

**Prequalification Team Inspection services
WHO INSPECTION REPORT
Vaccine manufacturer**

Part 1	General information
Manufacturers Details	
<i>Company information</i>	
Name of manufacturer	Panacea Biotec Limited. (PBL)
Corporate address of manufacturer	B – 1 Extn A – 27, Mohan Co-Operative Industrial Estate Mathura Road, New Delhi – 110 044 (INDIA) Phone: +91-11-41679000, +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	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
Unit	Vaccine Formulation Plant: Line (XX) , Line (XX) and Quality Control Laboratories
Inspection details	
Dates of inspection	05 to 09 December 2016
Type of inspection	- Routine for Diphtheria-Tetanus-Pertussis (whole cell)-Hepatitis B-<i>Haemophilus influenzae</i> type b (Easyfive-TT®), 1 and 10 doses in vials. - Approval for Bivalent Poliomyelitis Vaccine Type 1 & Type 3, Live (Oral bOPV), 20 doses in vials.
Representative from the National Regulatory Authority	The national regulatory authority of the country where the inspection took place was informed and Drugs Inspector from Central Drugs Standards Control Organization (CDSCO), Baddi, Himachal Pradesh took part in the inspection.
Areas inspected	Vaccine Formulation Plant: Line (XX), Line (XX) and Quality Control Laboratories
WHO product numbers covered by the inspection	- Diphtheria-Tetanus-Pertussis (whole cell)-Hepatitis B-<i>Haemophilus influenzae</i> type b (Easyfive-TT®), 1 and 10 doses in vials. - Bivalent Poliomyelitis Vaccine Type 1 & Type 3, Live (Oral bOPV), 20 doses in vials.
Introduction	
Brief summary of the manufacturing activities	Panacea Biotec Limited (PBL), Baddi has two separate facilities; one is 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 Biotec comprise of both bacterial and viral vaccines. PanEra Biotec Pvt. Ltd., Lalru, an associate company of Panacea Biotec is the manufacturer of Hepatitis B & Hib (PRP-TT) bulk antigens which are used in the WHO prequalified Easyfive™ vaccine.
General information about the company and site	The Baddi site is the campus where the pentavalent vaccine Easyfive-TT® (DTwP+ Hep-B+ Hib PRP-TT) is manufactured. The bOPV vaccine was being manufactured at VFP Okhla, New Delhi up to the year 2015. PBL has recently shifted the manufacturing of the bOPV vaccine to Vaccine Formulation and Filling Plant (VFP), Baddi, through technology transfer from VFP Okhla, New Delhi. BPL has obtained the manufacturing license for BPL Baddi in August 2016 from the Drugs Controller General (India) and Central License Approving Authority.
History	A tabular list of inspections conducted at VFP, Baddi was provided along with the Site Master File. The CAPAs compliance status was presented by the company as complied. The latest inspection report performed by the CDSCO in November 2016 for the approval of (XX) product Report was awaited at the time of WHO inspection. The company provided the detail of major changes implemented since the WHO inspection in 2013 included the introduction of additional vial line. The information on planned future changes was also presented by the company.
Brief report of inspection activities undertaken	
Scope and limitations	
Areas inspected	The inspection focused on the production including the formulation, the filling, the visual inspection, the labelling, the packaging, the storage, the dispatching and the quality control of Diphtheria-Tetanus-whole cell Pertussis-Hepatitis B-Haemophilus influenzae type b (Easyfive-TT®), 1 and 10 doses and the bivalent Poliomyelitis vaccine Type 1 & Type 3, Live (Oral bOPV) 20 doses in vials. The inspection covered the manufacturing Line (XX), Line (XX), quality control laboratories and the warehousing. PanEra Biotec Pvt. Ltd., Lalru, in charge of manufacturing Hepatitis B bulk antigen and Hib (PRP-TT) bulk conjugate which are used in Easyfive-TT® was not inspected during this inspection.
Restrictions	None.
Out of scope	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. Vaccine products other than Diphtheria-Tetanus-Pertussis (whole cell)-Hepatitis B-Haemophilus influenzae type b vaccine (Easyfive-TT®), 1 and 10 doses in vials and 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
	CCID	Cell Culture Infective Dose
	CFU	Colony-Forming Unit
	CIP	Cleaning In Place
	CoA	Certificate of Analysis
	CpK	Process capability
	DT	Diphtheria Toxoid
	DTP	Diphtheria, Tetanus and Pertussis
	DQ	Design Qualification
	EDI	Electronic DeIonization
	EM	Environmental Monitoring
	eQMS	Electronic Quality Management System
	FMEA	Failure Modes and Effects Analysis
	FTA	Fault Tree Analysis
	GMP	Good Manufacturing Practices
	GPT	Growth Promotion Test
	HEPA	High Efficiency Particulate Air
	Hib	<i>Haemophilus influenzae type b</i>
	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
	OMCL	Official Medicines Control Laboratory
	OQ	Operational Qualification
	PHA	Process Hazard Analysis
	PBL	Panacea Biotech Ltd
	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
	SIP	Sterilization In Place
	SMF	Site Master File
	SOP	Standard Operating Procedure
	UF	Ultra Filtration
	UN	United Nations
	UNICEF	United Nations Children's Fund
	URS	User Requirements Specifications
	UV	Ultraviolet-Visible Spectrophotometer
	VVM	Vaccine Vial Monitor
	VFP	Vaccine Formulation and Filling Plant
	WFI	Water for Injection
	WHO	World Health Organization

