Unit: Technical Assessment Unit

Public assessment report for biological products

Diphtheria - Tetanus - Pertussis (Whole cell) Vaccine Adsorbed

Administrative information:

Trade name of the medicinal product:	Diphtheria - Tetanus - Pertussis (Whole cell) Vaccine Adsorbed
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 Ltd., 212/2, Hadapsar, Pune 411028, Maharashtra, India
Applied Indication(s):	For the primary immunization of infants, above the age of six weeks, and of pre-school children against diphtheria, tetanus and whooping cough.
Pharmaceutical form(s) and strength(s):	Suspension for injection: vial of 5 ml (10 doses) Each dose contains: Diphtheria toxoid ≤ 25Lf (≥ 30IU) Tetanus Toxoid ≥ 5Lf (≥ 40IU) B.pertussis ≤ 16 OU (≥ 4IU) Adsorbed on aluminium phosphate Al ions ≤ 1.25 mg Thiomersal (Preservative) 0, 01%
Route of administration	IM injection
Type of registration (EMA/FDA – Local)	Imported

List of abbreviations

BCG	Bacille-Calmette-Guérin
GMT	Geometric mean of Ab titer
Hep B	Hepatitis B
Hib	Haemophilus influenzae type b
FHA	Purified Filamentous Hemagglutinin

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wP	Whole-cell pertussis
acP	acellular Pertussis
AE(s)	Adverse event(s)
DTP	Diphtheria, tetanus, and Pertussis
HBsAg	Hepatitis B surface Antigen
IPV	Inactivated Vero Trivalent Poliovaccine
OPV	Oral Poliovirus Vaccine
SIDS	Sudden Infant Death Syndrome
SIIL:	Serum Institute of India Limited
MNT	maternal neonatal tetanus
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, Tetanus and Pertussis Vaccine Adsorbed is prepared by combining purified Diphtheria toxoid, Purified Tetanus toxoid and killed Bordetella pertussis bacilli. The antigens are adsorbed onto aluminium phosphate as adjuvant. Thiomersal is added as preservative, the vaccine has appearance of a greyish - white suspension and does not contain horse serum protein. Therefore it does not induce any sensitization to sera of equine origin. The vaccine meets the requirements of WHO TRS 980, EP and IP.

Mode of action

DTP stimulates immunity to diphtheria, tetanus and pertussis by inducing production of specific antitoxins and antibodies. The diphtheria toxoid component provides protection only against the exotoxin elucidated by Corynebacterium diphtheriae, and local infection of the respiratory tract or skin with C. diphtheriae occurs occasionally in immune individuals. Primary immunization

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against diphtheria reduces the risk of developing Diphtheria and the severity of clinical illness. A single IM dose of DTP does not provide protection against diphtheria, tetanus, or pertussis. However, administration of the first 3 doses (usually at 2, 4 and 6 months of age) reportedly provides protection against pertussis in approximately 70-90 % of recipients and immunity to diphtheria and tetanus in more than 86 % of recipients; additional doses at 15-18 months and 4-6 years of age enhance protection through the preschool and early school years, respectively. The vaccine can be safely and effectively given simultaneously with BCG, Measles, Polio vaccines (IPV and OPV), Hepatitis B, Yellow fever Vaccine, Haemophilus influenzae-B and Varicella vaccine

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.

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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

III. Pertussis Vaccine (Inactivated):

- **General information**
  Composed of four inactivated strains of Bordetella pertussis treated to minimize toxicity while preserving potency. It is used for effective immunization against whooping cough.
- **Manufacture, process controls and characterization:**

- **Manufacturer**:
  The drug substance is manufactured by Serum Institute of India Pvt. Ltd., 212/2, Hadapsar, Pune 411028 Maharashtra State - India. Building no.6. Ground Floor and SEZ 7, Second Floor.
- **Description of Manufacturing Process and Process Controls**
  Pertussis (whole cell) bulk vaccine manufactured by Inactivation of Bordetella pertussis culture in Shake flask method as well as fermenter method.
  The manufacturing process for the active substances has been described. Appropriate in-process controls are applied to ensure consistency and quality. Full details for the manufacturing process are available in the MA file.

