Product Permission Document (PPD) of Poliomyelitis Vaccine, Live (Oral) I.P. Di-Valent (bivalent/b-OPV)

1. Introduction

Poliomyelitis is an acute infection caused by any of three serotypes of poliovirus that replicate initially in the gastrointestinal tract and rarely in the motor neurons of the anterior horn cells in the spinal cord, where replication of virus results in cell destruction and flaccid paralysis of the muscles the cells innervate(i.e., spinal Poliomyelitis). On occasion, brain stem cells innervating respiratory muscles can be affected, resulting in difficulties in breathing (i.e., bulbar paralysis). In addition to the acute paralysis, late manifestations with exacerbation of weakness or new paralysis (i.e., post polio syndrome) can be observed in a significant proportion of patient's decades after the acute paralytic episode.

Polioviruses are part of the Enterovirus genus and belong to the family Picornaviridae (ltalian: pico, implying small, and RNA, the nucleic acid component). Polioviruses are small (27 to 30 nm in diameter), nonenveloped viruses with capsids of icosa hedral symmetry enclosing a single-stranded, positive-sense RNA genome about 7500 nucleotides long. Polioviruses share most of their biochemical and bio physiologic properties with the other enteroviruses.

Poliomyelitis is a ubiquitous, highly contagious, seasonal viral disease (more pronounced in moderate-climate countries) caused by three serotypes of poliovirus (type 1, 2, and 3) that infect nearly every person in a given population in the absence of vaccination.
The Sabin strain is recommended by W.H.O. T.R.S. No. 904, 2002.
Poliovirus type 1 appears to be the most neurovirulent of the three serotypes. Most epidemic and endemic cases of poliomyelitis are caused by poliovirus type 1, followed by type 3 and type 2. Peak transmission occurs among infants and young children (tropical areas) and school-aged children (temperate zones). However, outbreaks in isolated communities can give rise to paralytic cases in many older individuals.

The history of early developments of oral vaccines can be reviewed in detail in reports of meetings published between 1958 and 1961 and in the corresponding chapter of the second editions of Vaccines. As with most major scientific achievements, crucial contributions came from a number of different investigative teams. Hilary Koprowski and colleagues reported the successful immunization of humans against poliomyelitis with a live poliovirus vaccine as early as 1950. Although theses attenuated strains were not selected for licensing, this work meant that, by 1960, when not only his strains but also several other candidate vaccines were well into their testing and field trial use, a 10 year record of evidence was available on patterns of response in humans who had received the type 2 strain in 1950.
Continued development and testing of candidate strains were conducted in three Institutions: the Children's Hospital Research Foundation, Cincinnati (A. B. Sabin); Lederle Laboratories, Wayne, NJ (V.J. Cabasso et al.); and the Wistar Institute, Philadelphia (H. Koprowski et. al.). The work with attenuated polioviruses was advanced toward practical usefulness, particularly by Sabin, who meticulously studied a number of progeny of single virus particles for neurotropism in monkeys and finally selected three for small experimental trials in humans. Much of the early efforts in the development of candidate strains were devoted to (1)

maintaining high degrees of infectivity in cell culture and the human intestinal tract, (2) inducing detectable levels of neutralizing antibody in a high proportion of susceptible (seronegative) recipients, (3) displaying low nerovirulence in monkeys, (4) demonstrating a lack of association with paralytic disease in humans, and (5) maintaining genetic stability after replication in the human host. The efforts of a number in investigators to develop and test suitable attenuated poliovirus strains came to fruition during 1955 to 1959, and large-scale field trials were held in many countries under a variety of conditions. Many of these trials in humans involved the sequential administration of monovalent formulations of poliovirus type 1, 2 and 3.

1.1. Submission file :-

The PPD Biological document provides an accurate record of technical date of the drugs product. This document is a condensed version of the quality overall summary & represents the final agreed upon key date from the drug submission review.

