Unit: Technical Assessment Unit

Public assessment report for biological products

(Diphtheria and Tetanus Vaccine Adsorbed (Pediatric))

Administrative information:

Trade name of the medicinal product:	Diphtheria and Tetanus Vaccine Adsorbed (Pediatric)
INN (or common name) of the active substance(s):	Pool of Purified Diphtheria Toxoid, Pool of Purified Tetanus Toxoid
Manufacturer of the finished product	Serum Institute of India Ltd.; 212/2, Hadapsar, Pune-411 028, India
Marketing Authorization holder	Serum Institute of India Ltd.; 212/2, Hadapsar, Pune-411 028, M.S., India
Applied Indication(s):	-The vaccine is recommended for use in childhood immunization instead of DTP vaccine when contraindications to the pertussis component exist. - The DT vaccine is recommended for children below 8 years of age.
Pharmaceutical form(s) and strength(s):	- 0.5 ml -1 dose, 5 ml-10 doses, 10 ml-20 doses Injectable. Suspension for injection. - Diphtheria Toxoid ≤ 25 Lf (≥ 30 IU) - Tetanus Toxoid ≥ 5 Lf (≥ 40 IU) - Adsorbed on Aluminium Phosphate, Al+++ ≤ 1.25 mg
Route of administration	Intramuscular Injection
Type of registration (EMA/FDA – Local)	Imported

List of abbreviations

Td	Diphtheria and Tetanus toxoid
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
DT	Diphtheria and Tetanus
DT(P)	Diphtheria and Tetanus Vaccine Adsorbed (Pediatrics)
DTP-HB-Hib	Diphtheria, Tetanus, Pertussis, Hepatitis B, and Haemophilus influenzae type b pentavalent vaccine
DTP	Diphtheria, Tetanus and Pertussis
GMT	Geometric mean titer
IM	Intramuscular
IU	International unit
PSUR	Periodic Safety Update Report
SIIL	Serum Institute of India Ltd.
UNICEF	United Nations Children's Fund
WHO	World Health Organization

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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 pediatric. (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, INDIA.
- Tetanus toxoid production is carried out in a dedicated building (Tetanus Block and Bldg. No.7, First 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.

- **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.

- **Specification**

Specifications of Purified Tetanus Toxoid is provided in MA file.

- **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.
  - This glass bottle is manufactured from low alkali borosilicate type 3.3-expansion glass.
  - The glass bottles are closed with sterile silicon bungs.
- **Stability of drug substance**
  Storage condition: 2-8 °C for 60 months (five years).

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.
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 state, INDIA.
- Diphtheria toxoid production is carried out in the first floor of Diphtheria block and Purification of Diphtheria toxoid is carried out in the ground floor of Diphtheria block.

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

At Serum Institute of India (SII), diphtheria toxoid is produced using Corynebacterium diphtheriae.
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.

- **Specification**
  Specifications of Purified Diphtheria Toxoid is provided in MA file.
- **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.
  - This glass bottle is manufactured from low alkali borosilicate type 3.3-expansion glass.
  - 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.

- **Physicochemical and Biological Properties**

Physicochemical and Biological properties of active ingredients of Diphtheria and Tetanus Vaccine Adsorbed (pediatric) 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 (Pediatric) 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:

- Official Site of Manufacturing and Quality Control:
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 (Pediatric).

- 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 (Pediatric) 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**

-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**

Container Closure System used for 10-dose vial of 5 mL DT vaccine adsorbed:

- Clear white 5ml flint tubular vial, Type I
- 13 mm plain gray bromobutyl rubber stoppers/plugs (V-50)
- 13mm Pantone PMS Yellow Flip off Aluminium Seals

Description and specification of primary packaging materials (glass ampoule) of Diphtheria and Tetanus Vaccine, adsorbed (Pediatric)were well described in MA file.

- **Stability of the drug product.**

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

- ✓ Store between 2-8°C,
- ✓ not to be frozen and not to be stored in ice compartments

3. Non –clinical aspect:

DT(P) stimulates immunity to diphtheria and tetanus by inducing production of specific antitoxins and antibodies in Pediatrics. Three injections of 0.5 ml at least four weeks apart followed by a fourth dose 6 to 12 months later. The vaccine should be injected intramuscularly.
No formal toxicity studies were done on DT vaccine, as per the prevalent regulatory norms. However, these studies have been previously conducted on DTP group of 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 SIIL DT vaccine are same as that of SIIL DTPw-HB vaccine (adsorbed), DTP-HB + Hib vaccine (liquid -lyophilized), DTP-HB-Hib vaccine (Fully liquid), DTP + Hib vaccine (liquid -Iyophilized) and DTP-Hib vaccine (liquid). In all these studies, multiples of human doses were found safe in rats, rabbits and mice.
Regarding the other pre-clinical studies viz. Embryo toxicity (i.e. development toxicity), Perinatal toxicity (i.e. developmental toxicity), Carcinogenicity and Genotoxicity) these studies are not applicable to vaccines according to the guidelines published by the WHO for Non-clinical evaluation of vaccines.
Also the safety of DT Vaccine is established by studies such as “Specific Toxicity”, and “Abnormal Toxicity”, which are conducted on every batch of the DT vaccine before being released into the market.

