Unit: Technical Assessment Unit

Public assessment report for biological products

*(*Diphtheria and Tetanus Vaccine*)*

Administrative information:

Trade name of the medicinal product:	Diphtheria and Tetanus Vaccine Adsorbed for Adults and Adolescents
INN (or common name) of the active substance(s):	NA
Manufacturer of the finished product	Serum Institute of India PVT. LTD. 212/2, Hadapsar, Pune 411028 Maharashtra state-INDIA
Marketing Authorization holder	Serum Institute of India PVT. LTD. 212/2, Hadapsar, Pune 411028 Maharashtra state-INDIA
Applied Indication(s):	-For primary vaccination and revaccination of adults and adolescents, who are having contraindications of DTP. - Primary vaccination and revaccination of children older than 7years.
Pharmaceutical form(s) and strength(s):	Suspension for injection: Clear transparent USP type I ampoule, 0.5 ml - 1 dose
Route of administration	injection
Type of registration (EMA/FDA – Local)	Imported

List of abbreviations

Td	Diphtheria and Tetanus toxoid
WHO	World Health Organization
EP	European Pharmacopoeia
IP	Indian Pharmacopoeia
BP	British Pharmacopoeia
TRS	Technical Report Series
MLD	Minimum Lethal Dose
Lf	Limes Flocculationis

mg	milligram
mL	milliliter
SII	Serum Institute of India
NIBSC	National Institute for Biological Standards and Control
USP	United States Pharmacopeia
SIIPL	Serum Institute of India Private Limited
SOP	Standard Operating Procedure
D	Diphtheria
T	Tetanus

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1. **General introduction about the product including brief description of the AI, its mode of action and indications:**
   Diphtheria and Tetanus Vaccine Adsorbed for adults and adolescents (Td) is prepared by combining purified Diphtheria toxoid and purified Tetanus toxoid. The antigens are adsorbed onto Aluminium phosphate as adjuvant. Thiomersal is added as preservative. The vaccine has the appearance of a greyish - white suspension.
   The vaccine meets the requirements of WHO, EP and IP when tested by the methods outlined in WHO, TRS (2014) 980, EP and IP.

2. **Quality aspects:**

2.2.1 Introduction

As mentioned in the aforementioned section.

2.2.2 Drug Substance (Active ingredient)

I. Tetanus:

- **General information**

Tetanus toxin, a potent neurotoxin, is synthesized intracellularly by Clostridium tetani as a single polypeptide chain.
The tetanus toxin is converted into toxoid wherein it retains its immunogenicity but loses its virulence.

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

Manufacturer: SERUM INSTITUTE OF INDIA LTD.
212/2, Hadapsar, Pune-411 028, Maharashtra, INDIAB. No. 7 Ground floor, First Floor SEZ 5 First floor, second floor.

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

The tetanus component is purified toxoid manufactured by the chemical detoxification of endotoxin produced by Clostridium tetani.
Tetanus toxoid is prepared from the toxin produced by the growth of this strain of Clostridium tetani in Semi-synthetic medium using fermentation technology.

Control of Materials.

List of raw materials used in the manufacture of crude tetanus toxoid, purification of tetanus toxoid with in-house specifications are mentioned in MA file.

Controls of Critical Steps and Intermediates

In-process controls test performed on the intermediate as Bacterial Purity, Sterility, Specific Toxicity and pH are performed.

Quality control test performed on the intermediate as Minimum Lethal Dose (MLD) and Specific Toxicity are performed.

- **Process Validation**

  All the important steps and procedures in the manufacturing have been validated.
  The results showed that the manufacturing process is consistent using three consecutive batches.

- **Manufacturing Process Development**

  The preparation of Tetanus Toxoid is based solely on WHO recommended procedures. There are no changes in the constitution of the product.

  - **Characterization**

    Physicochemical characterization: Clear brown colored solution.
    Biological characterization: Potency of purified Tetanus Toxoid is in the form of antigenic purity which is not less than 1000 Lf/mg of protein nitrogen.

  - **Specification**

    Specifications of Purified Tetanus Toxoid is provided in MA file.

  - **Analytical Procedures**

    Are included in details in the dossier including summaries of test principle, equipment, reagents, acceptance and validity criteria.
    The analytical method validation is performed for Lf/mL of Toxoid and protein nitrogen content tests.

  - **Batch analysis**

    Upon evaluation of submitted batch analysis results, consistency of production was observed.

  - **Reference Standards or Materials**

    At SII, the Working Standard of Tetanus Toxoid which is used to test Purified Tetanus Toxoid is calibrated using International Reference Standard.

