Product Permission Document (PPD) of Meningococcal Polysaccharide Vaccine(Group A & C)

Brand Name: Bi Meningo™

Meningococcal disease is a serious infection caused by a bacteria. Meningococcal bacteria can infect the blood, spinal cord, and brain. These conditions can be fatal.

Meningococcal disease can spread from one person to another through small droplets of saliva that are expelled into the air when an infected person coughs or sneezes. The bacteria can also be passed through contact with objects the infected person has touched, such as a door handle, or other surface. The bacteria can also be passed through kissing, or sharing a drinking glass or eating utensil with an infected person.

Meningococcal polysaccharide vaccine is used to prevent infection caused by meningococcal bacteria. The vaccine contains four of the most common types of meningococcal bacteria.

The bacterium *Neisseria meningitidis*, the meningococcus, is a Gram-negative, oxidase-positive diplococcus, identical in its staining and morphological characteristic to *Neisseria gonorrhoeae.* However, at an ultrastructural level, *Neisseria meningitidis* has a prominent polysaccharide capsule not seen in the gonococcus. The capsule is antiphagocytic and is an important virulence factor in meningococcal disease. *Neisseria meningitidis* strains are grouped on the basis of their capsular polysaccharide.

The capsular polysaccharide of *Neisseria meningitidis* are attractive vaccine candidates because they constitute the most highly conserved and most exposed bacteria-surface antigens. The use of capsular polysaccharide as immunoprophylactic agents against human disease caused by encapsulated bacteria is now firmly established. The capsular polysaccharides of the meningococcus are negatively charged and the obtained in a high molecular weight immunogenic form by precipitation. Meningococcal polysaccharide vaccines are efficacious to protect from meningitis disease in adults, but cannot provide full protection to infants under the age of 5. The duration of protection elicited by the meningococcal polysaccharide vaccine is not long lasting in adults and children above four years of age. For children from one to four years old the duration of protection is less than three years. Protective immunity to encapsulated bacterial pathogens such as *Neisseria meningitidis* is principally mediated by the reaction between antibody and capsular polysaccharide epitopes. In encapsulated gram negative bacteria, protection results primarily from a direct complement-mediated bactericidal effect. Vaccines have been prepared from the capsular polysaccharide of *Neisseria meningitidis* (Group A & C). These and other polysaccharides have been classified as T cell independent type 2(TI-2) antigens based on their inability to stimulate an immune response in animals that carry an X-linked immune B-cell defect (xid). TI-2 antigens tend to be characterized by high molecular weight, multiple repeat epitopes, slow degradations in vivo, and a failure to stimulate major histocompatibility complex (MHC) type II mediated T-cell help. TI-2 antigens generally are incapable of stimulating an immune response in neonatal humans under 18 months of age. This has spurred attempts to modify the capsular polysaccharide such that vaccines protective for all at-risk

groups will result. To date, the most successful approach has been to covalently bind carrier proteins to the polysaccharides, this engendering a vaccine capable of invoking a T-dependent response.

1.1. Submission file :-

File No.12-95/BMD-2005

1.2. NDS Approval date and control :-

Additional item permission issued vide Letter No: Drug/837/3481 dated 10/12/2009.

1.3. PPD –Biological revision date and control :-

PPD Biological Rev 00, dated 01/02/2014.

1.4. Proprietary Name:-

Bi Meningo™.

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

Purified Polysaccharide of Meningococcal Polysaccharide Vaccine (Group A & C)

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) :-

Reconstitute the lyophilisate with the entire content of the diluent provided with the vaccine. Shake gently for full reconstitution. The multi dose vaccine vial after opening can be kept at +2 to +8°C and used for up to 28 days after opening provided sterile

techniques have been used for withdrawing vaccine and expiry date have not passed.

1.10. Strength (s) :-

Each dose (0.5 ml) of vaccine contains:

- Purified Polysaccharide of *Neisseria meningitidis*
  - Group A.....50 µg
  - Group C.....50 µg
- Lactose I.P. (Stabilizer) .....5 mg
- Thimerosal I.P. (Preservative) .....0.05 mg

1.11. Route of Administration:-

Administer the vaccine (0.5 ml) by intramuscular or subcutaneous route.