4. Clinical aspect:

Clinical overview:
Diphtheria and Tetanus Vaccine Adsorbed (Pediatric) is a combined toxoid vaccine indicated for active immunization against diphtheria and tetanus in children below 7 years of age, particularly when vaccination with pertussis-containing vaccines is contraindicated. The vaccine has been licensed since 1974 and was prequalified by the World Health Organization (WHO) in 1995. It has been supplied through international procurement programs, including UNICEF and other United Nations agencies, and has extensive post-marketing experience, with more than 65 million doses reportedly administered worldwide.
The clinical development package included one Phase IV, open-label, single-arm study evaluating the immunogenicity and safety of a booster dose in children aged 4-6 years. Given the well-established protective antibody correlates for diphtheria and tetanus, immunogenicity data were considered an appropriate surrogate for clinical efficacy. Safety information was further supported by long-term post-marketing surveillance through Periodic Safety Update Reports (PSURs) and extensive worldwide use.

Clinical Efficacy

Clinical efficacy was assessed through immunogenicity endpoints using established serological correlates of protection, defined as antibody concentrations ≥0.1 IU/mL for both diphtheria and tetanus.

The Phase IV study enrolled 244 healthy children aged 4–6 years who had previously completed primary DTP immunization and the first booster dose. A total of 210 subjects were included in the per-protocol immunogenicity analysis.

One month following administration of a single booster dose, seroprotection rates increased from 69.5% to 98.1% for diphtheria and from 85.7% to 100% for tetanus. These increases were statistically significant ($p<0.001$ for both antigens).

Significant increases in geometric mean antibody titers (GMTs) were also observed. Anti-diphtheria GMTs increased from 0.35 IU/mL pre-vaccination to 2.01 IU/mL post-vaccination, while anti-tetanus GMTs increased from 0.56 IU/mL to 1.48 IU/mL.

These findings demonstrate a robust booster response and support the effectiveness of the vaccine in maintaining protective immunity against diphtheria and tetanus.

Clinical Immunogenicity

The vaccine demonstrated strong immunogenicity following booster administration in children aged 4-6 years. One month after vaccination, protective antibody levels were achieved in 98.1% of subjects for diphtheria and 100% of subjects for tetanus.

Furthermore, statistically significant increases in GMTs were observed for both vaccine antigens, indicating effective stimulation of immune memory and reinforcement of protection against diphtheria and tetanus.

The immunogenicity results are consistent with internationally accepted criteria for protection and support the use of the vaccine as a booster dose in the target pediatric population.

Clinical Safety

Safety was evaluated in 223 subjects in the intention-to-treat population and 210 subjects in the per-protocol population. The vaccine was generally well tolerated.

Solicited local adverse reactions were predominantly mild and transient:

- Pain at injection site: 42%
- Redness: 29%
- Swelling: 30%

Most local reactions resolved within 1–2 days without sequelae.

Solicited systemic adverse reactions were infrequent:

- Fever: 4%

Reported fevers were generally mild to moderate (38-39°C), resolved within 1–5 days, and did not result in complications.

Unsolicited adverse events included isolated cases of weakness, dizziness, rash, vomiting, cough, cold symptoms, anemia, enteric fever, and worm infestation. These events were assessed as not causally related to vaccination and resolved without sequelae.

One serious adverse event (hospitalization due to enteric fever) was reported. Following clinical evaluation, the event was determined to be unrelated to vaccine administration, and the subject recovered completely.

Post-marketing safety data collected through Periodic Safety Update Reports (PSURs) and extensive worldwide use involving millions of administered doses did not identify new or unexpected safety concerns.

Benefit-Risk Assessment

The benefits of Diphtheria and Tetanus Vaccine Adsorbed (Pediatric) are supported by:

- Established protective efficacy of diphtheria and tetanus toxoid vaccines.
- Demonstration of high post-vaccination seroprotection rates (98.1% for diphtheria and 100% for tetanus).
- Significant increases in antibody titers following booster administration.
- Extensive historical use and post-marketing experience worldwide.

The identified risks were primarily mild and transient local and systemic reactions consistent with the known safety profile of toxoid-containing vaccines. No vaccine-related serious adverse events were identified.

Considering the demonstrated immunogenicity, acceptable safety profile, and the well-established role of booster vaccination in maintaining protection against diphtheria and tetanus, the overall benefit-risk balance is considered favorable.

Overall Conclusion

Diphtheria and Tetanus Vaccine Adsorbed (Pediatric) demonstrated robust immunogenicity when administered as a booster dose in children aged 4-6 years, with post-vaccination seroprotection rates of 98.1% for diphtheria and 100% for tetanus, accompanied by statistically significant increases in antibody titers.
The vaccine exhibited an acceptable safety profile, characterized mainly by mild and transient local and systemic adverse reactions. One serious adverse event was reported and was assessed as unrelated to vaccination.
The clinical findings, together with extensive post-marketing experience, WHO prequalification status, and long-standing international use involving more than 65 million administered doses, support the effectiveness and safety of the vaccine in the indicated pediatric population. Overall, the benefit-risk balance of Diphtheria and Tetanus Vaccine Adsorbed (Pediatric) is positive and supports its use for booster immunization against diphtheria and tetanus in children.

5. General Conclusion and Recommendations if any:

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