Unit: Technical Assessment Unit

Public assessment report for biological products

(Diphtheria, Tetanus, Pertussis, Hepatitis B and Haemophilus influenzae type b conjugate Vaccine Adsorbed – single dose vial 0.5 ml & multi dose vial 5 ml.)

Administrative information:

Trade name of the medicinal product:	Diphtheria, Tetanus, Pertussis, Hepatitis B and Haemophilus influenzae type b conjugate Vaccine Adsorbed – single dose vial 0.5 ml & multi dose vial 5 ml.
INN (or common name) of the active substance(s):	**Each dose of 0.5 ml contains:** ▪ Diphtheria Toxoid ≤ 25 Lf (≥ 30 IU). ▪ Tetanus Toxoid ≥ 2.5 Lf (≥ 40 IU). ▪ B. Pertussis (whole cell) ≤ 16 OU (≥ 4 IU). ▪ HBsAg (rDNA) ≥ 10 mcg. ▪ Purified Capsular Hib Polysaccharide (PRP) conjugated to Tetanus Toxoid (carrier protein) 10 mcg. ▪ Adsorbed on aluminum phosphate, Al3+ ≤ 1.25 mg ▪ Thiomersal 0.005 %.
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):	Active immunization of infants, at or above the age of 6 weeks against Diphtheria, Tetanus, Pertussis, Hepatitis B and Haemophilus influenza type b.
Pharmaceutical form(s) and strength(s):	Suspension for intramuscular injection.
Route of administration	IM
Type of registration (EMA/FDA – Local)	Imported

List of abbreviations

1. AI – Active Ingredient
2. HBsAg – Hepatitis B Surface Antigen
3. Hib – Haemophilus influenzae type b
4. MA file – Marketing Authorization file
5. DT – Diphtheria Toxoid
6. TT – Tetanus Toxoid
7. IU – International Unit

8. Lf – Limit of flocculation (antigenic unit for diphtheria and tetanus toxoids)
9. PRP – Polyribosylribitol Phosphate (Hib capsular polysaccharide)
10. QC – Quality Control
11. WFI – Water for Injection
12. IP – Indian Pharmacopoeia
13. BP – British Pharmacopoeia
14. WHO – World Health Organization
15. D: Diphtheria.
16. SIIL: Serum Institute of India Ltd.
17. Td: Tetanus and Diphtheria.
18. T: Tetanus
19. DTP-HB-Hib: Diphtheria, Tetanus, Pertussis-Hepatits B-Haemophilus influenzae type b conjugate
20. LD50: Lethal dose 50

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1. General introduction about the product including brief description of the AI, its mode of action and indications.

The DTP-HB-Hib Adsorbed Vaccine, supplied by SII, is a homogeneous liquid preparation. It is indicated for active immunization of infants, at or above the age of 6 weeks against Diphtheria, Tetanus, Pertussis, Hepatitis B and Haemophilus influenza type b as it contains purified diphtheria and tetanus toxoids, inactivated Bordetella pertussis organisms, and highly purified, non-infectious particles of the hepatitis B surface antigen (HBsAg). In addition, it includes a Hib component, which is a bacterial subunit vaccine consisting of purified, non-infectious Haemophilus influenzae type b (Hib) capsular polysaccharide chemically conjugated to tetanus toxoid protein. The vaccine complies with the recommendations of the World Health Organization. It has been WHO-prequalified since September 2010.

The DTP-HB-Hib vaccine is available in two presentations: Single-dose vials (1 × 0.5 mL) and Ten-dose vials (1 × 5.0 mL).

2. Quality aspects:

2.2.1 Introduction

Mentioned in above general introduction.

2.2.2 Drug Substance (Active ingredient)

Purified diphtheria toxoids, Purified tetanus toxoids, Bordetella pertussis, Hepatitis B, and Haemophilus influenzae type b.

- **General information**

Purified diphtheria toxoids: A protein toxin inactivated by formaldehyde, which loses its toxicity but remains immunogenic. It provides strong and stable immune protection against diphtheria.
Purified tetanus toxoids: Produced from Clostridium tetani toxin that is detoxified with formaldehyde, retaining immunogenicity while losing virulence. It induces protective immunity against tetanus.
Pertussis Vaccine (Inactivated): Composed of four inactivated strains of Bordetella pertussis treated to minimize toxicity while preserving potency. It is used for effective immunization against whooping cough.
Hepatitis B Surface Antigen (HBsAg): Produced by recombinant DNA technology, with the gene cloned into bacterial vectors for antigen expression. It induces strong immune responses to prevent Hepatitis B infection.
Haemophilus influenzae type b (Hib) Conjugate: A polysaccharide antigen from Hib covalently linked to a carrier protein (Tetanus toxoid) to enhance immunogenicity. It provides effective protection against invasive Hib diseases such as meningitis.