1.12. Maximum Daily Dose :-

Not Applicable

2.0 New Active Substance (NAS) :

Meningococcal Polysaccharide Vaccine (Group A & C) is produced in all over the world for several decades. There is predefined parameters for the manufacturing of Meningococcal Polysaccharide Vaccine (Group A & C). All the products used in the production of vaccine is already known. Meningococcal Polysaccharide Vaccine (Group A & C) is produced by Bio-Med (P) Ltd. All excipients used have been previously used for manufacture of human vaccine(s). None of the excipients are novel.

S. Drug substance, name & manufacturer:-

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

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

BIO-MED (P) LTD.
C-96, Site No. 1,
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Fax : 0120-4340219
e-Mail :bmvaccine@yahoo.com
Website: www.biomed.co.in

S.1.2. Description of manufacturing process & process control:-

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 inoculums 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 formalin (0.5%)	Control of bacterial inactivation.
↓	
Bacterial cell separation by continuous flow centrifugation	Control of centrifugation speed.
↓	
Precipitation of polysaccharide from culture supernatant by addition of 0.2% cetavalone	• pH control • Temperature control	
Dissociation of polysaccharide –cetavalone complex	• Control of centrifugation speed. • Temperature control
↓	
Purification of 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 • Sialic Acid Content • Phosphorus Content • pH • Sterility test • Free formaldehyde • Cetrimide

S.1.3. Control of materials (name, manufacturer):-

As discussed in the point No. S.1.2.

S.1.4. Control of critical steps & intermediate (name, manufacturer):-

As discussed in the point No. S.1.2.

S.2. Characterization (name, manufacturer) :-

S.2.1. Elucidation of structure and other characteristics (name, manufacturer):-

S.2.1.1 Physicochemical Characterization :-

The vaccine contains 50 mcg of polysaccharide for each of the serogroup's (A & C) purified polysaccharide in a lyophilized form. Active Pharmaceutical Ingredient (API) of C serogroups is Sialic acid. Phosphate is an API for serogroup A. Lactose is used as a stabilizer.
Structures of the Capsular Polysaccharides of *Neisseria meningitidis* A & C :-

Group	Structure of repeating unit
A	→6)α-D-ManNAc(1-PO4→ 3 ↑ OAc
C	→9)α-D-NeuNAc(2→ 7/8 ↑ OAc

NMR analysis showed that the structures of the Polysaccharides of *Neisseria meningitidis* A & C isolates collected from Africa and used in the vaccine production are O-acetylation positive (O Ac +) and it is one of the requirement of International Conference on Harmonization ICH and WHO Guidance. O-acetylated polysaccharides influence the immunogenicity of meningococcal vaccines. It is well known that O acetylated at carbon 3 in serogroup A polysaccharide induces higher Serum Bactericidal Antibody (SBA) detectable anti- serogroup A antibodies in human. Serogroups C, W-135, and Y also have various degrees of O-acetylation, whereas, none O-acetylated of these serogroups can also produce protective immunogenicity against the disease. WHO/ICH requirement of O-acetylation positive for serogroups C, W-135, and Y is disadvantage for the vaccine manufacturers in the selection of high yielding polysaccharide producing O-acetylation groups.
The purified polysaccharide lot of Meningococcal Polysaccharide Vaccine is characterized as per the guidelines of W.H.O. T.R.S. No. 594 (1976), 658 (1981) & 904 (2002).

Analytical testing performed to characterize the purified polysaccharide lot of Meningococcal Polysaccharide Vaccine (Group A & C) are follows:-

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

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 Polysaccharide lot.

