

## Product Permission Document (PPD) of Vi Polysaccharide Typhoid Vaccine (Brand Name – Bio-Typh™)

### 1. Introduction

#### 1.1. Submission file :-

The product was licensed on Form 28-D dated 26/03/2004.

#### 1.2. NDS Approval date and control :-

Additional item on License No. 05/LVP/Sera & Vaccine/2004 dated 26/03/2004

#### 1.3. PPD –Biological revision date and control :-

PPD Biological Rev 01, dated 12/01/2015.

#### 1.4. Proprietary Name:-

Bio Typh™

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

Vi Polysaccharide Typhoid Vaccine

#### 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 : [bm vaccine@yahoo.com](mailto:bm vaccine@yahoo.com)  
Website: [www.biomed.co.in](http://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):-**

<b>Manufacturing Process</b>	<b>Controls</b>
Strain of <i>Salmonella typhi</i> 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 <i>S. typhi</i> ; (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	<ul style="list-style-type: none"> <li>• Culture media sterility</li> <li>• pH control</li> <li>• Dissolved oxygen control.</li> <li>• Temperature control</li> <li>• Rotation speed control</li> <li>• Control of bacterial purity</li> </ul> <p>By microscopic examination of Gram's stained smears (at least 10,000 organisms are inspected), motility test, inoculation into solid media.</p>
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	<ul style="list-style-type: none"> <li>•pH control</li> <li>•Temperature control</li> </ul>
Dissociation of Vi polysaccharide–cetavalone complex	<ul style="list-style-type: none"> <li>• Control of centrifugation speed.</li> <li>• Temperature control</li> </ul>
Purification of Vi polysaccharide by ethanol precipitation, cold phenol extraction	<ul style="list-style-type: none"> <li>• Control of centrifugation speed.</li> <li>• Temperature control</li> </ul>
Purified polysaccharide lot (Store at or below –20°C)	<ul style="list-style-type: none"> <li>• Moisture content</li> <li>• Protein content</li> <li>• Nucleic acid content</li> <li>• O-acetyl content</li> <li>• Molecular size</li> <li>• Identity</li> <li>• pH</li> <li>• Cetrimide</li> <li>• Sterility</li> <li>• Free Formaldehyde</li> </ul>

**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 Vi Polysaccharide Typhoid Vaccine is characterized as per the guidelines of W.H.O. T.R.S. No. 840,1994.

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

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

**S.2.1.2 Biological Characterization :-**

Each purified polysaccharide lot is tested for identity by rocket immuno electrophoresis.

**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:-**

<b>S. No.</b>	<b>Quality Control Test</b>	<b>Specifications as per WHO TRS 840, 1994</b>
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 Vi polysaccharide with reference to the dried substance.
2.	Protein content	Each purified Vi polysaccharide lot shall contain less than 10 mg protein per gram of polysaccharide as determined by the method Lowry et.al. using bovine plasma albumin as a reference.
3.	Nucleic acid content	Each purified Vi polysaccharide lot shall contain less than 20 mg of nucleic acid per gram of polysaccharide, on the assumption that the absorbance of 1gm/liter solution of nucleic acid solution contain in a cell 1 cm wide at 260 nm is 20 (0.025 mg/ml of nucleic acid solution at 260 nm is 0.5).
4.	Identity test	The identity of the purified Vi polysaccharide lot with an Inhouse standard Vi polysaccharide shall be established by immuno-precipitation.
5.	O-acetyl content	O-acetyl content of purified Vi polysaccharide lot shall be not less than 2.0 m mol/gm of Vi polysaccharide as determined method based on that described by hestrin.
6.	Molecular size	In molecular size assay, at least 50% of the recovered Vi polysaccharide from the column shall be eluted before a KD of 0.25 is reached.
7.	pH	The pH value of purified Vi polysaccharide lot of Vi Polysaccharide Typhoid Vaccine shall be $7 \pm 0.5$ .
8.	Cetrimide	Yellow precipitate formed in standard solution and there should be no precipitation in test sample.
9.	Free formaldehyde	0.2 g/l is the maximum limit for free formaldehyde in purified Vi Polysaccharide lot of Vi polysaccharide typhoid vaccine. The test sample should be not more intense in color than reference solution.
10.	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 Vi Polysaccharide Typhoid 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 <i>Salmonella typhi</i> (Strain Ty2)	25mcg
2.	Phenol I.P. (Preservative)	≤0.25%
3.	Isotonic saline Bufffered	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 isotonic saline, so as to content 50 microgram per ml of Vi polysaccharide.	<ul style="list-style-type: none"> <li>• pH control</li> <li>• Sterility</li> <li>• Identity</li> <li>• Vi polysaccharide content</li> <li>• Abnormal toxicity</li> <li>• Free formaldehyde</li> <li>• Antimicrobial Preservative</li> </ul>
Containerization, visual inspection of final containers, labeling, packing, storage (2-8°C)	<ul style="list-style-type: none"> <li>•Volume control</li> <li>•Temperature control</li> <li>•Humidity control</li> </ul>
Final lot of Vi Polysaccharide Typhoid Vaccine	<ul style="list-style-type: none"> <li>•Identity &amp; Vi polysaccharide content</li> <li>•Sterility</li> <li>•Bacterial Endotoxin test</li> <li>•Abnormal toxicity</li> <li>•pH</li> <li>•O-acetyl content</li> <li>•Free formaldehyde</li> </ul>