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

The drug substance is manufactured by Serum Institute of India Pvt. Ltd., 212/2, Hadapsar, Pune 411028 Maharashtra State - India.

The manufacturing process for the five 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.

All starting materials used in the production of DT, TT, B, pertussis, HB, and HiB are controlled according to relevant pharmacopeial standards to make sure they are safe and effective. Acceptance criteria for each critical step and intermediate such as step are proposed and justified.

Validation was conducted on three consecutive batches for DT, TT, B, pertussis, HB, and HiB. All results met the acceptance criteria Full validation protocol and reports are available in the MA file.

The manufacturing process of DT, TT, B, pertussis, HB, and HiB was developed and optimized. The development history is fully described in the MA file.

- **Characterization.**

All active substances were adequately characterized, with their physicochemical and biological properties described, and impurity profiles controlled; full details are available in the MA file.

Purified diphtheria toxoids: Purified diphtheria toxoid is a clear yellow solution with antigenic purity not less than 1500 Lf/mg of protein nitrogen. Impurities are removed during purification using ultrafiltration and diafiltration processes.

Purified tetanus toxoids: Purified tetanus toxoid is a clear brown solution with potency not less than 1000 Lf/mg of protein nitrogen. Non-immunogenic and low molecular weight impurities are controlled during purification.

Bordetella pertussis: Pertussis bulk vaccine is composed of inactivated Bordetella pertussis strains containing different agglutinogens. The potency of the bulk is not less than 4 IU per human dose.

Hepatitis B Surface Antigen (HBsAg): HBsAg characterization includes construction and testing of the recombinant production strain. The antigen is produced in yeast cells and further characterized to ensure purity and potency.

Hib Conjugate: Hib conjugate consists of PRP polysaccharide covalently linked to tetanus toxoid as carrier protein. Impurities such as protein and nucleic acids are controlled during polysaccharide purification.

- **Specification**

The release specifications for the fine active ingredients comply with the relevant standards. Full details are available in the MA file.

- **Analytical Procedures.**

Full validated analytical procedures for testing diphtheria toxoid, tetanus toxoid, Bordetella pertussis, HB, and Hib are provided in the MA file to ensure their quality and compliance with specifications.

- **Batch analysis.**

Three consecutive batches of diphtheria toxoid, tetanus toxoid, pertussis antigen, HB, and Hib were analyzed. All quality control results complied with the release specifications, confirming consistency and reproducibility of the manufacturing process.

- **Reference Standards or Materials.**
  Suitable reference standards are used for testing each of the five active substances. The standards are appropriately characterized, calibrated against international references where applicable, and details are available in the MA file.

- **Container closure system**
  For DT, TT, and B. Pertussis: Stored in sterile Borosil glass bottles, sealed with sterile silicon bungs, at 2–8 °C.
  Hepatitis B Surface Antigen (HBsAg): Stored in Schott Duran borosilicate glass bottles with sterilized caps, at 2–8 °C.
  Hib Conjugate: Stored in pre-sterilized glass bottles after 0.22 µm filtration, at 2–8 °C.

- **Stability of drug substance**
  Purified diphtheria toxoids: Stable up to 60 months at 2–8 °C; some batches up to 72 months. Stable 6 months under accelerated conditions.
  Purified tetanus toxoids: Stable up to 60 months at 2–8 °C; some batches up to 48 months. Stable 6 months under accelerated conditions.
  Bordetella pertussis: Stable up to 18 months at 2–8 °C; 2 months under accelerated conditions. proposed shelf life 12 months.
  Hepatitis B Surface Antigen (HBsAg): Stable up to 36 months at 2–8 °C; 6 months under accelerated conditions. Proposed shelf life 36 months.
  Hib Conjugate: Stable under recommended refrigerated storage 2–8 °C throughout proposed shelf life.

2.2.3 Drug product:

- **Description and Composition of the Drug Product:**
  The DTP-HB-Hib vaccine is a combined formulation containing purified diphtheria toxoid, tetanus toxoid, inactivated whole cell pertussis, recombinant hepatitis B surface antigen (HBsAg), and purified Hib polysaccharide conjugated to tetanus protein. The vaccine is adsorbed on aluminum phosphate (adjuvant) and contains thiomersal as preservative. The vaccine complies with WHO requirements.

It is supplied as a homogeneous liquid in single dose (0.5 mL) and multi-dose (5 mL) vials.