S.3. Control of Drug substance :-

S.3.1. Specification :-

S. No.	Quality Control Test	Specifications as per W.H.O. T.R.S. No. 594 (1976), 658 (1981) & 904 (2002)
1.	Moisture content	To calculate dry weight.
2.	Protein content	Each lot of purified polysaccharide shall contain less than 10 mg of protein per gram of polysaccharide for Groups A and C organisms as determined by the method of Lowry et. al. using bovine plasma albumin as a reference.
3.	Nucleic acid content	each lot of purified polysaccharide shall contain less than 10 mg of nucleic acid per gram of polysaccharide for groups a and c as determined by spectroscopy on the assumption that the absorbance of 10 gm per liter nucleic acid solution contained in a cell 1 cm wide at 260 is 200 (0.025 mg/ml of nucleic acid solution at 260 nm is 0.5).
4.	O-acetyl content	The O-acetyl content of the polysaccharide shall be equal to or greater than 2.0 m mol/g of polysaccharide for Group A, 1.5 m mol/g of polysaccharide for Group C
5.	Phosphorus content	Each lot of group A polysaccharide shall contain atleast 80 mg of phosphorus per gram of polysaccharide
6.	Sialic acid content	The sialic acid content of the purified polysaccharide, calculated as free N-acetyl neuraminic acid, shall be not less than 800 mg/g of the dry weight for Group C.
7.	Molecular size	At least 65% of the Group A and 75% of the Group C polysaccharide shall be recovered from the column before a distribution constant (K_D) of 0.5 is reached.
8.	Identity test	Each lot shall be tested for serological identity /specificity. The presence of group specific antigen(s) shall be confirmed.
9.	Sterility test	If no evidence of microbial growth is found, the preparation under examination complies with the test for sterility.
10.	pH test	The pH value of purified polysaccharide lot of Meningococcal Polysaccharide Vaccine shall be 7 $\pm$ 0.5.

11.	Cetrimide	Yellow precipitate formed in standard solution and there should be no precipitation in test sample.
12.	Free Formaldehyde	0.2 g/l is the maximum limit for free formaldehyde in purified polysaccharide lot of Meningococcal Polysaccharide Vaccine. The test sample should not more intense in color than reference solution.

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 Meningococcal 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 :-

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

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

BIO-MED (P) LTD.
C-96, Site No. 1,
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e-Mail :bmvaccine@yahoo.com
Website: www.biomed.co.in

P.1.2. Batch formula:-

The formulated vaccine Bi Meningo™ (Meningococcal Polysaccharide Vaccine (Group A & C)) is in freeze dried form and batch formula is given below:

S. No.	Ingredients	Quantity per dose (0.5 ml)
1	Purified Polysaccharide of *Neisseria meningitidis* Group A	50 µg
2	Purified Polysaccharide of *Neisseria meningitidis* Group C	50 µg
3	Lactose I.P. (Stabilizer)	5 mg
4	Thimerosal I.P. (Preservative)	0.05 mg

P.1.3. Description of Manufacturing process & process control

PRODUCTION FLOW DIAGRAM OF MENINGOCOCCAL POLYSACCHARIDE VACCINE FINAL LOT

Manufacturing Process	Controls
Purified Polysaccharide lot stored at or below -20°C.	
Preparation of final bulk by aseptic dilution with sterile normal saline, so as to contain 50 microgram per dose of polysaccharide(s).	• pH control • Sterility • Identity
Containerization, visual inspection of final containers, labeling, packing, storage (2-8°C)	• Volume control • Temperature control • Humidity control
Final lot of meningococcal polysaccharide vaccine	• Identity • Concentration of polysaccharide • Sterility • Pyrogenicity test • Test for Abnormal toxicity • Preservative content • Estimation of molecular size • Test for residual moisture • Sialic Acid Content • Phosphorus Content

The final bulk of Meningococcal Polysaccharide Vaccine is prepared by aseptic dilution of the purified polysaccharide lot based on the polysaccharide concentration. The dilution of the purified polysaccharide lot for the preparation of final bulk is done by adding stabilizer (Lactose), preservative (Thimerosal).

The final lot is prepared by aseptically dispensing the final bulk vaccine, in grade A conditions with grade B background, in tubular glass vials which have been final rinsed with water for injection and sterilized in dry heat sterilizer. During filling the volume of filling, room temperature, humidity, microbial load is periodically monitored.