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

Same as in 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 Vi Polysaccharide Typhoid Vaccine.

**P.3. Control of Drug Product:-****P.3.1. Specification (s)****1. For Final Bulk :**

S. No.	Quality Control Test	Specifications as per W.H.O. T.R.S. No. 840, 1994, Annexure 1
1.	Sterility Test	If no evidence of microbial growth is found, the preparation under examination complies with the test for sterility.
2.	Identity	The identity of the Vi polysaccharide shall be verified by immunochemical method.
3.	Vi Polysaccharide Content	Single human dose of 0.5 ml shall have 25 µg ± 30% of Vi polysaccharide.
4.	Antimicrobial Preservative Content	The phenol content in final bulk of Vi polysaccharide typhoid vaccine shall be less than 0.25%.
5.	pH	The pH value of final bulk of Vi polysaccharide typhoid vaccine shall be 7 ± 0.5.
6.	Abnormal toxicity	The final bulk product shall be considered satisfactory if all animals survive for atleast seven days without weight loss.
7.	Free Formaldehyde	0.2 g/l is the maximum limit for free formaldehyde in final bulk of Vi Polysaccharide typhoid vaccine. The test sample should not be more intense in colour than reference solution.

**2. For Final Lot:**

S. No.	Quality Control Test	Specifications as per W.H.O. T.R.S. No. 840, 1994, Annexure 1
1.	Identity & Vi polysaccharide content	Single human dose of 0.5 ml shall have 25 µg± 20% of Vi polysaccharide. The presence of immune precipitation bands confirms the identity of Vi polysaccharide.
2.	Sterility	If no evidence of microbial growth is found, the preparation under examination complies with the test for sterility.
3.	Bacterial Endotoxin test	Not more than 3750 I.U. per human dose.
4.	Abnormal toxicity	The test vaccine passes the test if more of animal dies or shows signs of ill health in 7 days following the injection. If more than one animal die, the preparation fails the test. If one of the animals dies 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.
5.	pH	The pH value of final lot of Vi polysaccharide typhoid vaccine I.P. shall be 6.5 to 7.5.

6.	O-acetyl content	The O-acetyl content in Vi polysaccharide typhoid vaccine should be within 0.085 ( $\pm$ 25 percent) $\mu$ mol per dose (25 $\mu$ g polysaccharide).
7.	Free formaldehyde	0.2 g/l is the maximum free formaldehyde in Vi- polysaccharide typhoid vaccine. The vaccine should not more intense in color 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°C) and at accelerated condition (20-25°C and 30-35°C) have been conducted on three consecutive lots Vi Polysaccharide Typhoid Vaccine. 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°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°C.

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

Every year one batch of Bio Typh<sup>TM</sup> 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 Lay out of the facility used for manufacturing of Bio Typh<sup>TM</sup> 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 :-**

Vi Polysaccharide Typhoid 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.