- **Control of Materials.**
  List of raw materials used are mentioned in MA file.
- **Controls of Critical Steps and Intermediates**
  In-process controls tests are performed.
  Quality control test performed on the intermediate 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: Pertussis bulk vaccine is whitish turbid liquid.

Biological characterization: The potency of bulk pertussis vaccine is not less than 4 IU in the volume recommended for the single human dose and the lower fiducial limit (P=0.95) of the estimated potency is not less than 2 IU.

- **Specification**
  Specifications of Pertussis Bulk 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 methods validation are performed as per latest edition of British Pharmacopoeia, European Pharmacopoeia, WHO TRS 941.
  Batch analysis
  Upon evaluation of submitted batch analysis results, consistency of production was observed.
- **Reference Standards or Materials**
  At SII, working Reference standard for whole cell Pertussis bulk vaccine is used to test Pertussis Bulk is calibrated using International Reference Standard.
- **Container closure system**
- Pertussis bulk vaccine is stored in a sterile glass bottle (Borosil) of 20 L capacity at 2-8°C. The glass bottles are closed with sterile silicon bungs.
- **Stability of drug substance**
  Storage condition: 2-8 °C for 12 months

2.2.3 Drug product:

- **Description and Composition of the Drug Product:**
  Diphtheria, Tetanus and Pertussis Vaccine Adsorbed is prepared by combining purified Diphtheria toxoid, Purified Tetanus toxoid and killed Bordetella pertussis bacilli. The antigens are adsorbed onto aluminium phosphate as adjuvant. Thiomersal is added as preservative, the vaccine has appearance of a greyish - white suspension and does not contain horse serum protein. Therefore, it does not induce any sensitization to sera of equine origin.

- Pharmaceutical Development including brief description on Components of drug product.
Formulation Development
Selection of blending procedure: The final selection of blending procedure is done after considering CORE OBJECTIVE, large quantity requirements, production suitability, stability of the product and reproducibility.
DTP Vaccine, Adsorbed is available as; Ten dose Vials (10 x 0.5 mL)
DTP composition:

- Antigen concentration: On the basis of existing WHO TRS the individual antigen concentration is selected and tested.
- Adjuvant: The basis of selection of adjuvant is, as per the existing WHO TRS
- Preservative: Thiomersal is used as preservative at 0.01% concentration.

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- Overages

No overages are added in the formulation of DTP Vaccine, Adsorbed.

- Physicochemical and Biological Properties

- **Manufacturing Process Development.**

SIIL received WHO prequalification for DTP vaccine facility for exporting of vaccines. Since then the company is exporting the vaccine to more across the globe After the approval , the developments which were done during the various stages of vaccine production can be highlighted as follows.

1. During the blending of DTP vaccine, the toxoids and 2% Thiomersal are again filtered through 0.2 micron as a precautionary measure
2. Batch size has been increased to 2800lts with the introduction of higher capacity blending vessels.
3. There is a facility having integrated washing, tunnel and filling sealing and online physical inspection of vials.of high speed.because of which 100 thousand vials per day can be filled.

- **Container closure system**

DTP Vaccine Adsorbed 5 mL - 10 Dose Vial: 5 mL clear transparent tubular vial USP type I glass Rubber stopper: 13 mm Grey Bromobutyl rubber Plugs (V-50) symmetrical with clean and smooth surfaces Flip off seal: 13 mm PMS Yellow colour flip off seal

- Microbiological Attributes.

Diphtheria-Tetanus-Pertussis Vaccine Adsorbed is a sterile product. Thiomersal in the final concentration of 0.01 % is used as an antimicrobial preservative.

- **Compatibility.**

The compatibility of the product has been proved from the established stability studies. The product is found to be stable up to 24 months from the date of manufacture.

- **Manufacture of the drug product:**

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

- Control of critical steps and intermediates

Critical steps are tightly controlled.

