

**Prequalification Team Inspection services
WHO PUBLIC INSPECTION REPORT
of the Vaccine manufacturer**

PART 1	General information
Manufacturers details	
<i>Company information</i>	
Name of manufacturer	Panacea Biotec Limited
Corporate address of manufacturer	B – 1, Extension A – 27, Mohan Co-Operative Industrial Estate Mathura Road, New Delhi – 110 044 (INDIA) Phone: +91-11-4167900, +91-11-41578000 Fax: +91-11-26940621, +91-11-26940199
Contact person	Dr Rajesh Jain, Joint Managing Director rajeshjain@panaceabiotec.com
Inspected site	
Address of inspected manufacturing site.	1. Malpur, Baddi, Dist. Solan, Himachal Pradesh – 173 205 Vaccine Formulation Plant: Line 1, Line 2 and Quality Control Laboratories Global positioning system (GPS) coordinates: Latitude: 30.9499 - 30 deg 57' N, Longitude: 76.8705 76 deg 22' E. D-U-N-S: 67-760-5923 2. Ambala – Chandigarh Highway, Lalru – 140 501, Punjab, INDIA. Global positioning system (GPS) coordinates: 30°30'15.2"N 76°48'39.3"E °
Unit / block	1. Baddi site: Vaccine Formulation Plant: Line 1, Line 2 and Quality Control Laboratories 2. Lalru site: Block IV and Block I, Quality control laboratories and Animal house.
Inspection details	
Dates of inspection	15 to 19 October 2018
Type of inspection	Routine
Representative from the National Regulatory Authority	The national regulatory authority (NRA) of the country where the inspection took place was informed and participated to the inspection:

Introduction	
General information about the company and brief summary of the manufacturing activities	Panacea Biotech Limited (PBL), Baddi has two separate facilities; one dedicated for Pharmaceutical dosage forms (Unit-I) and another for manufacturing of Human Vaccines (Unit-II). Each unit has independent Manufacturing, Quality Control, Utility Block, Warehouse, Quality Assurance and Effluent Treatment Plants. - Unit-I for Pharmaceutical Formulation Plant (PFP), dedicated for manufacturing of pharmaceutical dosage forms like capsules, soft gelatin capsules, tablets, ointments, liquid orals and separate oncology unit. - Unit-II for Vaccine Formulation Plant (VFP), dedicated facility for vaccine formulation and filling. The vaccines being manufactured by Panacea Biotech are Easyfive™ (DTwP+ Hep-B+ Hib PRP-TT), Polprotec™ (Inactivated Poliomyelitis Vaccine), Pandylflu™ (inactivated H1N1 split virion influenza vaccine) , DTwP, Easyfour-TT™, bOPV and other vaccines in the offing are- EasySix™, Easyfour Pol™, Myfive™ , Pneumococcal, and several others. PanEra Biotech Pvt. Ltd., Lalru, is in charge of manufacturing Hepatitis B bulk antigen & Hib (PRP-TT) bulk conjugate which are used in Easyfive™.
History	The history of the regulatory inspections of the last five years to the manufacturing was kindly provided by the company.
Brief report of inspection activities undertaken	
Scope and limitations	
Areas inspected	The inspection focused on the production and control of Diphtheria-Tetanus-Pertussis (whole cell)-Hepatitis B-Haemophilus influenza type b vaccine and bivalent Poliomyelitis Type 1 & Type 3, live viral vaccine. The inspection covered all the sections of the WHO GMP text, including quality assurance, sanitization and hygiene, complaints and recalls, self-inspection, personnel, training, personal hygiene, premises and equipment, materials, documentation, qualification and validation, production, quality control and utilities.
Restrictions	None
Out of scope	Products and vaccines other than Diphtheria-Tetanus-Pertussis (whole cell)-Hepatitis B-Haemophilus influenza type b vaccine and Bivalent Poliomyelitis Type 1 & Type 3, live viral vaccine were not inspected during this inspection.
Vaccines covered by the inspection	- Diphtheria-Tetanus-Pertussis (whole cell)-Hepatitis B-Haemophilus influenzae type b 1 and 10 doses in vials. - Bivalent Poliomyelitis Vaccine Type 1 & Type 3, Live (Oral bOPV), 20 doses in vials.