1.2. NDS Approval date and control :-

Drug/837/381 dated 16/01/2015 and Drug/837/2046 dated 24/02/2016

1.3. PPD –Biological revision date and control :-

PPD Biological Rev 00, dated 15/07/2013.

1.4. Proprietary Name:-

Poliomyelitis Vaccine, Live (Oral) I.P. Di-Valent (bivalent/b-OPV)

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

Poliomyelitis Vaccine, Live (Oral) I.P. Di-Valent (bivalent/b-OPV)

1.6. Company Name :-

BIO-MED (P) LTD.
C-96, Site No. 1, Bulandshahr Road
Industrial Area,
Ghaziabad – 201009 (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 :-

BIO-MED (P) LTD.
C-96, Site No. 1, Bulandshahr Road
Industrial Area,
Ghaziabad - 201009 (U.P.) INDIA
Phone : 0120-4157534, 4204862
Fax : 0120-4340219
E-Mail : bmvaccine@yahoo.com
Website: www.biomed.co.in.

1.8. Therapeutic or Pharmacological classification :-

Vaccine

1.9. Dosage form(s) :-

Liquid Vaccine

1.10 Strength (s) :-

Each dose of 0.1 ml contains:	
Ingredients	**Quanitity**
Monovalent bulk of poliomyelitis Type-1 (Attenuated, Sabin strain)	$\geq 10^6$ $CCID_{50}$
Monovalent bulk of poliomyelitis Type-3 (Attenuated, Sabin strain)	$\geq 10^{5.8}$ $CCID_{50}$
Kanamycin	20mcg/dose
1 M $Mgcl_2$ as Stabilizer	

1.11 Route of Administration:-

dOPV must only be administered orally.

1.12 Maximum Daily Dose :-

No daily dose of Poliomyelitis Vaccine, Live (Oral) I.P. Di-Valent (bivalent/b-OPV) is required. As it is not applicable for vaccine.

2. New Active Substance

No new active substance is used in the manufacturing of product.

S. Drug substance, name & manufacturer:-

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

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

PT. BIOFARMA (Persero)
Jl. Pasteur 28 Bandung 40161
Indonesia

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

Stage/Manufacturing Process		Control test employed
Control cells (4%)	:	• Tests for Haemadsorbing Viruses • Test for other adventitious agents.

Virus pool before filtration	:	• Virus Concentration
		• Sterility test
		• Test for mycobacterium
		• Test for adventitious agent in cell
		  • Cercopithecus kidney cell
		  • Macaca kidney cell
		  • Rabbit kidney cell
		  • Veri cell
		  • MRC-5 cell
		• Test for adventitious agent in animal
		  • Rabbit
		  • Mice
		  • Suckling Mice
		  • Guinea Pigs

Virus pool after filtration	:	• Identity test • Potency • Sterility test • RCT 40 Marker • D-Marker • Neurovirulence • Reverse transcriptase colorimetric • RI-MAPREC

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 :

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):-

Physicochemical Characterization

The pooled virus harvest of Polio Vaccine is characterized as per W.H.O. T.R.S. No. 904, 2002.

The single virus harvest before filtration is characterized by virus concentration, sterility test, test for mycobacterium, test for adventitious agent in cells, test for adventitious agent in animals and after filtration is characterized by Identity test, potency, sterility test, RCT 40 marker, D-maker, Neurovirulence reverse transcriptase colorimetric & RI-MAPREC.

Biological Characterization

Polio Virus Seed Lot(s)

The working virus seed lot of Polio virus is characterized by test for antibody to simian immune deficiency virus and test for antibody to SV-40.

Monkey kidney cell line

The primary monkey kidney cell line is characterized by test for Haemadsorbing virus and test for other adventitious agent.

Control Cell Culture

At least 4% of production cell cultures set aside as control cells are observed for by conducting tests like Haemadsorbing virus and other adventitious agents.

Single Virus Harvest

The filtered single virus harvest is characterized by Identity test, potency, sterility test, RCT 40 marker, D-maker, Neurovirulence & reverse transcriptase colorimetric.