Each dose of 0.5 ml contains:

- Diphtheria Toxoid ≤ 25 Lf (≥ 30 IU).
- Tetanus Toxoid ≥ 2.5 Lf (≥ 40 IU).
- B. Pertussis (whole cell) ≤ 16 OU (≥ 4 IU).
- HBsAg (rDNA) ≥ 10 mcg.
- Purified Capsular Hib Polysaccharide (PRP) conjugated to Tetanus Toxoid (carrier protein) 10 mcg.
- Adsorbed on aluminum phosphate, Al3+ ≤ 1.25 mg
- Thiomersal 0.005 %.

- **Manufacture of the drug product:**

The drug product is manufactured by Serum Institute of India Pvt. Ltd., 212/2, Hadapsar, Pune 411028 Maharashtra State - India.

The manufacturing process has three stages: (1) Formulation stage, (2) Blending, and (3) Filling and packaging stage.

Full details and description of the manufacturing process are provided in the MA file. Each step of the process is controlled through defined in-process controls (IPCs).

- **Control of critical steps and intermediates**

Critical steps include: (1) sterile filtration, (2) aseptic addition, and (3) pH adjustment. They are tightly controlled.

- **Process validation and / or evaluation.**

Validation were 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-HB-Hib 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.

- **Reference Standards or Materials.**

Reference standards used for testing are suitable, validated, and fully described in the MA file.

- **Container closure system.**

The DTP-HB-Hib vaccine is filled in Type I glass vials, sealed with bromobutyl rubber stoppers, and sealed with aluminium off cap. Full specifications are available in the MA file.

- **Stability of the drug product.**
  - Shelf life is 2 years
  - Stored at temperature 2 - 8 ◦C.
  - Don't freeze.
  - The liquid vaccine vial should be shaken before use to homogenize the suspension.

3. Non –clinical aspect:

The liquid DTP-HB-Hib vaccine of SIIL has been tested in toxicology studies, with two acute and three repeat dose studies in rats and rabbits. No mortality or abnormal clinical signs, no abnormal lab values nor gross pathological changes were observed in any animal. The LD50 was found to be more than 1ml. Local reactions were the only findings and were similar to control vaccine.

4. Clinical aspect:

Efficacy (Immunogenicity) conclusion:

Four Phase III clinical studies were presented; the first study Ia-DTP HB-Hib assessing the immunogenicity and reactogenicity of the DTP-wHB-Hib vaccine in infants aged 6-14 Weeks, in SIIL vaccine group, postvaccination Geometric Mean Titres were 1.39 IU/ml, 3.27 IU/ml, 42.86 U/ml, 393.4 mIU/ml and 6.55 µg/ml for anti-Diphtheria, anti-Tetanus, anti-Pertussis, anti-Hepatitis B and anti-PRP IgG antibodies. Corresponding values in Panacea vaccine group were 1.35 IU/ml, 3.034 IU/ml, 37.37 U/ml, 379.4 mIU/ml and 6.37 µg/ml respectively. The difference between the post-vaccination geometric mean titres of both the vaccine groups was statistically not significant ($p > 0.2$). Non-inferiority of SIIL vaccine to Panacea vaccine was concluded for all five components including long-term protection, wherever applicable.

The second study Ib-DTP HB-Hib assessing the immunogenicity and reactogenicity of the DTP-wHB- Hib vaccine in infants, in SIIL vaccine group, post-vaccination Geometric Mean Titres were 1.21 IU/ml, 3.00 IU/ml, 51.04 U/ml, 472.2 mIU/ml and 6.53 µg/ml for anti-Diphtheria, anti-Tetanus, anti-Pertussis, anti-Hepatitis B, and anti-PRP IgG antibodies. Corresponding values in Panacea vaccine group were 1.25 IU/ml, 3.19 IU/ml, 49.37 U/ml, 439.6 mIU/ml and 6.58 µg/ml respectively. The difference between the post-vaccination geometric mean titres of both the vaccine groups was statistically not significant ($p > 0.2$).

Non-inferiority of SIIL vaccine to Panacea vaccine was concluded for all five components including long-term protection, wherever applicable.

The Third study Ic-DTP HB-Hib, in SIIL vaccine group, postvaccination Geometric Mean Titres were 1.19 IU/ml, 3.19 IU/ml, 44.63 U/ml, 436.9 mIU/ml and 7.13 µg/ml for anti-Diphtheria,

anti-Tetanus, anti-Pertussis, anti-Hepatitis B and anti-PRP IgG antibodies. Corresponding values in Panacea vaccine group were 1.09 IU/ml, 3.01 IU/ml, 39.39 U/ml, 448.2 mIU/ml and 6.58 µg/ml respectively. The difference between the post-vaccination geometric mean titres of both the vaccine groups was statistically not significant ($p > 0.2$). Non-inferiority of SIIL vaccine to Panacea vaccine was concluded for all five components including long-term protection, wherever applicable.