Brief summary of the findings and comments**1. Pharmaceutical quality system**

There generally appeared to be adequate resources available for the management of the 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 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 Review (APR)

Quality Assurance department prepare Annual Product Review (APR) of each product at end of calendar year. APR includes process yields, rejections, validation details of key equipment, finished product analytical data, in-process analytical data, Out-Of-Specification (OOS), out-of-trend (OOT), process deviations, change controls, non-conformances, market complaints, returned goods, recalled products, environmental conditions during manufacturing operation, critical equipment performance etc. with respect to each product.

Overall, the provision for the annual product quality review was in place as per the implemented procedure. The CpK tool was considered for APR reviews. The APR for Easyfive-TT[®] 10 dose presentation covering the manufacturing period ranging from January 2015 to December 2015 was spot checked. A total of (XX) batches have been packed and one batch has been rejected due to the presence of white particles). (XX) batches for Easyfive-TT[®] one dose presentation meant for domestic market were manufactured in 2015.

The APR for Hib conjugate (PRP-TT) manufactured in (XX) site was spot checked. The tetanus toxoid (TT) used in the Hib-TT conjugate is being purchased from a third party company. The manufacturing of one batch was abandoned in August 2015 due to OOS in free PRP content. The timeframe of OOS investigation and completion was beyond the company policy however this was not documented and justified. The root cause of OOS was identified and accordingly CAPA was initiated.

The company has provided the corrective and preventive actions (CAPAs) adequately addressing the raised issues regarding timeframe for OOS investigation and completion.

Quality Risk Management (QRM)

Provisions for the QRM were in place.

The following documents were spot checked during the inspection:

- The procedure “Risk Management,
- The list of QRM for the year 2016,
- The QRM report “Risk assessment to allow deviation to postpone the scheduled requalification media fill test in line (XX),
- The Risk Assessment Form (Failure Mode Effect Analysis): Risk assessment to undertaking the manufacturing of various formulations of Oral Polio Vaccine on campaign basis in Line (XX) of vaccine formulation plant (VFP) Baddi.

• Change Control Management

Provisions were in place to manage change controls related to process, product, equipment, approved document, specifications, manufacturing facility, analytical techniques, approved vendors and any related environmental changes that has potential effect on the cGMP, product quality, safety, efficacy, stability and OH&S.

At the company, the responsibility was on the initiator department who may raise the related change (i.e. QA, QC, production etc.). The designated personnel in any department are responsible for the logging, review and monitoring of implementation activity of change proposal. Three types of quality changes have been classified as minor, moderate, major quality changes per the potential and impact on the quality, safety, purity, potency of a product. The time line for minor change control approval is set to be within (XX) days from the day of initiation by the QA. While the time of approval for change for moderate and major (notifiable) changes requires NRA prior approval before implementation. In some cases a change control may be referred to change control special committee for further assessment and recommendation.

Change control log book from January 2016 was spot checked.

Deviation Management

Provision for the deviation management was in place. The following deviations were spot checked during the inspection:

- Planned deviation related to preparation of volume of component (XX) as (XX) ml instead of (XX) ml and component (XX) as (XX) ml instead of (XX) ml issued on the (XX) December (XX);
- Unplanned deviation related to (XX) during visual inspection of filled vials issued on December (XX);
- Investigation report related to rejected batch due to the (XX) and related CAPA. Number (XX);
- Unplanned deviation related to (XX) observed in (XX) tank containing (XX) during incubation issued on the (XX) December (XX).

