Unit: Technical Assessment Unit

Public assessment report for biological products

(Adsorbed TD vaccine 10 doses)

Administrative information:

Trade name of the medicinal product:	Adsorbed Td vaccine - 10 doses.
INN (or common name) of the active substance(s):	Each 0.5 ml contains: Purified Tetanus Toxoid 7.5 Lf/dose Purified Diphtheria Toxoid 2 Lf/dose
Manufacturer of the finished product	PT. Bio Farma (Persero), Jl. Pasteur No. 28, Bandung 40161 - Indonesia.
Marketing Authorization holder	Biovac Egypt for Drugs, Sera and Vaccines, 7 Taha Hussein Street, Madkor, Giza - Egypt.
Applied Indication(s):	The vaccine is used for the active immunization of adults and children 7 years of age and older against diphtheria and tetanus.
Pharmaceutical form(s) and strength(s):	Suspension for injection
Route of administration	intramuscular injection
Type of registration (EMA/FDA – Local)	Imported

List of abbreviations

Abbreviation	
GMT	Geometric Mean Titer
TT	Tetanus Toxoid
Td	Tetanus and Reduced Diphtheria Toxoid
DTP	Diphtheria, Tetanus, and Pertussis Vaccine
U/ml	Units per Milliliter
hr	Hour

Abbreviation

min	Minute
p	Probability Value

Table of contents

1. **General introduction about the product including brief description of the AI, its mode of action and indications.**
   Adsorbed Td vaccine is vaccine containing tetanus and diphtheria toxoid: with a reduced dose of diphtheria component. 111e toxoids are adsorbed into aluminum phosphate. The potency of the vaccine/ single human dose less than 301U for diphtheria and not less than 40IU for tetanus. The vaccine is administrated by intramuscular.

2. **Quality aspects:**
   2.2.1 Introduction
   As mentioned in the general introduction
   2.2.2 Drug Substance (Active ingredient)
   - **General information**

   Nomenclature:
   Name of the drug substance (active ingredient): Tetanus toxoid, diphtheria toxoid.
   The structure:
   not applicable
   General properties:
   a) **Tetanus toxoid:** it is purified toxoid which is produced by detoxification of Clostridium tetani toxin.
   The tetanus toxoid is a clear brownish liquid with specific odor
   b) **Diphtheria toxoid**: is purified toxoid which is produced by detoxification of Corynebacterium diphtheriae lox in.

Manufacture, process controls and characterization:

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

- The preparation of tetanus toxin takes place in building which is dedicated to tetanus production only. All toxin preparations are performed in this dedicated facility with no direct connection with other laboratories.

- **Characterization.**

Characteristics of the strain of Clostridium tetani:

•Morphology (Gram Staining): Anaerobe obligate, non-saccharolytic, gram positive and negative rod shaped, and dimension: width 0.3 -0.5 µm. length 2 - 5 ~1m .

•Growth characteristics: Grown anaerobically on blood agar: swarming with hemolysis

Characteristics of the strain of Corynebacterium diphtheria:

•Morphology

On Telulit agar plate at 14 - 24 hours growth. colonies are about I - 2 mm diameter, circular, convex. entire edge, smooth surface, pale gray in color, usu11lly shows a well-marked 70ne of hemolysis.

On Tellulit agar plate at -t8 hours growth. colonies are about 2 -4 mm in diameter. dark grayish black in color, smooth, shiny surface, becoming flattened with an elevated center (poached egg appearance). entire edge soft consistency.

- **Specification**

All specifications of the DS are well described in the MA file

- **Analytical Procedures.**

Analytical procedures included summaries of test principle, equipment, reagents, acceptance and validity criteria and their reference

- **Reference Standards or Materials.**

All reference standards used during manufacturing are well described in the MA file

- **Container closure system**

Purified Tetanus and Diphtheria Toxoid: are packed into polypropylene bottle.

They are filled into polyethylene bottle aseptically and through filtration process. then closed and sealed well. The bottles are labeled with identity information.

(Batch no. titer. volume, manufac1ure date, storage, number of bottles. expiry date).

- **Stability of drug substance**

The protocol of accelerated stability study of purified diphtheria toxoid and purified tetanus toxoid.

a) Accelerated stability study of purified tetanus toxoid:

The results shows that purified tetanus toxoid is s table for 2 weeks at 37 =1° C and I month at 25- 2 °C

b) Accelerated stability study of purified diphtheria toxoid:

Purified diphtheria toxoid is stable for I week at± 37 "C and I month at 25 ° C.

c) ReHI time stability study of Purified Tetanus Toxoid:

Purified Tetanus Toxoid is stable until 4 years when stored at 2 -8 °C,

d) Real time stability study of Purified Diphtheria Toxoid:

Purified diphtheria toxoid bulk is stable until 4 years when stored at 2 - 8 °C.

2.2.3 Drug product:

- **Description and Composition of the Drug Product:**
  The vaccine containing tetanus and diphtheria toxoid with a reduced dose of diphtheria component. one dose of vaccine has a potency of less than 30 I U of diphtheria toxoid. and not less than 40 IU of tetanus toxoid. The toxoids are adsorbed into aluminum phosphate. This vaccine is administrated by intramuscular injection.