S.2.2. Impurities (name, manufacturer):-

Impurities in Polio virus can arise from the following

The virus seed lot(s) :-

Source of master seed lot of attenuated Polio virus Sabin strain was the WHO authorized Institution.

A quantity of fully characterized virus of uniform composition, derived from a master seed lot. The working seed lot is used for the production of vaccines.

There are two types of working seed lots are prepared from respective master seed lots like for

Type 1 was Sabin Type 1; IS-90C,

Type 3 was Sabin Type 3; IIIS-79A.

Monkey kidney cell line

Poliovirus vaccine is a sterile suspension of two types of poliovirus : Type 1& Type 3. Each of the two strains of poliovirus is individually grown in continuous line of monkey kidney cells cultivated on micro carriers. It is recommended by WHO that the cells for cultivation be taken from monkeys bred in captivity. Like the cell cultures used, the monkey colony should be shown to be free from extraneous viruses and other pathogens.

The culture media

Nature and concentration of antibiotics used in production cell : Erythromycin 20 mcg/ml
Kanamycin 100 mcg/ml
culture maintenance medium

S.3. Control of Drug substance (name, manufacturer):-

S.3.1. Specification (name, manufacturer):-

Single Harvest

S. No.	Name of the Test	Specifications
1.	Sterility Test	No evidence of microbial growth is observed in any of the inoculated bottles then the preparation being examined complies with the test for sterility.
2.	Virus Concentration	≥ 7.5 log $CCID_{50}$/ml
3.	Identity Test	Neutralized by homologus antiserum.
4.	RCT marker	≥ 5.0 log PFU/ml
5.	Test on Neutralized single harvest	No evidence of CPE in test sample.

Virus Pool (Before Filtration)

S. No.	Name of the Test	Specifications
1.	Virus Concentration	≥ 7.5 log $CCID_{50}$/ml
2.	Sterility Test	No evidence of microbial growth.
3.	Test for Mycobacterium	No evidence of mycobacterium growth.
4.	Test for adventitious agents in cells	No evidence of CPE in the test sample.
5.	Test for adventitious agents in animals	No animal show extraneous viruses infection signs, not less than 80% of the animals survive the test period.

Virus Pool (After Filtration)

S. No.	Name of the Test	Specifications
1.	Identity Test	Neutralized by homologus antiserum.
2.	Virus Concentration	≥ 7.5 log $CCID_{50}$/ml
3.	Sterility Test	No evidence of microbial growth.
4.	RCT 40 marker	≥ 5.0 log PFU/ml
5.	D- marker	≥ 2.0 log PFU/ml
6.	Neuro Virulence	MLS of sample - MLS of reference < C1
7.	Reverse transcriptase colorimetric	Negative, OD of sample < cut of value
8.	RI-MAPREC	Sample density <WHO 95/542 reference density.

The stability characteristics of Polio virus bulk concentrate (each of the two monovalent types) manufactured in Bio Farma in Bandung facilities.

S.3.2. Stability (name, manufacturer):-

Based on the current stability study, the official assigned validity of monovalent bulk at the storage of -80°C is ten years for type-1, and eight years for type-3.

Protocol of stability study, results and conclusions

Stability study are conducted to ascertain the effects of environmental factors on the stability of the product to determine storage condition, product expiration dating, and effects of accidental exposure to higher temperature during transportation or storage at peripheral site.

Conventional type of product consists of biological products in which the active component and hence the biological activity, is dependent and sensitive to environmental factors such as temperature changes, shear. To avoid maintenance of biological activity and to avoid degradation, stringent conditions for their storage are necessary.
Stability testing with well-defined testing programme should be designed considering environmental conditions that can affect the products potency, purity and quality. Assays for biological activity should be part of the stability studies.

Stability indicating profile shall be selected so that it provides assurance that changes in the sterility, identity, safety and potency of the product will be detected.