CAPA management

Provisions for the corrective and preventive actions plans were in place. The CAPA initiated subsequently to the last WHO inspection in 2013 was spot-checked and found satisfactory.

Management review

Provision for the management review was in place. Monthly quality review meetings with the heads of all departments including CQA representatives are held. Quarterly quality review meetings with joint managing director for all sites are held. The main quality elements reviewed are related to risk management, overall site CAPA, regulatory inspection CAPA, self-inspection, vendor management, product complaint, incident, deviation, OOS, change control and training.

The quarterly quality review report – January to December 2016 has been spot checked and found satisfactory.

Batch release procedure for vaccines

The finished product is released or rejected as per approved written procedure. The SOP dated (XX) describes the procedures for final release of finished product was spot checked. The SOP is applicable to all batches of finished products manufactured at PBL, Baddi. (XX) vials of single dose and (XX) vials of 10 dose vials of finished product along with summary protocol documents are sent to Central Drugs Laboratory (CDL) for testing and certification. The certification takes maximum (XX) 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 2014 – 2016 was spot checked. (XX) batches were released in 2014, (XX) batches in 2015 and (XX) batches were release so far in 2016.

The Endotoxin testing on the final container of Easyfive-TT[®] vaccine is encouraged to be implemented as stated in the WHO TRS 980, sections A.3.2 and A.5.

2. Good manufacturing practices for pharmaceutical products

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.

3. Sanitation and hygiene

Most of the premises were generally maintained at an acceptable level of cleanliness. The company had provisions for personal hygiene and sanitation in its production facility. Manufacturing areas are provided with airlocks for personnel and materials entries and exits. Gowning procedures for access to the classified manufacturing areas were in place. Cleaning, disinfecting and decontaminating procedures along with the environmental monitoring program were in place to control the non-viable and viable contamination levels in the production areas.

4. Qualification and validation

Overall, 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. Validation and qualification protocols and reports were spot checked as presented below.

✓ Sterile filtration validation

The company has implemented the sterile filtration of the bOPV formulated bulk. At VFP Baddi, only (XX) consistency lots have been manufactured in Line (XX). The data from these (XX) consistency batches were used to support the PSF submission for (XX) product prequalification.

The formulation used is presented below:

The validation protocols for the sterile filtration of the bOPV formulated bulk were available however the validation report was not available for review by the company and by the inspector when requested during inspection on 5 December 2016. On 6 December 2016, the company has shared with the inspector data from non-formal validation reports regarding the bacterial retention (performed with (XX) medium), the product bubble point ratio determination and the extractable volume. The bacterial retention was performed with (XX) medium and not with bOPV due to the inhibitory effect of the antibiotics in the final formulation.

✓ Campaign change

The provision for campaign change in VFP, Baddi between bOPV vaccines and inactivated vaccines was in place. So far, bOPV is the only vaccine containing live virus manipulated manufactured at VFP, Baddi. (XX) consistency batches of (XX) product have been manufactured on line(XX)on campaign basis. During the inspection, the first (XX) product batch was being aseptically filled in Line (XX).

The campaign change is approved by QA. Overall, to start the polio campaign, the left over materials are removed, the material is decontaminated and washed and the rooms and equipment are cleaned and disinfected. In addition, (XX) consecutive septic filling runs are carried out with (XX) and the filled (XX) is tested for identification of residuals of (XX) viruses. So far, all the results were reported by the company as not containing residual virus.

Swab samples were considered during cleaning validation for (XX) runs, but not considered for the monitoring of the cleaning of the equipment in contact with the product.

The formulation tank for OPV is a fixed tank located under LAF in a room of grade B. In the same room, (XX) mobile tanks used for the formulation of inactivated vaccines are located.

The cleaning of external surfaces of equipment is performed using the (XX) disinfectant. The cleaning of the manufacturing areas is performed using disinfectants.

Fogging is performed by (XX). The fogging is performed according to the procedure for fogging in clean area of production facility.

The company failed to provide appropriate validation reports of the fogging process through AHUs (XX) intended for campaign change including the change from bOPV to inactivated vaccines. Therefore, the company failed to demonstrate the effectiveness of the fogging process in the manufacturing line (XX) and in the manufacturing line (XX)

The company has provided the CAPA to address the raised issue.

✓ Cleaning validation of fixed formulation and blending vessels used for (XX) product in line (XX)

CIP and SIP validation studies are carried out annually on the formulation and blending vessels.

