Product Permission Document (PPD) of Typhoid Polysaccharide Vaccine I.P. (Brand Name – Bio-Typh™)

1. Introduction

Typhoid Polysaccharide Vaccine is a preparation of purified Vi capsular polysaccharide obtained from *Salmonella typhi* Ty2 strain of known origin and history that has the capacity to produce Vi polysaccharide, and which have been characterized by suitable biochemical, physicochemical, serological or molecular methods.

Capsular polysaccharide is a partly 3-0-acetylated repeated units of 2-acetylamino-2-deoxy-D-galactopyranuronic acid with a-(1-74)-linkages.

A clear solution containing purified Vi capsular polysaccharide of *Salmonella typhi* for prevention of typhoid fever.

1.1. Submission file :-

The product was licensed on Form 28-D dated 20/03/2004.
F-No. 12-09/BIOMED/14-BD

1.2. NDS Approval date and control :-

i. Drug/837/8324 dated 01/07/2010
ii. Drug/837/717 dated 23/01/2015 and counter signed by CLA vide letter No: Drug/837/3286 dated 19/05/2017

1.3. PPD –Biological revision date and control :-

PPD Biological Rev 01, dated 01/06/2017.

1.4. Proprietary Name:-

Bio Typh™

1.5. Non Proprietary name and common name of drug Product:-

Typhoid Polysaccharide Vaccine I.P.

1.6. Company Name :-

BIO-MED (P) LTD.
C-96, Site No. 1,
Bulandshahr Road Industrial Area,
Ghaziabad - 201 009 (U.P.) INDIA
Phone : 0120-4157534, 4204862
Fax : 0120-4340219
e-Mail :bmvaccine@yahoo.com
Website: www.biomed.co.in

1.7. Name of Indian Distributer/Agent :-

Not Applicable as we are indigenous manufacturer of vaccine.

1.8. Therapeutic or Pharmacological classification :-

Vaccine/injectables

1.9. Dosage form(s) :-

Liquid Vaccine

1.10 Strength (s) :-

One Dose (0.5 ml) contains:

Vi polysaccharide of *Salmonella typhi* (strain Ty2) 25mcg
Phenol I.P. (Preservative).....≤ 0.25%
Isotonic saline (buffered) q.s.....0.5ml

1.11 Route of Administration:-

Intramuscular or Subcutaneous route.

1.12 Maximum Daily Dose :-

Not Applicable

2. New Active Substance (NAS) :

There is no new active substance used.

S. Drug substance (name & manufacturer)

S.1. Manufacturer (name, manufacturer) and Address:-

S.1.1. Manufacturer(s) (name, manufacturer):-

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S.1.2. Description of manufacturing process & process control (name, manufacturer):-

Manufacturing Process	Controls
Strain of *Salmonella typhi* ty2V, obtained from Statens Serum Institute, Denmark, capable of producing the Vi polysaccharide.	Record of history and characterization
Seed propagation and establishment of master seed lot (freeze dried). Stored at or below -20°C. Passage level – P0	The cultures have following characteristics: (1) stained smears made from a culture shall be typical of *S. typhi*: (2) the cultures shall utilize glucose without production of gas; (3) the colonies on agar shall be Oxidase-negative; (4) a suspension of a culture shall be agglutinated specifically with an appropriate anti-Vi antiserum or colonies shall form haloes on an antiserum-containing agar plate.
Seed propagation and establishment of working seed lot (freeze dried). Stored at or below -20°C. Passage level – P1	
Preparation of precultures from working seed lot for inoculum for fermenter. (20 ml, 250 ml, 5000 ml)	Bacterial purity, identification by microscopic examination of Gram's stained smears (at least 10,000 organisms are inspected), motility test.
Fermenter culture (110 liters), Passage level – P5	• Culture media sterility • pH control • Dissolved oxygen control. • Temperature control • Rotation speed control • Control of bacterial purity By microscopic examination of Gram's stained smears (at least 10,000 organisms are inspected), motility test, inoculation into solid media.
Harvesting and inactivation by adding formaline (0.5%)	Control of bacterial inactivation.
Bacterial cell separation by continuous flow centrifugation	Control of centrifugation speed.
Precipitation of Vi polysaccharide from culture supernatant by addition of 0.2% cetavalone	•pH control •Temperature control
Dissociation of Vi polysaccharide–cetavalone complex	• Control of centrifugation speed. • Temperature control
Purification of Vi polysaccharide by ethanol precipitation, cold phenol extraction	• Control of centrifugation speed. • Temperature control
Purified polysaccharide lot (Store at or below –20°C)	• Moisture content • Protein content • Nucleic acid content • O-acetyl content • Molecular size • Identity • pH • Cetrimide • Sterility • Free Formaldehyde • Bacterial Endotoxins

S.1.3. Control of materials :-

As discussed in the point No. S.1.2.

