Unit: Technical Assessment Unit

Public assessment report for biological products

TT Vaccine

Administrative information:

Trade name of the medicinal product:	TT Vaccine
INN (or common name) of the active substance(s):	Each dose (0.5 ml) contains: Purified Tetanus toxoid 10 Lf
Manufacturer of the finished product	PT. Bio Farma, Jl. Pasteur No. 28, Bandung 40161- Indonesia.
Marketing Authorization holder	PT. Bio Farma, Jl. Pasteur No. 28, Bandung 40161- Indonesia.
Applied Indication(s):	For prevention of tetanus/neonatal tetanus Tetanus toxoid should also be given in situation where a risk of developing tetanus from any other source exists(e.g. Injuries).
Pharmaceutical form(s) and strength(s):	suspension for Injection
Route of administration	Intramuscular injection
Type of registration (EMA/FDA – Local)	Imported

List of abbreviations

EMA	**European Medicines Agency**
FDA	**Food and Drug Administration**
WHO	**World Health Organization**
TT	**Tetanus Toxoid**
CSL	**Commonwealth Serum Laboratories**
CAPA	**Corrective and Preventive Actions**

Table of contents

1. General introduction about the product including brief description of the AI, its mode of action and indications……....3
2. Quality aspect……..…….…3
2.1 Introduction……....3
2.2 Drug substance (Active ingredients) ……..…3
2.3 Drug product……..5
3. Non-clinical aspects……..……7
4. Clinical aspects……..……..7
5. General Conclusion and Recommendations if any……..8

1. **General introduction about the product including brief description of the AI, its mode of action and indications.**
   Tetanus toxoid is purified toxoid which is produced by detoxification of Clostridium tetani toxin. The strain used for production is Massachusetts D4 strain obtained from The Commonwealth Serum Laboratories (CSL), Australia. The 04 strain were received in 1984 in a form of a freeze-dried ampoule identified by no. 04/T0/82 (freeze dried on 21 /05/82). This strain is of the Harvard descendant which has been adapted in semisynthetic medium. Tetanus toxoid is a clear brownish liquid with specific odor, which has purity not less than 1000 Lf/per mg of protein (nondialysable) nitrogen.

2. **Quality aspects:**

2.2.1 Introduction

As mentioned above in the general introduction

2.2.2 Drug Substance (Active ingredient)

- **General information**

  General properties:

  Tetanus toxoid: it is purified toxoid which is produced by detoxification of Clostridium tetani toxin. The strain used for production is Massachusetts 04 strain obtained from the commonwealth serum Laboratories (CSL), Australia. The 04 strain were received in 1984 freeze dried ampoule no.: 04/T0/82(freeze dried on 21/5/82) this strain is of the Harvard descendant which has been adapted in semi-synthetic medium. The tetanus toxoid is a clear brownish liquid with specific odor, which has purity not less than 1000 LF/mg of protein nitrogen

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

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

  Purified Tetanus Bulk Production

  Origin of Source culture:

  The strain for production is Massachusetts 04 strain obtained from the Commonwealth Serum Laboratories (CSL), Australia, received in 1984 in the form of a freeze-dried ampoule identified by the number 04/T0/82 which was freeze dried on the 21-05-82. The strain is the Harvard descendant adapted in semi-synthetic medium.

  Master Seed and Working Seed:

  The primary seed lot culture was produced by cultivation of Cl. tetani, derived from the master seed lot, in Pittman's medium as an intermediate medium, and the passage into production medium. The bacterial suspension is filled into ampoules, freeze dried, sealed under vacuum, and labeled. Freeze drying of this lot was done 12-12-1984 and allocated a batch number 04/Tl/84, then 14-9-1989 batch number 04/Tl/89 A and 04/Tl/89 B, then 3-9-

1992 batch number 04/Tl /92. These were allocated as primary seed for routine production (75%), and for stock (25%). The seed lots are stored at < - 20°C.

Working seed:

The seed preparation is prepared under laminar air flow cabinet placed in class C room. The working seed is prepared using the same procedure as the primary seed, and is used for routine production. The working seed lots are stored at <-20°C.

- **Control of Materials.**

Biological starting materials used for the production of Tetanus Toxoid Bulk constitute the following:

NZ Case

Appearance: Yellowish powder, specific odor, hygroscopic

Country of origin: Australia or New Zealand

Storage: room temperature

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

Control of critical steps as mentioned above in "description of manufacturing process and process control"

- **Process Validation**

- Validation of detoxification process is very important. Validation of tetanus toxin detoxification process was done to prove that the new incubator room (ID No. 125-IncR-02) is legible to be used in tetanus toxin detoxification process.
- Detoxification is part of tetanus toxoid production process, in which tetanus toxoid is inactivated by adding adequate amount of formaldehyde into toxin and followed by incubation of the mixture under certain conditions of temperature and time.
- Validation report of tetanus toxin detoxification process is provided.

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

Elucidation of structure and other characteristics:

Characteristics of the strain of Clostridium tetani

<u>morphology (Gram Staining):</u>

Anaerob obligate. non sacharolytic. gram positive and negative rod-shaped

dimension:

width 0. 3 - 0. 5 pm. length 2 - 5 pm

<u>Growth characteristics:</u>

Grown anaerobically on blood agar: s\vanning with hemolysis

Purified Tetanus Toxoid

Appearance: a clear brO\vnish liquid. with specific odor

Titre: 1800 Lf/mL - 2200 Lf/mL

Purity: not less than 1000 Lf per mg of protein (nonclialysable) nitrogen

- **Specification**
  Purified Tetanus Toxoid
  Appearance: a clear brom1ish liquid with specific odor
  Titre: 1800 Lf/ ml - 2200 Lf/ml
  Storage: at 2 - 8 °C in a well-closed container.