Vials are half stoppered with butyl stoppers (pre-sterilized by radiation), collected and loaded into freeze drier. The lyophilization cycle have been validated and the moisture content of consecutive seven batches of final lot of Meningococcal Polysaccharide Vaccine meets the specifications of Technical Report Series. After lyophilization cycle sterile nitrogen is introduced in the lyophilizer and vials are full stoppered. On removal from the lyophilizer the vials are sealed with aluminium caps. The sealed vials are visually inspected, labeled, packed and stored at 2-8°C.

P.1.4. Control of critical steps & intermediate :

Refer point no. P.1.3.

P.2. Control of excipients:-

P.2.1. Excipients of Human or Animal Origin :

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

P.3. Control of Drug Product:-

P.3.1. Specification (s):

Final Bulk

S. No.	Quality Control Test	Specifications as per W.H.O. T.R.S. No. 594 (1976), 658 (1981) & 904 (2002)
1.	Sterility Test	If no evidence of microbial growth is found, the preparation under examination complies with the test for sterility.
2.	Identity	Purified monospecific polysaccharide shall be shown to be serologically identical & specific.

Final Lot

S. No.	Quality Control Test	Specifications as per W.H.O. T.R.S. No. 594 (1976), 658 (1981) & 904 (2002)
1.	Identity	Purified monospecific polysaccharide shall be shown to be serologically identical & specific.
2.	Concentration of polysaccharide	Shall contain the declared content (50 µg/dose) of each Group-specific polysaccharide(s) ± 30%, using the purified polysaccharide(s) incorporated in the vaccine.
3.	Sterility	If no evidence of microbial growth is found, the preparation under examination complies with the test for sterility
4.	Pyrogenicity Test	If the sum of difference between maximum and initial temperature of three rabbits is less than 1.4°C and if response of individual rabbit is less than 0.6°C, the preparation being examined passes the test.
5.	Test for Abnormal Toxicity	The test animals shall be observed for seven days and the injection shall cause neither significant symptoms nor death during this period (their weight at the end of the test period is not less than that at the time of injection).
6.	Estimation of Molecular Size	At least 65% of the Group A & 75% of the Group C polysaccharide shall be recovered from the column before a distribution constant (K_D) of 0.5 is reached.
7.	Test for Residual Moisture	The average residual moisture shall be not greater than 2.5% and no vial shall have residual moisture content of 3% or greater.
8.	Preservative Content	Preservative content shall be between 0.0085% to 0.0115% per dose of 0.5 ml.
9.	Phosphorus Content	In final lot of Meningococcal Polysaccharide Vaccine (Group A & C)shall contain atleast 75 mg of phosphorus content per gram of polysaccharide for Group A.

10.	Sialic Acid Content	In final lot of Meningococcal Polysaccharide Vaccine (Group A & C)shall contain atleast 750 mg of sialic acid content per gram of polysaccharide for Group C.

P.3.2. Container Closure System :

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

- Glass Vials :-

  2ml and 5 ml, 13 mm USP type I clear tubular glass vial for single and multi-dose.

- Rubber closures :-

  13 mm Grey Butyl Slotted Rubber Stopper (Sterile ready for use).

- Aluminium Seals :-

  13 mm flip off GN-17 aluminium seals.

Materials used for the final packing of vaccine diluent are as follows:

- Glass vial :-
- 2ml and 5 ml, 13 mm USP type I clear tubular glass vial for single and multi-dose.
  diluent.

- Rubber Closures: -

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

- Aluminium Seals :-

  13 mm flip off white (WE1) aluminium seals.

P.4. Stability:-

P.4.1 Stability Summary and Conclusion:-

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 Meningococcal Polysaccharide Vaccine (Group A & C). 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 atleast 36 months. Based on the results of stability studies shelf life of 24 months was assigned for final lot of vaccine at recommended storage condition of +2 to +8°C.

P.4.2 Post approval stability protocol and stability commitment (name, dosage form):

Every year one batch of Bi Meningo™ 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 Bi Meningo™ 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 :-

Meningococcal vaccine is a polysaccharide freeze dried vaccine therefore there is not found viral adventitious agents.

Materials of Biological Origin :-

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