S.1.4. Control of critical steps & intermediate:-

As discussed in the point No. S.1.2.

S.2. Characterization:-

S.2.1. Elucidation of structure and other characteristics:-

S.2.1.1 Physicochemical Characterization :-

The purified polysaccharide lot of Typhoid Polysaccharide Vaccine is characterized as per the guidelines of Indian Pharmacopoeia and W.H.O. T.R.S. Guidelines.

Analytical testing performed to characterize the purified polysaccharide lot of Typhoid Polysaccharide Vaccine are follows :-

- Nucleic acid content determination
- Protein content determination
- O-acetyl content determination
- Moisture content determination
- Identity test
- Molecular size
- Bacterial Endotoxins
- pH
- Cetrimide
- Free formaldehyde
- Sterillity

S.2.1.2 Biological Characterization :-

Each purified polysaccharide lot is tested for identity by rocket immuno electrophoresis and sterility by direct inoculation method

S.2.2. Impurities:-

The impurities such as protein, nucleic acid and bacterial endotoxins were removed during the purification process of the Purified Vi Polysaccharide Typhoid bulk.

S.3. Control of Drug substance:-

S.3.1. Specification:-

S. No.	Quality Control Test	Specifications as per Indian Pharmacopoeia
1.	Moisture content	The loss on drying or moisture content is determined by thermogravimetry method and is used to calculate the results of the chemical tests of purified polysaccharide with reference to the dried substance.
2.	Protein	Each purified Vi polysaccharide lot shall contain less than 10 mg protein per gram of polysaccharide calculated with reference to the dried substance.
3.	Nucleic acids	Each purified Vi polysaccharide lot shall contain less than 20 mg of nucleic acid per gram of polysaccharide, calculated with reference to the dried substances.
4.	O-Acetyl groups	Not less than 2 mmol per gram of polysaccharide, calculated with reference to the dried substance.
5	Molecular size	In molecular size assay, at least 50% of the Vi polysaccharide is found in the pool containing fractions eluted before a K_o = 0.25.
6.	Identification	The identity of the purified Vi polysaccharide lot with an in house standard Vi polysaccharide shall be established by immunochemical method.
7.	Bacterial endotoxins	Not more than 150 I.U. per microgram of polysaccharide.
8.	pH	The pH value of purified Vi polysaccharide lot of Typhoid Polysaccharide Vaccine shall be 7+0.5.
9.	Cetrimide	Yellow precipitate formed in standard solution and there should be no precipitation in test sample.
10.	Free formaldehyde	0.2 g/l is the maximum limit for free formaldehyde in purified Vi Polysaccharide lot of Typhoid Polysaccharide Vaccine. The sample should not be more intense in color than reference solution.
11.	Sterility	If no evidence of microbial growth is found, the preparation under examination complies with the test for sterility.

S.3.2. Stability:-

Stability study at real time (at or below -20°C) and accelerated condition (2-8°C) was carried out on three lots of purified polysaccharide lot (bulk) of Typhoid Polysaccharide Vaccine. The conditions of study and number of batches considered are satisfactory.

From the result of stability study it was concluded that the drug substance was found to be stable in real time (at or below -20°C) and accelerated condition (2-8°C). Hence, shelf life of 5 years was assigned for the product under recommended storage conditions (at or below -20°C).

P. Drug product (name, Dosage form)

P.1. Manufacturer (name, Dosage form):-

P.1.1. Manufacturer(s) (name, dosage form):-

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P.1.2. Batch formula:-

S.No.	Ingredients	Quantity per dose (0.5 ml) or single dose presentation
1	Vi polysaccharide of *Salmonella typhi*	25mcg
	Phenol I.P. (Preservative)	≤0.25%
2	Isotonic saline(Buffered)	0.5 ml

P.1.3. Description of Manufacturing process & process control

Manufacturing Process	Controls
Purified Vi Polysaccharide lot stored at or below -20°C.	
Preparation of final bulk by aseptic dilution with sterile normal saline I.P., so as to content 50 microgram per ml of Vi polysaccharide.	• Sterility • Antimicrobial Preservative
Containerization, visual inspection of final containers, labeling, packing, storage (2-8°C)	• Volume control • Temperature control • Humidity control
Final lot of Typhoid Polysaccharide Vaccine I.P.	• Identification • Assay (Vi polysaccharide content) • Sterility • Bacterial Endotoxins • Abnormal toxicity • pH • O- acetyl groups • Free formaldehyde

P.1.4. Control of critical steps & intermediate (name, dosage form)

As per Point No. P.1.3

P.2. Control of excipients:-

P.2.1. Excipients of Human or Animal Origin (name, dosage form):

There is no use of excipient of human or animal origin for the manufacture of Typhoid Polysaccharide Vaccine I.P.