Initial CIP validation was performed in February 2016 through (XX) runs using specific chemical for coverage pattern studies and . (XX) was used as soiling agent. The cleaning validation was completed during the (XX) consistency batches of bOPV in May 2016; the results from final rinse as well as swabs were considered acceptable. However, no recovery studies for residuals were considered. The (XX) media used for MFT for the same vessels was not considered to demonstrate effective cleaning procedures.

The company has provided the report of recovery study as corrective and preventive action (CAPA) for addressing the raised observation on demonstration of effective cleaning procedure.

✓ Validation/revalidation of the autoclave in line (XX)

Leak test and Bowie Dick test are performed (XX) and (XX) schedules respectively. The vent filter is integrity tested on specified frequency. In total (XX) loads are sterilized in this autoclave.

The initial qualification was performed through (XX) runs empty, (XX) runs for the minimal and (XX) runs for maximal loads. The drying of the loads was not considered during the qualification and is not verified during the routine process. The annual qualification was carried out through (XX) runs minimal and (XX) runs maximal for hard-goods and for liquid-goods. The steam non-condensable gas, steam superheat and steam dryness tests are performed annually before starting the qualification.

The results of rubber stoppers have been spot checked and found acceptable. It was reported that issues during the filling with regard to stuck rubber stoppers were frequent. A CAPA was initiated with the involvement of the supplier of the rubber stoppers.

The same validation approach used for the sterilizing autoclave is used for the decontamination autoclave in Line (XX).

✓ Filling machine Line (XX)

IQ, OQ and PQ protocols and reports were available. For bOPV vaccine, 3 ml vials are filled with 2.2 ml filling volume.

The validation/qualification of the filling volume was performed through (XX) runs using (XX) batches where (XX) syringes were sampled per each run and the volume was weighted off line. The filled volume was drawn from the gross weight and the tare weight of the filled and emptied vials. The IPC to check the filled volume during the filling drawn from this validation/qualification was to sample every (XX) plus $\pm$ (XX) min. The company failed to demonstrate the consistency of the filling volume through the filling process and to justify the frequency of IPC for filling volume every (XX) min.

✓ Container Closure Integrity Test (CCIT)

Three media fill tests were performed and reported as conclusive. After filling, stoppering and sealing the vials, samples were tested for (XX) test with (XX) chemical.

✓ Sealing machine

The IQ, OQ and PQ of vials sealing machine in line (XX) were available. The detection of misplaced and the absence of rubber stopper was not challenged. The process validation is not considered to be sufficient.

The company has provided the corrective and preventive actions (CAPAs) plan for addressing the raised observation.

✓ Aseptic process simulation

The provision for the aseptic process simulation for the dispensing, formulation and aseptic filling processes were in place according to the relevant procedures. The worst-case for 3 ml vial format was bOPV and Easyfive-TT[®] was considered as the worst case for 2 and 5 mL vials as it represents the largest batch size. The MFT protocol includes a simulation of minimum, optimal (nominal or routine speed) and maximum machine speed during the filling.

✓ HVAC

Qualification and validation reports of HVAC system have been spot checked.

The review of “Protocol and report for requalification of HVAC system and installed HEPA filters for various equipment” showed the following deviations:

- The non-viable particles qualification in operation conditions were not defined in the requalification PQ. The PQ of the filling room was not done in operation conditions. The operators were simulating the working conditions however, the machine was not running.

The company has provided the corrective and preventive actions (CAPAs) adequately addressing the raised observation

✓ Washing machine

The validation and revalidation report of the vial washing machine has been spot checked.

The “Validation and revalidation report for vial washing machine” regarding line(XX) showed that the washing validation of the 3 mL format of the vials was not considered and no rational and/or documentation has been provided to justify this decision.

The company has addressed this observation by providing risk assessment study for justifying the non-usage of of (XX) ml vial format in validation.

✓ Cleaning of the filling machine accessories

The cleaning, preparation, storage of the filling machine accessories was spot checked.

The manual cleaning validation of machine accessories (line (XX)) coming in contact with the vaccines such as pistons, needles, manifold, tanks were not validated and the SOP for cleaning does not detail the operations for cleaning of critical equipment such as stopper bowl and the washing of non-product contact parts.

The company has provided the corrective and preventive actions to address the raised observation adequately.

✓ Depyrogenation tunnel

The validation protocol and reports of the depyrogenation tunnel have been spot checked.