Abbreviations	AHU	Air Handling Unit
	ALCOA	Attributable, Legible, Contemporaneous, Original and Accurate
	APR	Annual Product Review
	APS	Aseptic Process Simulation
	BMR	Batch Manufacturing Record
	BPR	Batch Production Record
	CA	Compressed Air
	CAPA	Corrective Actions and Preventive Actions
	CC	Change Control
	CFU	Colony-Forming Unit
	CIP	Cleaning In Place
	CoA	Certificate of Analysis
	CpK	Process capability
	DQ	Design Qualification
	EDI	Electronic DeIonization
	EM	Environmental Monitoring
	FMEA	Failure Modes and Effects Analysis
	FTA	Fault Tree Analysis
	GMP	Good Manufacturing Practices
	GPT	Growth Promotion Test
	HEPA	High Efficiency Particulate Air
	HVAC	Heating, Ventilation and Air Conditioning
	IQ	Installation Qualification
	LAF	Laminar Air Flow
	LIMS	Laboratory Information Management System
	MB	Microbiology
	MBL	Microbiology Laboratory
	MF	Master Formulae
	MFT	Media Fill Test
	MR	Management Review
	NCA	National Control Authority
	NCL	National Control Laboratory
	NRA	National Regulatory Agency
	OQ	Operational Qualification
	PHA	Process Hazard Analysis
	pH	(-ve) logarithm of H ⁺ concentration
	PLC	Programmable Logic Controller
	PM	Preventive Maintenance
	PQ	Performance Qualification
	PQR	Product Quality Review
	PQS	Pharmaceutical Quality System
	PSF	Product Summary File
	PW	Purified Water
	QA	Quality Assurance

	QC	Quality Control
	QCL	Quality Control Laboratory
	QMS	Quality Management System
	QRM	Quality Risk Management
	RA	Risk Assessment
	RCA	Root Cause Analysis
	RO	Reverse Osmosis
	SH	Single Harvest
	SIP	Sterilization In Place
	SMF	Site Master File
	SOP	Standard Operating Procedure
	UN	United Nations
	UNICEF	United Nations Children's Fund
	URS	User Requirements Specifications
	UV	Ultraviolet-Visible Spectrophotometer
	VVM	Vaccine Vial Monitor
	WcP	Whole cell pertussis
	WFI	Water for Injection
	WHO	World Health Organization

PART 2: Brief summary of the findings and comments

1. Pharmaceutical quality system

There generally appeared to be adequate resources available for the management of the quality management system (QMS). Senior management demonstrated support to the system. Quality assurance and quality control activities were functioning with appropriate independence from the production unit. The head of quality control is responsible for testing of raw material / packaging material and finished products as per written standard operating procedures (SOP) and test results are recorded in established formats. The head of production reviews the batch processing (BPR) and related records. The BPRs are checked for their completeness and correctness. The head of quality assurance is responsible for release of finished products. The head of warehouse is responsible for storage of finished product at appropriate temperature and dispatch of vaccine as per defined procedures.

Annual Product Quality Review (APQR):

Quality Assurance department prepare the APQR of each product at end of calendar year. Overall the APQR includes process yields, rejections, validation details of key equipment, finished product analytical data, in process analytical data, out-of-specification, out-of-trend, process deviations, change controls, non-conformances, market complaints, returned goods, recalled products, environmental conditions during manufacturing operations, critical equipment performance etc. The procedures for the APQR were in place.

✓ APQR of the drug substance of Hepatitis B vaccine (rDNA):

APQR of the bulk drug substance of Hepatitis B vaccine (rDNA) for the year 2017 was spot checked. The APQR covered batches manufactured between 01.01.2017 and 31.12.17.

No OOS was reported in 2017. Two complaints were recorded.

In 2016, two complaints were received for the batches of the bulk drug substances of Hepatitis B (rDNA).

✓ APQR of the drug substance of Hepatitis B vaccine (rDNA):

PQR related to Hib PRP-TT manufactured in 2017 was reviewed. A different document is usually prepared to control the production of PRP, before conjugation, the last lot of PRP was manufactured in October 2015. Several batches of PRP-TT were manufactured in 2017, using batches of PRP produced in 2015. One lot was discarded for three concomitant OOS in release tests. Root cause was evaluated and found to be connected with improper handling of the formulation tank.

✓ APQR of bOPV vaccine:

The APQR of bOPV type 1 & 2 of 0.1 mL/20 dose presentation covering the manufacturing period from January to December 2017 was spot checked. Several lots of bOPV were produced using bulks of OPV Type 1 and OPV type 3 provided from PT Bio Farma, Indonesia. These batches were nationally marketed as per the Indian Health Ministry bids.