  - Container closure system and their compatibility.
  Red rubber stopper is c1osed as closure for the vials. Aluminum caps are used as flip of cap are used to seal the vial VVM type. 30 label is applied on adsorbed Td vaccine. Each box of adsorbed Td vaccine contains I 0 vial

- **Manufacture of the drug product:**
  - Description of manufacturing process and process controls along with manufacturers and responsibilities.
  PT. Bio Farma (Persero), Jl. Pasteur No. 28, Bandung 40161 - Indonesia.

  - **Reference Standards or Materials.**

No	Test	Reference standard	Remarks
1	Flocculation of Tetanus Toxoid	Standard of Tetanus Toxoid : T-0613 Standard of Anti Tetanus Serum : ST ATS 126-07	In house reference
2	Flocculation of Diphtheria Toxoid	Standard of Diphtheria Toxoid : D-0600 Standard of Anti Diphtheria Serum : ST ADS 36-07	In house reference

  - **Container closure system.**
    The adsorbed TD vaccine. It is filled into vial aseptically, closed with rubber stopper and sea led by aluminum flip-offed cap and stored in 2-8 •c cold room
  - **Stability of the drug product.**
    Stability summary and conclusion
    • The results for accelerated stability of the l01s (041016. 041026, 041036) obtained demonstrate that the vaccine is s1able up 10 6 months at 37 ± I and 25 ± 2 "C.
    • The result for real time stability study of the lots (04l016. 041026, 041036) obtained demonstrate that the vaccine is stable for 4 years at temperature o-f 2—8 C
    Post-approval Stability Protocol and Stability Commitment:

Long-term stability studies test frequency shall be 3 months' time interval in the first car. and then the frequency shall be 6 months for the second year and thereafter on yearly ba5is. Long-term stability studies shall be conducted up to 6 months or 1 year beyond the shelf life of the product.

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 & II studies for this vaccine according to the applied guidelines.

4. **Clinical aspect:**

   ➢ **Clinical Efficacy and Immunogenicity**

   A randomized, double-blind, phase II clinical study comparing the Td (Bio Farma) vaccine with TT vaccine in 296 healthy adolescents aged 10 -18 years. to evaluate the protective immune response against diphtheria and tetanus 28 days after booster vaccination.

   Anti-Diphtheria:
   - Seroprotection (≥0.01 IU/ml) achieved in 99.3% of Td group and 89.9% of TT group.
   - Long-term protection rate (≥0.1 IU/ml): 93.2% in Td vs 35.1% in TT.
   - ≥4-fold antibody increase: 86.7% in Td vs 2.2% in TT.
   - Seronegative to seropositive transition: 95.2% in Td vs 11.8% in TT.
   - GMT for diphtheria was significantly higher in Td group ($p < 0.0001$).

   Anti-Tetanus:
   - Both Td and TT groups achieved 100% seroprotection (≥ 0.01 IU/ml).
   - ≥ 4-fold antibody increase: 96.6% (Td) vs 98.6% (TT).
   - GMT increase significant in both groups, slightly higher for TT, indicating Td provided comparable immunogenicity.

   Conclusion: Td vaccine induced strong seroprotective immune responses against both diphtheria and tetanus, showing superior diphtheria protection and comparable tetanus protection to TT vaccine.

   ➢ **Clinical Safety**

A total of 296 adolescents (148 Td, 148 TT) were included in the safety analysis. No serious or severe adverse events were reported. Pain at the injection site was the most common symptom in both groups, mild and transient.

Immediate reactions (within 30 min):
- Pain: 20.3% (Td) vs 18.2% (TT), p=0.658.
- Redness: 4.1% (Td) vs 3.4% (TT).
- Swelling: 4.1% (Td) vs 2.7% (TT).
- Fever: 0.7% (Td) vs 3.4% (TT).

Delayed reactions (30 min -72 h):
- Pain: 30.4% (Td) vs 38.5% (TT), p=0.142.
- Redness: 14.2% (Td) vs 20.3% (TT).
- Swelling: 12.7% (Td) vs 18.0% (TT).
- Induration: 6.1% (Td) vs 8.8% (TT).
- Fever: 4.7% (Td) vs 6.7% (TT).

Late reactions (4 - 28 days): Minimal events observed, with 0.7% pain and induration in TT group only.

Conclusion: Both Td and TT vaccines were well tolerated. No serious adverse events were reported. The overall safety profile of Td vaccine was comparable to TT, confirming it is safe for adolescent use.

- **Overall Conclusion**

The Td (Bio Farma) vaccine demonstrated high immunogenicity, particularly against diphtheria, and comparable protection to TT vaccine for tetanus. It showed excellent safety and tolerability in adolescents. These findings indicate that Td (Bio Farma) vaccine is safe, immunogenic, and effective for booster immunization in adolescents aged 10 - 18 years, meeting WHO and GCP requirements.

5. General Conclusion and Recommendations if any:

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