  - **Container closure system**

    Pool of purified Tetanus Toxoid is stored in a sterile glass bottle of 20 L capacity at 2-8º C. The glass bottles are closed with sterile silicon bungs

  - **Stability of drug substance**

    Storage condition: 2-8 °C for 60 months

II. Diphtheria:

- **General information**

Diphtheria toxin is a protein, which has been well characterized. It has 535 amino acids. With the help of trypsin it can be fragmented into two dissimilar Fragments called A and B.
Neither Fragment A nor B is toxic on its own, even in high concentrations. Diphtheria Toxoid is the formaldehyde inactivated Diphtheria toxin that remains antigenically intact but loses its virulence.

The physical appearance of the drug substance is clear yellow color solution. The drug substance is stored in 20 L glass
bottle at 2-8°C. The Potency of Pool of purified Diphtheria Toxoid is in the form of antigenic purity which is not less than 1500 Lf/mg of protein nitrogen
-**Nomenclature**: NA

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

Manufacturer: SERUM INSTITUTE OF INDIA LTD.
212/2, Hadapsar, Pune-411 028, Maharashtra, INDIAB. No. 7 Ground floor, First Floor SEZ 5 First floor, second floor.

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

At Serum Institute of India (SII), diphtheria toxoid is produced using Corynebacteriumdiphtheriae.
Toxin is concentrated, partially purified and subsequently detoxified. And the toxoid is further purified to produce purified diphtheria toxoid. The manufacturing and testing are performed in accordance with recent WHO TRS.

Control of Materials.

List of raw materials used in the Preparation of Semi synthetic Medium for production of Diphtheria Toxoid and Manufacturing of purified Diphtheria Toxoid are mentioned in MA file.

Controls of Critical Steps and Intermediates

In-process controls test performed on the intermediate as Gram Staining and Purity on Nutrient Agar are performed.
Quality control test performed on the intermediate as Antigenic purity and Specific Toxicity are performed.

- **Process Validation**

All the important steps and procedures in the manufacturing have been validated.
The results showed that the manufacturing process is consistent using three consecutive batches.

- **Manufacturing Process Development**

The preparation of Diphtheria Toxoid is based solely on WHO recommended procedures. There are no changes in the constitution of the product.

- **Characterization**

Physicochemical characterization: Clear yellow colored solution.
Biological characterization: Potency of Purified diphtheria toxoid is in the form of antigenic purity which is not less than 1500 Lf/mg of protein nitrogen.

- **Specification**

Specifications of Purified Diphtheria Toxoid is provided in MA file.

- **Analytical Procedures**

Are included in details in the dossier including summaries of test principle, equipment, reagents, acceptance and validity criteria.
The analytical method validation is performed for Lf/mL of Toxoid protein nitrogen content and Thiomersal content.

- **Batch analysis**
  Upon evaluation of submitted batch analysis results, consistency of production was observed.
- **Reference Standards or Materials**
  At SII, the Working Standard of diphtheria Toxoid is calibrated using 4th International Standard 2010 (WHO NIBSC).
- **Container closure system**
  Pool of purified Diphtheria Toxoid is stored in a sterile glass bottle of 20 L capacity at 2-8º C. The glass bottles are closed with sterile silicon bungs.
- **Stability of drug substance**
  Storage condition: 2-8 °C for 60 months

2.2.3 Drug product:

- **Description and Composition of the Drug Product:**
  Diphtheria and Tetanus Vaccine Adsorbed for adults and adolescents (Td) is prepared by combining purified Diphtheria toxoid and purified Tetanus toxoid.
  The antigens are adsorbed onto Aluminium phosphate as adjuvant.
  Thiomersal is added as preservative, the vaccine has the appearance of a greyish - white suspension. The vaccine meets the requirements of WHO, EP and IP when tested by the methods outlined in WHO, TRS (2014) 980, EP and IP.
  The vaccine is presented in a clear transparent USP type I ampoule: 0.5 ml - 1 dose.

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

The drug substances of the Td vaccine are as below:
1. Purified Diphtheria toxoid derived from a culture of Corynebacterium diphtheriae.
Purified diphtheria toxoid complies to the requirements of WHO TRS 980, B.P. Ph. Eur. and I.P.
2. Purified tetanus toxoid derived from a culture of Clostridium tetani.
Purified tetanus toxoid complies with the requirements of WHO TRS 980, B.P. Ph. Eur. and I.P.

Excipients used in the manufacturing of Td vaccine are aluminium phosphate, thiomersal, water for injection.

- Formulation Development

The manufacturing and marketing authorization for SIIPL, Diphtheria and Tetanus Vaccine Adsorbed for Adults and Adolescents was prequalified by the World Health Organization for sale to United Nations agencies on 04 April 1995.