No Batch rejection or failures of consignment was reported in 2017.

No complaint or adverse events post immunization were reported from the vaccine lots marketed domestically as part of NIP.

The stability profile for 3 batches released in 2017 was spot checked and all test results were within acceptance criteria.

✓ APQR of Easy Five TT vaccine:

The PQR is compiled on an annual (calendar year) basis and it covers different quality related aspects of the finished products as referenced by WHO guidelines. It is recommended to enhance the analysis of the PQR data to keep monitoring of the quality of the finished product, including but not limited to, consistency of manufacturing processes.

Quality Risk Management:

Procedure for QRM was in place.

The following risk assessments (RA) were reviewed:

- Panacea is planning to introduce pneumococcal vaccine manufacturing. A risk assessment for analyzing the risks associated to the introduction of this inactivated vaccine in the filling was initiated, but clear evaluation of possible mix-ups and contaminations has not yet been performed and the suitability of the existing cleaning procedures has not yet been demonstrated. A thorough risk assessment and risk management should be in place before the introduction of pneumococcal vaccine into the filling.
- Dengue live vaccine has been filled as the last manufacturing activity before revamping. A RA was performed for the introduction of a new live vaccine in this line and mitigation measures were introduced to minimize the risk of cross-contamination (single use materials whenever possible, dedicated glassware and needles, etc.).

Deviation management:

Procedure for handling incidents and deviation was in place. The SOP describes methods for managing the incidents for all departments. The timeline for completion of incidents is based on the type of the deviation.

Change control:

Procedure for change control was in place.

The change controls related to both facilities were reviewed and no observations were raised.

CAPA management:

The procedure for corrective and preventive actions was in place. The CAPA monitoring for effectiveness, evaluation and CAPA closure was considered in the procedure. The CAPA initiated subsequently to the last WHO inspection in 2016 was spot-checked.

Management review:

The procedure for management review was in place. The overall KPI in terms of % of plan adherence and % of overdue of the following quality elements (risk management, overall site CAPA, regulatory inspection CAPA, self-inspection, vendor management, product complaint, incident, deviation, OOS (product related, excluding stability), change control, training, preventive maintenance and work orders were covered.

The monthly quality report of September 2018 including the KPI from January to September was spot checked. The Quarterly quality report is consisting of reviewing number of KPI of quality metrics.

Documentation:

Overall, an adequate documentation management system was in place in both facilities: documents were readily available and basically reflecting the activities conducted.

Batch release procedure for vaccines and Lot Summary Product review:

The releasing or rejection process of finished product was conducted as per approved written procedures. The SOP is applicable to all batches of finished products manufactured at PBL, Baddi. The QA Head is responsible for final release of vaccines. The Lot Summary Product (LSP) along with 25 vials of 20 doses of bOPV vaccine are sent to the central drug laboratory (CDL) Kasauli for testing and certification/approval of vaccine lots by the national control laboratory. The certification takes place at maximum 45 days. Once certificate is obtained from CDL the batch will be dispatched for the market by the warehouse. The release will include the final release order signed by the QA Head and a copy of the CDL certificate. List of batches released into the international and domestic market for the period from 2017 was spot checked.

Complaints

This section was not inspected in detail during this inspection.

Product recalls:

This section was not inspected in detail during this inspection.

Pharmacovigilance:

This section was not inspected in detail during this inspection.

Self-inspection:

The self-inspection system was established, implemented and maintained at Panacea Biotech (Baddi site) as evidenced by review of the self-inspection SOP, self-inspection plan for 2018, audit team, risk assessment for determination of frequency of self-inspection of different departments (e.g. production, engineering, QC, etc.), and self-inspection checklist. In addition, the proper functioning of the self-inspection system was verified by reviewing few examples of self-inspection findings along with their corrective actions.

Quality audits and suppliers' audits and approval:

Vendor qualification was in place. Vendors were categorized as critical and non-critical, and an updated list of the approved supplier was provided during inspection.

After an initial questionnaire, samples of reagents/materials, as applicable, are evaluated. An audit plan is foreseen for all suppliers independently from the criticality and a requalification is performed every 3 years. A system for checking annually the compliance was also in place.

The supply of rubber stoppers used in both bOPV and EasyFive was spot checked, and no observations were raised.

Contract production, analysis and other activities:

The Quality agreement with the contract production of OPV drug substances was spot checked.

Personnel:

Organizational charts showing the relationships between different departments, including QA, Production, QC, Warehouse and Engineering with identification of the key personnel are provided. Production is independent for quality control department. Curricula vitae and the job responsibilities for key personnel, with qualification, experience and responsibility are provided.