As bulk material is to be stored after manufacture, but before formulation and final manufacturing, stability studies on bulk material should be carried out.

Post-approval stability program

Post approval stability studies not required until and unless there is any change in the manufacturing process or product composition.
Storage and shipping conditions of drug substance
The filtered virus pool is stored at or below -60°C in plastic bottles.

Transfer/shipping conditions of the filtered virus pool shall be done in frozen condition in Eutherm Polyurethane Insulated Boxes with dry ice to maintain the temperature during shipping.

P. Drug product (name, Dosage form) :-

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

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

BIO-MED (P) LTD.
C-96, Site No. 1, Bulandshahr Road
Industrial Areas,
Ghaziabad - 201009 (U.P.) INDIA
Phone : 0120-4157534, 4204862
Fax : 0120-4340219
E-mail : bmvaccine@yahoo.com
Website: www.biomed.co.in

P.1.2. Batch formula (name, dosage form) :-

Each dose of 0.1 ml contains:	
Ingredients	**Quanitity**
Monovalent bulk of poliomyelitis Type-1 (Attenuated, Sabin strain)	$\geq 10^6$ $CCID_{50}$
Monovalent bulk of poliomyelitis Type-3 (Attenuated, Sabin strain)	$\geq 10^{5.8}$ $CCID_{50}$
Kanamycin	20mcg/dose
1 M $Mgcl_2$ as Stabilizer	

P.1.2.1 Description of Manufacturing process & process control

Manufacturing Process	Control / Tests
Virus pool after filteration (stored at or below -60°C) ↓ Aseptic dilution by excipients (magnesium chloride, Hanks balanced salt solution, sodium bicarbonate) for preparation of final bulk ↓ Filling, containerization and sealing ↓ Visual Inspection ↓ Labeling & Packing (Store at or below -20°C)	Virus pool after filteration • Identity test • Potency • Sterility test • RCT 40 Marker • D-Marker • Neurovirulence • Reverse transcriptase colorimetric • RI-MAPREC Final bulk • Sterility test (Bacterial and fungal) Final lot • Sterility test (Bacterial and fungal) • Potency test & Identity test • Stability test

P.1.2.2 Control of critical steps & intermediate (name, dosage form)

Preparation of final bulk

The final bulk of Poliomyelitis Vaccine, Live (Oral) I.P. Di-Valent (bivalent/b-OPV) is prepared by aseptic dilution of the virus pool based on the assay (virus concentration). The blending, mixing of final bulk is done aseptically under grade A conditions using sterile equipments/ glassware's.

The process of preparation of final bulk is validated by conducting sterility test for bacterial and mycotic sterility as per Indian Pharmacopoeia.

Preparation of final lot

The final lot is prepared by aseptically dispensing the final bulk vaccine, in grade A conditions with grade B background, in 3 ml capacity tubular glass vials which have been final rinsed with water for injection I.P. and sterilized in dry heat sterilizer. During filling the volume of filling, room temperature, humidity, microbial load is periodically monitored.

Sterilization of vials of glass vials in dry heat sterilizer is validated by conducting the performance qualification of the dry heat sterilizer by chemical, biological (spore strip test, physical (temperature recording using calibrated temperature recording devices with traceability to National Physical Laboratory) and bacterial endotoxin test.

The rubber stoppers used are supplied as sterile (radiation) ready to use meeting the requirements of the Indian Pharmacopoeia.

Aseptic filling of final lot is validated using media fill validation of the filling process, microbial monitoring by settle plate and swab method during the filling operation,

performance qualification of the HVAC system (Laminar Air Velocity, Laser Particle Counting, DOP testing, Air change Assessment).

P.2. Control of excipients:-

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

Excipients of human or animal origin are not used in the manufacturing of Poliomyelitis Vaccine, Live (Oral) I.P. Di-Valent (bivalent/b-OPV).