In the fourth study, in SIIL vaccine group, post-vaccination Geometric Mean Titres were 1.27 IU/ml, 3.15 IU/ml, 46.11 U/ml, 433.0 mIU/ml and 6.72 µg/ml for anti-Diphtheria, anti-Tetanus, anti-Pertussis, anti-Hepatitis B and anti-PRP IgG antibodies. Corresponding values in Panacea vaccine group were 1.23 IU/ml, 3.22 IU/ml, 41.75 U/ml, 420.2 mIU/ml and 6.61 µg/ml respectively. The difference between the post-vaccination geometric mean titres of both the vaccine groups was statistically not significant ($p >0.2$).

Safety (reactogenicity) conclusion:

The first study Ia-DTP HB-Hib, in both the groups, pain at injection site, redness and swelling were common local adverse events. All local adverse events were mild and subsided with or without concomitant medication. Fever was the common systemic adverse event in both the groups. Other systemic adverse events were irritability, persistent crying, vomiting and loss of appetite. The adverse events observed in both the groups resolved with or without concomitant medication. No serious adverse event occurred in any group. Also, there was no case of neurological adverse event or anaphylaxis in any of the groups. Considering overall adverse events profile, non-inferiority of DTPw-HB-Hib (SIIL) was demonstrated in comparison to DTPw-HB-Hib (Panacea Biotech Ltd).

The second study Ib-DTP HB-Hib In both the groups, pain at injection site, redness, and swelling were common local adverse events. All local adverse events were mild and subsided with or without concomitant medication. Fever was the common systemic adverse event in both the groups. Other systemic adverse events were irritability, persistent crying, vomiting, and loss of appetite. The adverse events observed in both the groups resolved with or without concomitant medication. No serious adverse event occurred in any group. Also, there was no case of neurological adverse event or anaphylaxis in any of the groups.

Considering the overall adverse events profile, superiority of DTPw-HB-Hib (SIIL) is demonstrated in comparison to DTPw-HB-Hib (Panacea Biotech Ltd).

In the third study Ic-DTP HB-Hib In both the groups, pain at injection site, redness, and swelling were common local adverse events. All local adverse events were mild which subsided with or

without concomitant medication. Fever was the common systemic adverse event in both the groups. Other systemic adverse events were irritability, persistent crying, vomiting, diarrhoea and loss of appetite. The adverse events observed in both the groups resolved with or without concomitant medication. No serious adverse event occurred in any group. Also, there was no case of neurological adverse event or anaphylaxis in any of the groups. Considering overall adverse events profile, non-inferiority of DTPw-HB-Hib (SIIL) is demonstrated in comparison to DTPw-HB-Hib (Panacea Biotech Ltd).

Non-inferiority of SIIL vaccine to Panacea vaccine was concluded for all five components including long-term protection, wherever applicable.

In the fourth study, in both the groups, pain at injection site, redness, and swelling were common local adverse events. All local adverse events were mild, which subsided with or without concomitant medication. Fever was the common systemic adverse event in both the groups. Other systemic adverse events were irritability, persistent crying, vomiting, diarrhoea, loss of appetite, and URTI. The adverse events observed in both the groups resolved with or without concomitant medication. No serious adverse events occurred in any group. Also, there was no case of neurological adverse event or anaphylaxis in any of the groups.

Considering overall adverse events profile, superiority of DTPw-HB-Hib (SIIL) is demonstrated in comparison to DTPw-HB-Hib (Panacea Biotech Ltd).

Based upon the results of the phase III clinical trial, it was concluded that DTPw-HB-Hib vaccine manufactured by Serum Institute of India Ltd., Pune, is safe, immunogenic, and comparable to the standard commercially available WHO-prequalified Easy Five vaccine of Panacea Biotech Ltd. The immunogenicity was proved in the schedule and dose same as that of the National Immunization Schedule. Vaccine recipients had adverse events similar to those observed in other studies and quoted by WHO. In conclusion, the benefit associated with the receipt of this vaccine greatly outweighs the minimal risk associated with vaccination.

5. General Conclusion and Recommendations if any:

The DTP-HB-Hib Adsorbed Vaccine, manufactured by Serum Institute of India Ltd., is a safe, effective, and high-quality combination vaccine providing active immunization against Diphtheria, Tetanus, Pertussis, Hepatitis B, and Haemophilus influenzae type b in infants from six weeks of age. Comprehensive quality, non-clinical, and clinical evaluations demonstrated that the vaccine meets WHO standards, maintains stability and consistency across batches, and induces strong immunogenic

responses comparable to WHO-prequalified reference vaccines. No serious adverse events were observed, and all reported reactions were mild and self-limiting. Overall, the benefits of vaccination with this product significantly outweigh the minimal associated risks.