➤ Training and personnel hygiene:

The company had provisions for personal hygiene and sanitation in its production facility. Smoking, eating, drinking, chewing, and keeping plants, food, drinks, smoking material and personal medicines was not permitted in production, laboratory and storage areas. Wrist-watches, cosmetics and jewelry were not observed as being worn in clean areas. Production areas are provided with changing rooms for personnel entries and exits. Gowning procedures for access to the classified manufacturing areas were in place. Changing rooms were provided with photos describing the gowning procedures.

Health requirements for new and regular employee were in place. Health check and status of vaccination of the operators are checked at the time of hiring and on regular basis by the HR as per the company procedure.

Training of personnel was managed according to the relevant procedure. In general, a training plan for new employees as well as for experienced operators was in place. An individual training matrix was also annually developed by the head of each department with the support of a training coordinator.

Gowning qualification of the aseptic operators was managed through the relevant procedure. Annual requalification was considered.

At Lalru site, the aseptic operators are qualified for gowning initially through three runs during three consecutive days. The aseptic operators are requalified every two years. At the end of sterile processing activity, the aseptic operators are routinely sampled for gowning in addition to finger dabs.

The qualification of the aseptic operators could be improved by making sure to include the media simulation activities in the formal qualification of the aseptic operators and to maintain the aseptic qualification through the participation to the media simulations.

2. Production system

In general terms, resources were available, including qualified and trained personnel, premises, equipment and services, materials, containers and labels, procedures and instructions, laboratories and equipment for in-process and other controls. Manufacturing processes were generally defined and reviewed. Instructions and procedures were generally available. Qualification and validation of equipment, manufacturing processes and quality control testing methods were in place. Operators were instructed to carry out procedures, and records were made for the production operations.

➤ Seed/Cell lots

A seed lot system was in place for the HepB and Hib antigens manufactured at the site. 2 locations were present in the facility and in Quality Control laboratories.

➤ Haemophilus influenzae type b:

Hib antigen is currently manufactured exclusively in one dedicated manufacturing block.

In 2017, the introduction of *Streptococcus pneumoniae* into the facility was initiated in order to produce clinical batches of Pneumococcal polysaccharide vaccine. Small scale batches were produced in the area up to August 2018.

A Change Control document was generated for the introduction of this new microorganism in the facility and a risk assessment was performed.

A cleaning validation study was initiated and considered as prerequisite for introducing *Streptococcus* in the facility.

➤ HepB production.

The production process of Hepatitis B Vaccine (rDNA) Bulk Drug Substance was inspected in detail and included the following:

- Multiplication and Fermentation
- Harvesting and Disruption of the Biomass
- Acid precipitation
- Purification Processes
- Final Filtration

➤ Environmental Monitoring:

EM was conducted according to the procedure that foresees sampling for Non-Viable and Viable Particles. Microbiological monitoring was performed in manufacturing areas of grade C on a weekly basis with disregard of the manufacturing activities. There was no provision to assure that EM needs to coincide and to be performed during the manufacturing operations when relevant.

From the cross-contamination stand point, the EM at change-over was conducted for three consecutive days after last cleaning (three cleanings are applied) and was supplemented with methods to detect the presence of the specific microorganisms used in previous campaign (chocolate agar for Hib, blood agar for *Streptococcus pneumoniae*).

➤ EasyFive

The prequalified EasyFive is presented in single dose (0,65 ml) and in 10 doses (6 ml), both containing thiomersal as preservative. The same vaccine can also be filled in PFS for domestic market.

The production process of Hepatitis B Vaccine (rDNA) Bulk Drug Substance was inspected in detail.

➤ **bOPV:**

The prequalified bOPV is presented in 20 dose vials. Currently bOPV is manufactured with bulks provided from PT BioFarma (Indonesia), since the original process with bulks manufactured by Sanofi has been discontinued. After refurbishment of the facility from July 11th to August 8th 2018, a new process validation batches of bOPV, with the addition of the sterile filtration, have been manufactured with a defined batch size. Results of such validation (including both process validation and sterilising filter validation) were expected to be finalized by mid-November 2018.

Manual visual inspection and labelling of bOPV vials were performed after filling. During the visit, visual inspection was going on: 6 operators were requested to break reading every 30 minutes for 10 minutes. Proper and regular eye-check as well as challenge test of operators with defective vials were in place.