P.3. Control of Drug Product:-

P.3.1. Specification (s)

SPECIFICATION FOR FINAL BULK OF TYPHOID POLYSACCHARIDE VACCINE

S. No.	Quality Control Test	Specifications as per I.P
1.	Sterility	If no evidence of microbial growth is found, the preparation under examination complies with the test for sterility.
2.	Antimicrobial Preservative	The antimicrobial preservative (phenol content) in final bulk of Typhoid Polysaccharide Vaccine I.P. shall be less than 2.5g/l (0.25%).

SPECIFICATION FOR FINAL LOT OF TYPHOID POLYSACCHARIDE VACCINE

S. No.	Quality Control Test	Specifications as per I.P
1.	Identification	The identity of the Vi polysaccharide shall be verified by immunochemical method. The presence of immuno precipitation bands confirms the identity of Vi polysaccharide.
2.	Assay (Vi Polysaccharide Content)	Single human dose of 0.5 ml contains 25 μg of Vi polysaccharide. The estimated amount of polysaccharide per dose is 80% (20μg/dose) to 120% (30μg/dose) of the content stated on the label (25 μg/dose).
3.	Sterility	If no evidence of microbial growth is found, the preparation under examination complies with the test for sterility.
4.	Bacterial Endotoxins	The content should be not more than 150 I.U. per mcg of polysaccharide i.e. not more than 3750 I.U. per human dose of 25μg.
5.	Abnormal Toxicity	The test vaccine passes the test if none of animals dies or shows signs of ill health in 7 days following the injection. If more than one animal dies, the preparation fails the test. If one of the animals die or show signs of ill health, repeat the test. The test sample passes the test if none of the animals in the second test dies or show any signs of ill health in the time interval specified.
6.	pH	The pH value of final lot of Typhoid Polysaccharide Vaccine I.P. shall be 6.5 to 7.5.
7.	O- acetyl groups	The O-acetyl groups in Typhoid Polysaccharide Vaccine should be 0.085 (± 25 percent) μmol per dose (25 μg polysaccharide).
8.	Free formaldehyde	0.2 g/l is the maximum limit for free formaldehyde in Typhoid Polysaccharide Vaccine. The vaccine should not be more intense in colour than reference solution.

P.3.2. Container Closure System (name, dosage form):

Various material used for the final packing of vaccine are as follows.

i) Glass Vials:-

2 ml, 13 mm clear tubular type I glass vial for single dose & 5 ml, 13 mm clear tubular type 1 glass vial for multi dose.

- **Rubber closures :-**

13 mm Grey butyl, 'Bioclean RFU' Rubber stopper.

- **Aluminium Seals :-**

13 mm flip off BE-11 aluminium seals.

ii) Prefilled syringe

USP Type-1 prefilled syringe with fixed needle.

P.4. Stability:-

P.4.1. Stability Summary and Conclusion (name, dosage form) :

Stability studies real time (2-8^{o}C) and at accelerated condition (20-25^{o}C and 30-35^{o}C) have been conducted on three consecutive lots Typhoid Polysaccharide Vaccine I.P. The test results prove good stability of the product. Test specifications for release of final lot were met after storage at recommended storage condition (2-8^{o}C) for at least 42 months. Based on the results of stability studies shelf life of 30 months was assigned for final lot of vaccine at recommended storage condition of +2 to +8^{o}C.

P.4.2. Post-approval Protocol and Stability Commitment:

Every year one batch of Bio Typh^{TM} is subjected to real time stability study as per the approved protocol.

A. Appendices :- Module 3.2.A

A.1 Details of equipment and facilities for production of drug product

For Layout of the facility used for manufacturing of Bio Typh^{TM} and list of equipments refer to Module 3 Point No. 3.2.A.

A.2. Adventitious Agents Safety evaluation:-

For non-viral adventitious agents :-

The routine manufacturing control of adventitious agents, such as bacteria, mycoplasma and fungi, typically using well-established analytical procedure like sterility test.

Test for sterility is applied to pharmacopoeial articles that are required according to the pharmacopoeia to be sterile.

The test is designed to reveal the presence of micro-organisms in the sample used in the test; interpretation of the results of testing is based on the assumption that all units of an article or the entire bulk product or the contents of every container of the filled product in a lot or batch, had they been tested, would also have given the same results. Since all the units or the bulk or all the containers cannot be tested a sufficient number of samples of units or containers should be examined to give a suitable degree of confidence in the results of the tests.

Media used for the tests should comply with the growth promotion test. Fluid thioglycollate medium is primarily intended for the culture of anaerobic bacteria; however, it will also detect aerobic bacteria, soyabean-casein digest medium is suitable for the culture of both fungi and aerobic bacteria.

For viral adventitious agents :-

Typhoid Polysaccharide vaccine is a polysaccharide vaccine there is not found viral adventitious agents.

Materials of Biological Origin :-

There is no material of biological origin used in manufacturing of this product.