia.

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

Within each manufacturing process stage, critical process parameters and critical quality attributes were determined

- **Characterization.**

-Elucidation of Structure and Other Characteristics

Tetanus Toxin produced by the organism Clostridium Tetani, is a single polypeptide chain with a mean molecular weight of around 150 KDa which is detoxified by using of formaldehyde to alter Tetanus toxoid to non-toxic tetanus toxoid so that it can be used as an immunogen. Cross-linking between toxin molecules or between toxin and other proteins in impure preparations could influence the size, distribution and purity of the detoxified toxoid.

-Impurities:

Tetanus bulk purified: The Bulk Purified Tetanus Toxoid meets the requirements of purity as per pharmacopeia and no characterization on the impurities has been carried out

- **Specification**

Specifications of the drug substance are provided .

- **Reference Standards or Materials**.

Internal reference standard of tetanus toxoid (adsorbed) is prepared, filled and lyophilized in glass vials. The internal reference standard of tetanus toxoid (adsorbed) is tested against NlBSC standard of tetanus toxoid (adsorbed) for potency test.

- **Container closure system**

BPTT is stored in 10 L or 20 L Poly propylene bottles at 2-8°Ctheir specification are submitted in the file

- **Stability of drug substance**

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

All the three batches of Bulk Purified Tetanus Toxoid manufactured have completed the stability studies and are complying with the specifications and no significant trend changes have been observed during the stability.

Post approval stability protocol and stability Commitment: As per the policy on stability, one batch of finished product is charged for stability every year.

Stability data: - Accelerated and real-time stability studies are conducted on three batches of bulk purified tetanus toxoid (BPTT). so Accelerated stability study is conducted at 20 - 25° C for a period of six months at an interval of OM, I M, 2M, 3M and 6M. Real time stability study is conducted at 2-8° C for a period of 36 months at an interval of

OM, 3M, 6M, 9M, 12M, 18M, 24M, 30M and 36M. Till date up to 9M study is completed and the rest of the intervals are on-going.

2.2.3 Drug product:

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

Adsorbed Tetanus Vaccine is a sterile preparation of refined tetanus toxoid for intramuscular use only.. The vaccine meets the requirements of WHO and BP. The vaccine is a whitish turbid suspension in which the mineral carrier tends to settle on keeping. The final product appears as whitish turbid suspension in which the adjuvant tends to settle down on keeping.

Presentations: Adsorbed Tetanus Vaccine BP is supplied as following two presentations. 10 doses - Vial containing 10 doses (5ml of liquid vaccine) & 20 doses - Vial containing 20 doses (I0ml of liquid vaccine) **Shelf life**: 36 Months

Composition: Each dose of 0.5 ml contains: Tetanus Toxoid ≥ 40 IU
Adsorbed on Aluminium Phosphate (AIP04) ≥ 1.5 mg
Thiomersal BP 0.0 I% wlv

-There is no reconstitution needed for Adsorbed Tetanus Vaccine BP. It is homogeneous white suspension intended for intramuscular injection

- **Overages**

10% overages are added for Tetanus Toxoid bulk.

- **Manufacturing Process Development**.

previously mentioned in details in drug substance

- **Container closure system and their compatibility.**

The primary packaging material used is USP type I glass vials for all the three presentations with grey bromobutyl rubber stoppers and flip off seals Stability studies have indicated the compatibility of the drug product with the container closure system. No reduction in potency has been observed in the stability studies as a result of adsorption to the containers. The TT Vaccine is filled in USP type I glass vials and closed using bromobutyl rubber stoppers with sealing by aluminum flip-off seals.

- **Microbiological Attributes**.

Thiomersal in the concentration of 0.0 1% is used as a preservative in all the presentations. The preservative used ensures the microbiological quality of the product during manufacture and storage.