3. Facilities and equipment system

Site tour of formulation and filling facilities:

The Filling lines were recently subjected to revamping to achieve the segregation of live vs. inactivated vaccines. One manufacturing line is currently dedicated to live viruses (bOPV and the upcoming Dengue vaccine which foresees a lyophilization step) and another manufacturing line is dedicated to inactivated vaccines.

Revamping was managed through change control. Areas were released after revamping upon completion of full requalification of HVAC and completion of MFTs.

During the visit, filling of bOPV was taking place, while in the other manufacturing line a simulation of formulation and filling operations were set up for inspection purposes.

The facility was found in appropriate conditions and adequately designed. High differential pressures were set to ensure proper air flows and EM programme was in place. Critical environmental parameters (non-viable particle measurements, differential pressure, temperature, humidity) were at an acceptable level of control. Operators moved adequately during operations and QA personnel were present in the facility to witness manufacturing steps at all times.

Both filling lines were equipped with open RABS and several gloves were present for routine interventions during filling. Gloves were cleaned and disinfected before and after each use with sterile IPA 70% and subjected to weekly fumigation applied for critical manufacturing areas, to mitigate the microbial contamination.

The Warehouse and cold storage block located in a separate building adjacent to vaccine manufacturing block at Baddi Site was visited. The ground floor is dedicated for receipt of raw materials, active ingredients, packaging materials and dispatch of finished goods under cold chain. Ground floor has separate sampling and dispensing area. First floor is used to store the finished product (under quarantine and approved stage). Part of first floor and second floor is dedicated for storage of packaging material.

Procedures for shipments for domestic and international destinations were in place. The ice packs are stored in appropriate conditions. Handling of bulks and finished material were in place. Color codes of labels for materials under test (Quarantined pending release), approved and/or rejected were in place as per relevant procedure. The passed materials were placed in approved area and the rejected materials were shifted to area of rejected material.

Cold room was used to store Hep B and Hib PRP-TT bulks (sourced Lalru), Pertussis and Diphtheria bulks (sourced PT Bio Farma). The color codes for quarantine and under test were evident. The Approved materials room was visited and approved samples of VVM2 and VVM14 were stored in deep freezer. Approved materials were labelled with green labels.

Site tour of hep B and Hib drug substances manufacturing facilities:

A vaccine manufacturing block was dedicated to the manufacturing of Hepatitis B Vaccine (rDNA) Bulk Drug Substance. Overall, the manufacturing block was adequately designed with logical flow of material, product and personnel.

Hib bulk manufacturing takes place in a dedicated manufacturing block. The same facility is used for manufacturing pneumococcal vaccines. Adequate segregation between live and inactivated manufacturing areas and logical flow of the manufacturing operations was observed during the facility tour.

Upstream processing was conducted in several adjacent rooms (culture propagation, fermentation, harvesting, centrifugation, CDAP precipitation) and a separated area was dedicated to downstream processing (TT modification, activation, conjugation). The manufacturing facility was classified with grade C, with the exception of the sterile filtration operations carried out under grade A with grade B surrounding area. VB-IV has been visited and found in good conditions of cleaning.

Several not in use pieces of equipment were present in the area, with no justification (at least 10 vessels and one sampling booth were observed).

Pressure differentials were set in order to achieve containment of live microorganisms as well as to introduce additional measures of contamination control, however:

- During the tour several ΔP were found outside the acceptable range;
- No action was initiated since pressure differentials were not linked to any alarming system, being manually recorded three times/day.

The inoculation area, where streaking of Hib on plates takes place, followed by initial incubation in flasks was equipped with a biosafety cabinet, a static incubator and a rotating incubator.

- Temperature of such incubators (CPP) was not continuously monitored.

Fermenters were present in the upstream area and open connections were conducted under portable LAF.

Temperature of refrigerators/deep freezers was monitored (not controlled) by a computerized system. The system was not capable of recording data for more than 30 days, however daily printing and review of data was performed. Periodic evaluation of temperature excursions was in place. Procedure was in place to manage alarms. Individual alarms were spot-checked, and actions taken were found adequate. Moreover, a frequent preventive maintenance program was in place for freezers/deep freezers/liquid N₂ containers, to prevent failure.

➤ **Waste management:**

Procedures for handling and disposal of waste, decontamination and disposal of used contaminated materials and waste management of biological and chemicals in the production areas and quality control were in place and followed in case of contamination.