- **Analytical Procedures.**
  As mentioned above and all the reference documents are mentioned according to each method separately.

- **Batch analysis.**
  Three consecutive batch analysis are provided for purified tetanus toxoid

- **Reference Standards or Materials.**

Test	Reference standard	Remark
Flocculation of Tetanus Toxoid	Standard of Tetanus Toxoid: T-061 3 Standard of Anti Tetanus Serum: ST A TS 126-07	In house reference

- **Container closure system**
  Purified Tetanus are packed into polypropylene bottle. They are filled into polypropylene bottle aseptically and through filtration process, then closed and sealed well. The packed toxoid is labeled with identity information (batch no., volume, manufacture date, storage, number of bottle).
  • Specifications of polypropylene bottle (its characteristics, tests and requirements are mentioned)

- **Stability of drug substance**
  Real time stability study purpose is to determine shelf life of purified Tetanus Toxoid produced by Biopharma. The study is performed by evaluating the stability data of final products which are produced using related bulk in stability study of intermediates, retrospectively.

2.2.3 Drug product:

- **Description and Composition of the Drug Product:**
  The vaccine contains purified tetanus toxoid. The toxoid is adsorbed onto 3 mg/mL

Aluminum phosphate. Thimerosal 0.1 mg/mL is used as a preservative. One dose of 0.5 mL has a potency of at least 40 IU.

Composition:

Each dose (0.5 ml) of vaccine contains:
Purified tetanus toxoid 10 Lf
Aluminum phosphate 1.5 mg
Thimerosal 0.05 mg

- Pharmaceutical Development including brief description on Components of drug product.
Not Applicable
- Formulation Development
- Overages
- Physicochemical and Biological Properties
- Manufacturing Process Development.
- Container closure system and their compatibility.
- Microbiological Attributes.
- Compatibility.

- **Manufacture of the drug product:**

- Description of manufacturing process and process controls along with manufacturers and responsibilities are all well described in the MA file .

- Product specification:

- Description of the product specifications (state the reference whether compendial or in-house) and the excipients (mention excipient specifications) as well.
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- **Reference Standards or Materials.**
  I. Reference of tetanus toxoid: T-0613
  2. Reference of anti-tetanus serum: ST A TS 126-07

- **Container closure system.**
  • TT Vaccine is packed in a well-closed vial 5 ml. TT vaccine is filled into vial aseptically, closed with rubber stopper and sealed by aluminum cap.
  • Labeling of the vaccine is done in the packaging department by means of labeling machines. During labeling, batch number and expiry date are printed on each label. Labeled vaccines are brought to an adjacent room in the packaging facility to be packed into boxes.
  • The boxes are stored in crates and each crate is weighed; once filled, the crates are immediately stored in 2 - 8 °C cold room.
  **Recommendation: This part is to be evaluated by CAPA

- **Stability of the drug product.**

TT vaccine is within specification until expiry dates

3. **Non –clinical aspect:**

The applicant didn't submit any preclinical studies based on that the product is not a new product, as it has been in the market for more than 25 years, so no need for assurance of safety in animals regarding the accumulated clinical data available.

4. **Clinical aspect:**

- **Clinical Efficacy and Immunogenicity**

• In adolescents (150 participants, aged 10–18 years): The study showed 100% of participants achieved seroprotective antibody concentrations (≥0.01 IU/ml) 28 days post-vaccination. Approximately 98.6% exhibited a 4-fold or greater rise in antibody titers. The geometric mean titer (GMT) significantly increased from 0.44 IU/ml to 14.4 IU/ml ($p < 0.001$), confirming robust immunogenicity across all age groups.

• In pregnant women and their infants (prospective and retrospective studies): Two TT doses given one to two months apart produced 100% seroconversion in both mothers and newborns. Antibody transfer from mother to child was confirmed through umbilical cord blood analysis. Higher antibody levels were achieved with a two-month interval between doses. Retrospective follow-up indicated protective antibody levels declined gradually from 80.8% to 53.6% over four years, suggesting the need for booster doses.

Conclusion: The TT (Biofarma) vaccine demonstrated high immunogenicity, achieving full protection and effective maternal–infant antibody transfer.

- **Clinical Safety**

• In adolescents: No serious adverse events were reported. Mild local and systemic reactions were transient and self-resolving. Common local reactions included pain (18-38%), redness (3-20%), swelling (2-18%), and induration (4-9%). Systemic reactions, mainly mild fever (3-7%), were infrequent.

• In women of childbearing age (488 participants): The most frequent local reaction was pain at the injection site (53% on day 1, decreasing over time). Other local reactions included redness (12%), swelling (10%), itchiness (10%), and nodules (3%). Systemic events such as dizziness (2-3%), urticaria (4%), fever (2-3%), and dyspnea (<1%) were mild to moderate. No severe or life-threatening events were observed.
Conclusion: The TT (Biofarma) vaccine is safe and well tolerated, with only mild and temporary local or systemic reactions reported.

- **Overall Conclusion**

The TT (Biofarma) vaccine has been proven to be safe, effective, and highly immunogenic. It provides complete short-term protection, ensures effective antibody transfer from mother to

infant, and demonstrates excellent tolerability across age groups. The data support its use for routine immunization in adolescents, women of childbearing age, and during pregnancy.

5. General Conclusion and Recommendations if any:

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