- Process validation and / or evaluation.

Validation are performed and all parameters and final bulk results met the acceptance criteria. Validation reports are available in the MA file.

- **Product specification:**

Release specifications for the DTP vaccine comply with I.P, and WHO TRS specifications. Detailed SOPs, validation protocols, and reports for in-house methods are available in the MA file.

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- **Reference Standards or Materials.**
  Reference standards used for testing are suitable, validated, and fully described in the MA file.
- **Container closure system.**
  The DTP vaccine is filled in 5 mL clear transparent tubular Vial USP type I ,sealed with Rubber Stopper Grey Bromobutyl rubber Plugs (V-50) symmetrical with clean and smooth surfaces and PMS Yellow colour flip off seal. Full specifications are available in the MA file.
- **Stability of the drug product.**
  The finished product self-life decided as 24 months (2 years)
  upto a period of 24 months when the vaccine is stored at the recommended storage conditions of +2 to +8°C

3. Non –clinical aspect:

-No formal pharamacology or toxicity studies were done on DTP vaccine, as stated by the applicant. However, the non-clinical studies are performed on DTP group of vaccines, which contain similar or more quantities of tetanus toxoid, diphtheria toxoid & B.pertussis.
-The strain, and all other technical details of diphtheria toxoid, tetanus toxoid & B.pertussis used for SIIL DTP 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 – lyophilized) and DTP-Hib vaccine (liquid).

4. Clinical aspect:

➢ **<u>Clinical Overview</u>**

Diphtheria, Tetanus and Pertussis Vaccine, Adsorbed is manufactured by **Serum Institute of India** Limited (SIIL) in accordance with the guidelines laid down by **World Health Organization** (WHO), Geneva.

It is used for the **primary** immunization of **infants**, above the **age of six weeks**, and of **pre-school children** against **diphtheria**, **tetanus** and **whooping cough**. The vaccine can be **safely** and **effectively** given simultaneously with **BCG, Measles, Polio** vaccines (**IPV and OPV**), **Hepatitis B**, **Yellow fever** Vaccine, **Haemophilus influenzae-B** and **Varicella** vaccine.

Though **no pre-licensure** clinical studies **(Phase I, II or III)** were done on **DTP** Vaccine Adsorbed, it was licensed in July 24, 1974 by the Indian Drug Regulatory Authorities, as per the prevalent regulatory norms in India. The same was also **prequalified** by **WHO** in 1995.

Five Phase IV clinical studies are performed on **DTP Vaccine** and the **safety** and **efficacy** of the **antigenic** components is established.

➢ Clinical Efficacy and Clinical Immunogenicity:

Two Phase IV clinical studies have been performed on **DTP** Vaccine to assess the **immunogenicity** produced by the antigens present in it.

Immunogenicity and or **seropositivity** results of **DTP** Vaccine Adsorbed, is sufficient to demonstrate clinical **efficacy** as, containing known antigens for which the level of **protective** antibody is **well established**.

Immunogenicity and or **seropositivity** of **DTP** Vaccine is studied comparatively. In this, comparison is made based on the **technique** used in manufacturing. **DTP** Vaccine is manufactured by two different techniques one is by **shake-flask** and another by **fermentor**.

In **study I** the results showed that both the **Vaccines** are **efficacious** and induced mean **antibody** levels against all **3 components** of **Vaccine** were protective for more than **2 years**, when **booster** dose is recommended.

Post immunization antibody levels produced **DTP** Vaccine manufactured by **both** the **Fermentor** and **shake flask** technique is **efficacious and safe**.

In **study II** the results showed that both the Vaccines produced by **Shake Flask** and **Fermentor** technique are **safe and efficacious** giving **similar immunological** response to the **infants aged 6-14 weeks**.

➢ Clinical Safety

Five Phase IV studies have been performed on **DTP** Vaccine to assess the **reactgenicity**. The **results** of these studies **shown** that **DTP** Vaccine of Serum Institute of India Ltd. (SIIL) **is safe**.