➤ **Qualification and validation:**

Provisions for qualification and validation were in place and covers premises, equipment, utilities and systems, processes and procedures at periodic intervals and when changes have been made. Preventive maintenance programme and calibration plan were in place.

Preventive maintenance programme and calibration plan were in place.

The qualification and validation of the following equipment was spot checked.

- Validation of cold room;
- Validation of aseptic process through media simulations;
- Blending vessel/Formulation;
- Water system production;
- Depyrogenation Tunnel;
- Container closure integrity testing (CCIT) for final bulk drug substance and sampling containers;
- Cleaning validation;
- HVAC systems;
- Validation of aseptic process through media simulations;
- Fermenter;
- Autoclaves.

4 Laboratory control system (Quality Control)

A dedicated set up of QC laboratories for all BPL vaccines was situated at Baddi and Lalru sites from the production areas. The laboratories are designed to perform different tests as per compendial requirements.

Samples receipt was performed manually and based on sample request form generated by the warehouse and production area according to the relevant procedures.

The procedure for receipt, distribution and testing of sample product received by QC Department, Baddi Site was spot checked. There was no clear information in the procedure to explain the method for retention of reported test results.

Cold rooms, refrigerators and deep freezers ($\leq -20^{\circ}\text{C}$) are available for storage of samples, reference standards, retained samples and other materials. A separate area for preparation of glassware/other laboratory aids was also provided.

Analytical laboratory was provided for performing chemical and analytical tests on raw and packaging material. Equipment and instrument were appropriately qualified and calibrated. However, on the last 6 years, the spectrophotometer was not serviced or calibrated by an external contractor to check filters and critical parts, this should be considered.

A separate Immunology and cell culture laboratory for potency testing of vaccine and a microbiology laboratory for carrying out microbiological testing and a separate animal house for animal testing/animal breeding were available.

A separate stability area with stability chambers has been provided for carrying out the stability studies. Retained samples for in vivo testing are retained for one year after the expiry date of the finished product.

The logbook of Total Organic Carbon (TOC) Analyzer pertaining to test results, calibration and service was spot checked. There is only one TOC Analyzer in the Baddi QC laboratory and is serviced once every 6 months by an external contractor. In July 2017 there was OOL of TOC test result and an investigation was carried out.

There was no service request form submitted by QC. As per the service agent's report, the cleaning frequency of the analyzer was recommended.

Cold room 2 to 8°C located at Baddie QC Department was visited. Two temperature sensors observed and the temperature was recorded during the visit at 4.5°C. The cold room is calibrated once every six months; the last calibration was on the 24 July 2018. This cold room is connected to a central monitoring system. Samples inside cold room were well labeled and organized. The temperature trend was spot checked, all temperature records were within 3 to 7°C. Several liquid nitrogen tanks were located in cold room. These tanks are being used for storage of cells.

➤ ***Management of OOS test results:***

Handling of out of specification (OOS) and out of trend (OOT) results were conducted as per the relevant procedure.

➤ ***Qualification of in-house reference standard and Trending of Reference standard:***

In-house Working Diphtheria Reference standard was being used for in vivo Diphtheria Toxoid Potency testing in GP. The IHWRS was monitored and calibrated regularly. It was standardized against the previously used IHWRS and was calibrated against national reference standard NRS/DT/1/2013) and International reference preparation NIBSC-07/216.

The trend analysis from 15 in vivo potency tests using IHRS during January to June 2018 was spot checked. Investigation report was reviewed in relation to OOT for Diphtheria Toxoid Potency testing assay. Most of the test results of 15 assays were within the Mean ± 2 SD.

➤ ***Validation of Sterility test method***

Procedures for Analytical method validation was in-place.

Sterility test method validation for sterility testing by membrane filtration method for Easyfive-TT and bOPV were carried out in September 2011 and June 2017.

Tests performed during the validation were; Growth Promotion Test (GPT), Sterility test, Bacteriostasis and Fungistasis, Stasis test (After 14 days of incubation of finished product sterility test) and Negative control was used. The test results indicated that the Bacteriostasis and Fungistasis activity inherent in the product did not adversely affect the reliability of the test results of test method validation.

Furthermore, GPT is being performed on each Culture media lots at the time of receipt and release from QC department with ATCC Cultures and Environmental isolates.

➤ ***Validation of OPV Potency Test***

Method validation of potency test was reviewed. The validation method was completed on 18 Jun 2018 using 3 lots of bOPV finished product produced with bulks from Biofarma. The new validation method deemed to be in compliance with ICH Q2 R1 to cover the validation criteria i.e. Linearity, Precision (repeatability and Reproducibility), Accuracy, specificity, robustness.