- **Manufacture of the drug product:**

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

Name	Responsibities
M/s Biological E. Limited Manufacturing Facility Address: Plot No. 1, Phase ·11,.Shapoorji Pallonji Biotech Park, Kolthur Village, Shameerpet Mandal, Ranga Reddy (District), - Andhra Pradesh, INDIA - 500078 Telephone Number: 91-40-30128162 Facsimile Number: +91-40-30128159	Manufacturing of Bulk Purified Tetanus Toxoid (at Gaganpahad facility) / Formulation, Filling, Packing & Distribution of Adsorbed Tetanus Vaccine BP (Drug Product) (at Shameerpet Facility

- **Control of critical steps and intermediates**

The blended bulk is the only intermediate in the manufacturing process and it is controlled by: Description, Sterility, pH, Thiomersal Content, Specific Toxicity,Aluminium Content, Free Formaldehyde..

- **Process validation and / or evaluation.**

Consistency of the production is show by the analytical results for the three validation batches. Batch analysis data for the three consecutive batches Validation protocol and reports for the blending filling activity and manual optical inspection are found.

- **Product specification:**

-The final product specification is well described in the MA file

- **Reference Standards or Materials.**

At Biological E .Limited, internal reference standard is established with the NIBSC standard Each vial of current internal reference standard (IRS/TET/O 1/06) contains 310 IU of Tetanus Toxoid. The IRS establishment report for Tetanus Toxoid (Adsorbed) enclosed

- **Container closure system.**

-The primary packaging material used in USP type I glass vials for all the three presentations with grey bromobutyl rubber stoppers and Green Blue flip off seals

-Specification of container closure system are found.

- **Stability of the drug product.**

Three batches of single dose and multi dose (ten dose) were placed on stability at 2-8°C (real time) and at 25±2°C (accelerated conditions)

-The three consistency batches under cGMP conditions manufactured at the Shameerpet facility were selected for the stability studies. The batches were placed on stability at 2-8° C (real time) for 60 months & 20-25°C (accelerated) for 6 months and at 35-37° C (stress) for 8 weeks.

3. Non –clinical aspect:

The applicant didn't submit pre preclinical study based on that the product is not a new product, so it is not necessary to conduct preclinical, phase I & JI studies for this vaccine. A bridging clinical study will be enough to demonstrate the safety and immunogenicity according to the applied guidelines.

4. Clinical aspect:

➢ **Clinical Efficacy and Immunogenicity Conclusion**

Across three Phase IV clinical studies, the Tetanus Toxoid (TT) vaccine manufactured by Biological E Ltd. demonstrated strong immunogenicity and high efficacy in adults, children, and pregnant women.

- In all studies, participants achieved a ≥ 4-fold increase in anti-tetanus antibody titres by Day 60, with geometric mean titres (GMTs) significantly higher than baseline ($p < 0.0001$).
- The vaccine induced neutralizing antibody responses consistent with protection against tetanus and maintained its immunogenicity despite changes in the manufacturing process.

- Comparative analyses showed the Biological-E TT vaccine was non-inferior and comparable to the commercial control (SII-TT vaccine).

These findings confirm that the Biological-E TT vaccine provides robust and sustained immune protection across different age and physiological groups.

➢ **Clinical Safety Conclusion**

The TT vaccine showed a favorable safety and tolerability profile across all clinical trials.

- No serious adverse events were reported.
- The most common local reactions were mild pain and redness at the injection site (6-7%), and mild fever or malaise (1- 4%).
- All adverse events were transient and self-limiting, within acceptable reactogenicity ranges.
- Laboratory assessments revealed no clinically significant changes in hematological or biochemical parameters.

Overall, the vaccine was well tolerated, with a low rate of mild, short-lived reactions and no safety concerns identified in either adults or pregnant women.

➢ **Overall Conclusion**

The results from the three post-marketing and bridging Phase IV studies confirm that the Tetanus Toxoid vaccine produced by Biological-E Ltd. is safe, effective, and highly immunogenic.

- It elicits strong and durable antibody responses consistent with protection against tetanus.
- The vaccine maintains consistent efficacy and safety even after changes in the manufacturing process.
- Its proven performance in adults, children, and pregnant women supports its continued use in routine immunization programs for tetanus prophylaxis and maternal–neonatal protection.

5. General Conclusion and Recommendations if any:

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