These studies showed that there were **no serious adverse events**. However, there are other **common adverse events** like **Redness**, **Irritability**, **Anorexia**, **Drowsiness**, **Vomitting**, **Diarrhoea** and **Excessive Crying**. The adverse resolved without any concomitant medications.

Results of **reactogenicity** in **study I** and **II** also shown that **DTP** Vaccine manufactured by **both** the **technique** were **well tolerated** and the **adverse events** observed were **comparable** and well within the range quoted in the literature.

In **study III**, the **adverse events** reported were local **pain (23 %)**, **Local swelling (9 %)**, **Local Redness (8 %)**, **Local nodule (1 %)** and **Fever > 38 ºC** is **30 %**.

No case of **Fever > 40.50 ºC**, **Vomiting**, **Encephalopathy**, **SIDS**, **Infantile spasm** and **anaphylaxis** were reported. This result proves that the **DTP** Vaccine of **Serum Institute of India** Ltd. is **comparable** to other **whole cell DTP** Vaccines with respect to **reactogenicity**.

In **Study IV**, which is carried out with the **primary objective** of assessment of **adverse local, systemic** and **neurological adverse events** following administration of **DTP** Vaccine Adsorbed of **Serum Institute**

of India. Secondary objective of this study was to compare the occurrence of **adverse events** with a comparative group which received another commercially **available DTP** Vaccine of Aventis.

In **study V**, which is intented to treat and **Per protocol analysis** study **is carried out to assess** the **local and systemic adverse events** and results of this study is given in as follows;

	Intention To Treat (ITT)	Per-Protocol Analysis (PP)
Reported Solicited Local Reactions		
Pain	74.81 %	75.29 %
Redness	17.05 %	17.25 %
Swelling	31.56 %	31.75 %
Nodule	2.42 %	2.47 %
Reported Solicited Systemic Reactions		
Fever	47.62 %	48.03 %
Irritability	45.27 %	46.35 %
Anorexia	11.11 %	11.26 %
Drowsiness	1.56 %	1.54 %
Vimiting	2.40 %	2.45 %
Diarrhoea	1.39 %	1.36 %
Excessive Crying	0.22 %	0.23 %

DTP Vaccine Adsorbed, manufactured by the Serum Institute is very **safe** and **tolerable** in a large population of Indian toddlers of **15-24 months age**, when given as the **first booster** dose. Few reactions may occur which are **mild** to **moderate in severity** and **resolve without any sequelae**. The **incidences of reactions** are in the line with published literature.

- **Benefit-Risk Assessment**

Benefits:

DTP Vaccine is used for **prevention** of Diphtheria, Tetanus and Pertussis. **These diseases** are important cause of **infant death** worldwide.

Introduction of **3 doses of DTP** followed by **booster doses** in the **national immunization schedule** resulted in a **decline** in the **incidences** of these **diseases dramatically**.

Risk:

- Administration of DTP Vaccines causes **local reaction like pain**, **swelling**, **tenderness** at **the injection site**, and **systemic reactions** like **fever**, **irritability**, **persistent crying**, **vomiting** and **diarrhoea**.
- All **adverse events** are **mild** and **resolve without** any sequelae. **Febrile convulsions** may occur in **1 case** in **12,500** doses administered, **hypnotic-hypo responsive** episodes may occur in **one case** in **1750** doses administered. Incidence of **anaphylaxis** is **rare** and may occur in **two** cases in **100,000** doses administered It has been proven that there is **no causal** link between **DTP** Vaccine and **infantile spasms**, **encephalopathy** and **sudden infant death** syndrome.

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- **Clinical Conclusion**

Overall, the available clinical, immunogenicity, safety, and post-marketing evidence demonstrates that SIIL DTP Vaccine, Adsorbed is an effective, immunogenic, safe, and well-tolerated vaccine for primary immunization and booster vaccination in infants and young children. The overall benefit-risk balance remains positive and supports its continued use in routine pediatric immunization programs.

5. General Conclusion and Recommendations if any:

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

(DTP ITO)