➤ ***Qualification of reference standard:***

The In-house reference standard was calibrated once a year against the National Reference Standard # BOPV (1+3) 01/2013/P (NRS). The trend analysis of in-house reference number for the period from 2 January 2018 to 7 October 2018 was spot checked and found acceptable.

➤ ***Stability:***

The procedure for stability of biologicals was spot checked. The number of batches and test samples required for stability study was specified. For instance, for new product and consistency batches on commercial scale, the first 3 batches should be tested for long term stability, accelerated and stress stability test. Stability data were available for up to 18 months for batches produced in the year 2016 and for up to 12-month time point for batches produced in the year 2017.

The stability profile for 3 batches released in 2017 was spot checked and all test results were within acceptance criteria.

The freeze thaw cycles stability study of 3 finished product bOPV type 1 & 3 were spot checked. The product is stable for up to 7 cycles.

Two intermittent stability studies from 2016 bulks were spot checked. The study included 18 months real-time storage at -20°C followed by accelerated temperature for 6 months at 2 to 8°C. Study #1 is still ongoing and results from 20 months are within the acceptance criteria. While study # 2 the stability study was conducted firstly on 2 to 8°C for 6 months and then samples transferred to -20°C. The test results were within the acceptance criteria for up to 9 months at -20°C.

Freeze thaw stability study on bulks type 1 & 3 was spot checked. The bulks are stable for up to 7 cycles. During routine production, the bulks can only be exposed to a maximum of 3 freeze/thaw cycles.

➤ ***Holding storage period stability validation:***

Hold time studies were spot checked and found satisfactory.

➤ ***Environmental monitoring results:***

The environmental monitoring program was in place and includes the non-viable particle count monitoring, pressure differentials, temperature and relative humidity, microbiological monitoring of air, surfaces and personnel. Frequency and acceptance criteria are provided for each parameter. Alert and action limits are established and there was a process for reviewing these through annual reviews of the environmental monitoring data. In case of the out of limited, the identification is considered. In-house isolates are considered for the growth promotion test of the used media in the environmental monitoring. The vaccine formulation room where the final sterile filtration of the HepBsAg takes place is fumigated before each aseptic processing.

5 Materials system

The storage, sampling testing, releasing or rejecting of starting materials, packaging materials, bulk and finished products is performed according to implemented specifications and SOPs.

Controls are in place at receipt, checking, sampling, storage, release, storage of approved materials in segregated areas (quarantine, approved and rejected) with adequate labeling. Yellow color label are used for “received”, white color label are used for “sampled”, green color label are used for “approved” and a red label for “rejected” materials.

The tests for incoming materials, the bulk and finished products are performed in QC department.

The products are sampled, labeled and kept in a quarantine area in warehouse till clearance by QA. QC issues a test report and sends it to QA for lot release.

Upon detection of any lot or product being rejected in in-house QC and by Central Drug Laboratory (Kasauli), the situation is notified to the concerned relevant department at the company. Rejected materials and products (incoming materials, intermediate and final bulk products, and final lot) are marked with a 'Rejected' label and separated in designated areas. Rejected products are assessed by the QA to arrange for its final disposal. A team is formed for this purpose and for investigating the causes of the rejection and planning corrective actions. Rejected materials and products may be destroyed or returned to supplier as relevant. The destruction of products is performed as per SOP. QA supervises and assures the destruction. Records of the destruction are maintained which include the identification of batches destroyed and its quantities. The same apply for incoming materials.

6 Packaging and labelling system and International shipping

Packaging configuration of the international shipment was spot checked. The shipping validation process was spot checked. The international shipment at -20 °C and below at continuous external temperature of 43 °C was validated in accordance with the WHO guideline on international packaging and shipping of vaccines WHO/IVB/05.23 (Class A packaging: The vaccine must be packed to ensure that the warmest temperature inside the insulated package does not rise above +8 °C in continuous outside ambient temperatures of +43°C for a period of at least 48 hours). Three independent runs of the study were conducted using 8 sensors placed at different locations of the fully loaded 5 ply boxes (16 x 30 vials) at ambient temperature of + 43 °C. The study results revealed that the minimum and maximum temperatures from 3 runs met the acceptance criteria established by WHO guideline WHO/IVB/05.23 (Min minus 7.5 °C and Max + 4.6 °C).