P.3. Control of Drug Product:-

P.3.1. Specification (s) (name, dosage form):

SPECIFICATION FOR FINAL BULK OF POLIOMYELITIS VACCINE LIVE (ORAL) I.P. Di-Valent (bivalent/b-OPV)

S. No.	Quality Control Test	Specifications
1.	Sterility	If no evidence of microbial growth is found, the preparation under examination complies with the test for sterility.

SPECIFICATION FOR FINAL LOT OF POLIOMYELITIS VACCINE LIVE (ORAL) I.P. DI-VALENT (BIVALENT/B-OPV)

S. No.	Quality Control Test	Specifications
1.	Sterility test	If no evidence of microbial growth is found, the preparation under examination complies with the test for sterility.
2.	Potency test and identity test	Mean virus titer for a single human dose should be not less than $10^{6.0}$ $CCID_{50}$ for type 1 and $10^{5.8}$ $CCID_{50}$ for type 3 and identity shall be established by neutralization test.
3.	Stability Test	The estimated difference between the total virus concentration of the unheated & heated vaccine (at 37^0C for 48 hours) is not greater than 0.5 log10 infectious virus units ($CCID_{50}$) per single human dose.

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

a). For glass vial

The container used for manufacture of final lot of Poliomyelitis Vaccine, Live (Oral) I.P. Di-Valent (bivalent/b-OPV) is of 13 mm metro flint USP Type 1, glass vial, stoppered sealed with a grey butyl rubber stopper (pre-sterilized by radiation, ready for use) and sealed with 13 mm tear down aluminium seal. The container closure system have been tested and found to be leak proof.

b). For Plastic vial

Vaccine is packed 2 ml L.D.P.E. Repsule with white Polystyrene Cap.

P.4. Stability (name, dosage form):-

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

Vaccine is stable for at least 2 years when stored at or below -20^{0}C & for at least 6 months when kept at +2^{0}C to +8^{0}C.
Also as part of testing of each batch stability at 37^{0}C for 48 hours is done.

P.4.2. Post-approval Protocol and Stability Commitment (name, dosage form):

Stability studies of final lot have been done (accelerated, real time, real temperature) on commercial scale final lot batches.

A. Appendices :- Refer 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 Poliomyelitis Vaccine, Live (Oral) I.P. Di-Valent (bivalent/b-OPV) and list of equipment's refer to Module 3 Point No. 3.2.A.

A.2. Adventitious Agents Safety evaluation (name, dosage form, manufacturer) :-

Polio Virus Seed Lot(s)

The master seed lot and working seed lot of Polio virus were characterized for absence of extraneous agents using cell culture, animal inoculation, mycoplasma, mycobacteria, bacteria and fungi.

The working virus seed lot was tested for neurovirulence in monkeys.

Monkey kidney cell line

The manufacturing working cell bank of Monkey kidney cell were characterized for absence of extraneous agents using cell culture, retro viruses, animal inoculation, egg inoculation, mycoplasma, mycobacteria, bacteria and fungi.

Control Cell Culture

At least 4% of production cell cultures set aside as control cells were observed for cytopathic agents, haemadsorbing agents and for extraneous agents in cell cultures.

Virus harvest

Virus harvest of Poliomyelitis Vaccine, Live (Oral) I.P. Di-Valent (bivalent/b-OPV) is characterized for absence of extraneous agents using cell culture, mycoplasma, mycobacteria, bacteria and fungi.

Virus Pool

Virus pool of Poliomyelitis Vaccine, Live (Oral) I.P. Di-Valent (bivalent/b-OPV) was characterized for absence of extraneous agents by sterility test for bacteria and fungi.

Final Bulk

Final Bulk of Poliomyelitis Vaccine, Live (Oral) I.P. Di-Valent (bivalent/b-OPV) was characterized for absence of extraneous agents by sterility test for bacteria and fungi.

Final Lot

Final lot of Poliomyelitis Vaccine, Live (Oral) I.P. Di-Valent (bivalent/b-OPV) was characterized for absence of extraneous agents by sterility test for bacteria and fungi.