- Overages

No overages are added in the formulation of Td Vaccine, Adsorbed

- **Physicochemical and Biological Properties**

Physicochemical and Biological properties of active ingredients of Diphtheria and Tetanus Vaccine Adsorbed for Adults and Adolescents are previously described above in Specifications of Purified Diphtheria Toxoid and Purified Tetanus Toxoid as well.

- Manufacturing Process Development.

Development batches of small-scale using state technology and equipment or pilot scale developmental batches prepared in qualified equipment.

- Container closure system and their compatibility.

Filling is done in USP type I ampoules for single dose.
Stability studies have demonstrated compatibility of the container closure system with the drug product. No decrease in potency of the drug product as a result of absorption to the primary packaging materials during storage has been found.

- **Microbiological Attributes**

Diphtheria and Tetanus Vaccine Adsorbed for Adults and Adolescents is a sterile product.
Thiomersal is used as an antimicrobial preservative.
Compliance with the specifications for Sterility has been shown throughout the shelf life of the product

- Compatibility.

The compatibility of the product has been proved from the established stability studies.

- **Manufacture of the drug product:**

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

Manufacturer:

SERUM INSTITUTE OF INDIA LTD. 212/2, Hadapsar,
Pune-411 028, Maharashtra, INDIA

- **Control of critical steps and intermediates**

Samples are drawn after satisfactory blending and formulation. The samples will be tested as per specifications of Bulk for Adsorbed Diphtheria and Tetanus Vaccine for Adults and Adolescents

- Process validation and / or evaluation

Analytical data from consecutive batches of final bulk and final lot of vaccine demonstrates the consistency of production, there by validating the entire process.

- **Product specification:**

-Specifications for Bulk and final lot of Diphtheria and Tetanus Vaccine Adsorbed for Adults and Adolescents are described in MA file.
-The tests and specifications are selected based on WHO TRS / BP / Ph. Eur. / IP. Our Td Vaccine complies with these requirements
-Upon evaluation of the submitted batch analysis results, consistency of production was reflected. And all the batch results were satisfactory and comply with acceptance criteria.

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

-Specifications for the ingredients are according to BP/Ph.Eur./IP and are regarded adequate to guarantee proper control of quality of ingredients
-Analytical Procedures are well described in the submitted dossier.
-Specifications and SOPs of the Excipients and Certificate of Analyses from suppliers and applicants of excipients used in formulation of Diphtheria and Tetanus Vaccine Adsorbed for Adults and Adolescents are submitted.
-No excipients of human origin are added during formulation.
-No novel excipients have been used in the formulation.

- All excipients used in the formulation of Td Vaccine are as per Pharmacopoeia and hence Analytical Method Verification for these excipients are performed.

- **Characterization of impurities**.
- No specific impurities are to be estimated in the final product. The impurities present in each antigen (where applicable) are removed at bulk level.

- **Reference Standards or Materials.**

In house / National reference standards are used in analysis of Td Vaccine; The certificates for the above standards are enclosed.

- **Container closure system**

Description and specification of primary packaging materials (glass ampoule) of Diphtheria and Tetanus Vaccine, adsorbed for adults and adolescents were well described.

- **Stability of the drug product.**

-Based on available stability data,
approved Shelf Life: 2-8 ºC
approved Storage Conditions: 36 months

3. Non –clinical aspect:

The applicant stated that No formal toxicity studies were done on Td vaccine.
However, the submitted studies have been done on DTP group of SII vaccines, which contain similar or more quantities of tetanus toxoid & diphtheria toxoid. The strain and all other technical details of diphtheria toxoid &tetanus toxoid used for SII Td vaccine are same to those of SIIL **DTPw-HB vaccine (adsorbed)**,DTP-HB+Hib vaccine (liquid-lyophilized),…..etc.. Since SII Td vaccine was registered **more than 25 years,** thus the scientific evaluation of safety and efficacy will mainly rely on the clinical data.

4. Clinical aspect:

Efficay (Immunoigenicity) conclusion:

Two-Phase IV studies were presented: one assessing the reactogenicity and immunogenicity in children aged 7-17 years (N=706), the other assessing the parameters in adults aged 30-65 years (N=62). The seroprotection rate in both studies for Anti-diphteria and Anti-tetnus titers in both studies exceeding the pre-specified limit of of IgG antibody titre ≥ 0.1 IU/ml is 94.7% & 98% for children six weeks after vaccination and 100% and 100% for adults respectively.

Safety (Reactogenicity) conclusion:

The reactogenicity of Td Vaccine in these children demonstrated low levels of adverse events with mild pain at injection site. In adults, all local and systemic adverse reactions were resolved without any sequelae.

Td vaccine is safe and immunogenic when given in three doses in adults of 30-65 years with definite need of Td vaccination in adult. Although first dose is recommended for all school going children, at the age of seven years.

5. General Conclusion and Recommendations if any:

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