PART 3: Conclusion

Based on the areas inspected, the people met, and the documents reviewed, and considering the findings of the inspection, including the deficiencies listed in the Inspection Report, as well as the Corrective Actions taken and planned, and committed to be implemented, **Panacea Biotech Ltd.** located at

- **Malpur, Baddi, Dist. Solan, Himachal Pradesh – 173 205** and
- **Ambala – Chandigarh Highway, Lalru – 140 501, India**

was considered to be operating at an acceptable level of compliance with WHO GMP guidelines.

All the non-conformances observed during the inspection that were listed in the full inspection report as well as those reflected in the WHO Public Inspection Report (WHOPIR), were addressed by the manufacturer, to a satisfactory level, prior to the publication of the WHOPIR.

This WHOPIR will remain valid for 3 years, provided that the outcome of any inspection conducted during this period is positive.

PART 4: List of GMP guidelines referenced in the inspection report

1. WHO good manufacturing practices for pharmaceutical products: main principles. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Eighth Report Geneva, World Health Organization, 2014 (WHO Technical Report Series, No. 986), Annex 2.
Short name: WHO TRS No. 986, Annex 2
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_986/en/
2. WHO Good Manufacturing Practices: water for pharmaceutical use. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fourth-Sixth Report. Geneva, World Health Organization, 2012 (WHO Technical Report Series, No. 970), Annex 2
Short name: WHO TRS No. 970, Annex 2
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_970/en/
3. WHO guidelines for sampling of pharmaceutical products and related materials. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-Ninth Report. Geneva, World Health Organization, 2005 (WHO Technical Report Series, No. 929), Annex 4
Short name: WHO TRS No. 929, Annex 4
http://whqlibdoc.who.int/trs/WHO_TRS_929_eng.pdf?ua=1
4. Supplementary guidelines on good manufacturing practices: validation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fortieth Report. Geneva, World Health Organization, 2006 (WHO Technical Report Series, No. 937), Annex 4
Short name: WHO TRS No. 937, Annex 4
http://whqlibdoc.who.int/trs/WHO_TRS_937_eng.pdf?ua=1
5. WHO Good Practices for Pharmaceutical Quality Control Laboratories. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957), Annex 1
Short name: WHO TRS No. 961, 957), Annex 1
<http://www.who.int/medicines/publications/44threport/en/>
6. WHO Good Practices for Pharmaceutical Products Containing Hazardous Substances. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957), Annex 2
Short name: WHO TRS No. 957, Annex 2
<http://www.who.int/medicines/publications/44threport/en/>
7. WHO good manufacturing practices for sterile pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 6
Short name: WHO TRS No. 961, Annex 6
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

8. WHO guidelines on transfer of technology in pharmaceutical manufacturing WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 7
Short name: WHO TRS No. 961, Annex 7
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1
9. Model guidance for the storage and transport of time-and temperature-sensitive pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 9
Short name: WHO TRS No. 961, Annex 9
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1
10. General guidelines for the establishment maintenance and distribution of chemical reference substances. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-First Report Geneva, World Health Organization 2007 (WHO Technical Report Series, No.943) Annex 3
Short name: WHO TRS No. 943, Annex 3
http://whqlibdoc.who.int/trs/WHO_TRS_943_eng.pdf?ua=1
11. WHO good practices for pharmaceutical microbiology laboratories. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 2
Short name: WHO TRS No. 961, Annex 2
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1
12. WHO guidelines on quality risk management. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Seventh Report Geneva, World Health Organization, 2013 (WHO Technical Report Series, No. 981), Annex 2
Short name: WHO TRS No. 981, Annex 2
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_981/en/
13. WHO guidelines on variation to a prequalified product. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Seventh Report Geneva, World Health Organization, 2013 (WHO Technical Report Series, No. 981), Annex 3
Short name: WHO TRS No. 981, Annex 3
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_981/en/
14. WHO guidelines for drafting a site master file. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 14
Short name: WHO TRS No. 961, Annex 14
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1
15. WHO General guidance on hold-time studies WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 4
Short name: WHO TRS No. 992, Annex 4
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

16. WHO Technical supplements to Model Guidance for storage and transport of time – and temperature – sensitive pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 5

Short name: WHO TRS No. 992, Annex 5

http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

17. WHO good manufacturing practices for biological products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fiftieth Report Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 3

Short name: WHO TRS No. 996, Annex 3

http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex03.pdf

18. Guidance on good data and record management practices. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fiftieth Report Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 5

Short name: WHO TRS No. 996, Annex 5

http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex05.pdf