5. Complaints

QA is responsible for handling complaints, as per approved written procedure. Upon receipt of complaint, QA reviews it. Product complaints are classified as critical, major and minor. Details of complaints are being entered into a complaint form as per SOP. Based on the nature of investigation, a retained sample is analyzed side by side with market samples if provided. In case of a critical complaint of Adverse Effect Following Immunization (AEFI), the complaints are forwarded within 24 hours to Global Pharmacovigilance department of the company. A joint investigation report is prepared along with Quality Control and Production department and information/reply is given to complainant. There is an annual compilation and review of all the complaints product wise.

The procedure for handling of AEFI with or without lack of efficacy or product quality complaints was in place. The timeline for initiating the investigation and requirement to report on AEFI to the local health authority within (XX) days were implemented. One AEFI case was reported from the local market. The case reported in a neonatal following immunization with (XX) product on (XX), with a severe convulsion, vomiting and cyanosis. In total, (XX) number of AEFI cases reported from the period 2013 to 2015. These cases were already submitted to WHO PQT as per the Annual Safety Reports.

6. Product recalls

Quality Assurance department is responsible for handling product recall as per approved procedure. For taking the decision to recall batch of commercial product and Investigational medicinal product, QA must inform and align with the Head CQA as well as top management. Head QA must keep top management informed of progress in product recall. On receipt of any complaint on the product safety, efficacy, purity, identity, etc. the same is investigated as per handling of product complaints. During the course of investigation and assessment of degree of seriousness of health hazard to population, in case the product is defective the company undertakes a voluntary recall or recall directed by the competent regulatory authority. Categorization of defect(s) (class I-III) in products and root causes are used as guidance for ascertaining severity of complaint and time frame for the product recall.

Mock Recall (MR)

The regular conducting of Mock Recall for PBL, Baddi is in place. Starting from the year (XX), the MR has been conducted once a year by QA. The selection criteria comprise that the MR is carried out for at least one batch of any product that has been largely distributed into the market. The SOP lacks instructions about the agreement requirement with the second party involved in the recall system.

The SOP was spot checked which consists of requirements for the recall process such as: list of addresses, phone numbers, batch number and quantities received/distributed by the dispatched department. The SOP also rated the effectiveness of the recall system as to be 100%. Information needed in the recall application form consists of the name of the product, vaccine quantities, manufacturing and expiry dates.

In 2016 the company has conducted MR of (XX) product for the domestic market in India through the marketing office of PBL in Delhi.

In 2015 MR was conducted for (XX) market in collaboration with the (XX) on (XX) product. The tracking record of the consumed and available doses was matching the distributed amount. However, in the summary of the 2015 Mock Recall report, it was identified the quantity left in stock was mentioned (XX) containers instead of (XX) containers. This is inconsistent with the reconciliation provided by (XX).

The company should consider implementing control measures for good documentation practice to confirm the correct information are recorded and hence prevent any future misinterpretation.

There was no agreement in place between the engaged second party (XX) and PBL. This does not comply with the requirements.

The company has taken the corrective and preventive actions for adequately addressing the raised observation on good documentation practice

7. Contract production, analysis and other activities

PBL receive the following drug substances for the manufacturing of (XX) product and (XX) product from WHO prequalified manufacturers.

The quality agreement with the manufacturers and the suppliers of the drug substances were missing. The available agreements were lacking details in terms of clarity of responsibilities of the different parties.

The customer agreement on conditions and warranties related to the supply of the polio monovalent from (XX) manufacturer was available. The end date was 31 December 2016.

The quality agreement between Panacea and (XX) Manufacturer/Supplier for (XX) drug substance covered the period from (XX) to (XX). This quality agreement was not renewed.

A quality agreement was available between PBL, Baddi and (XX) covering the supply of various different vaccine drug substances. The list of the active ingredients was in an appendix (XX) without any identification as an attachment to the quality agreement. The testing carried out in (XX) was not covered in the quality agreement.

There was no current quality agreement for the (XX) drug substance from (XX) Manufacturer.

The company has taken the corrective and preventive actions (CAPAs) adequately addressing the raised issues on quality agreements with bulk suppliers..

8. Self-inspection, quality audits and suppliers' audits and approval

✓ Self-inspection

Provisions for self-inspection were implemented.

Self-inspections were performed by announced or unannounced audits for production, QC, QA, Warehouse, Engineering, EOHS, Administration and human resources.

The following documents were spot checked:

- SOP Self inspections.
- List of audit planned program (announced audits) for years 2015 and 2016;
- Audit of production performed on (XX) conducted on logbooks, training records and facility;
- Audit of production (unannounced) performed on (XX) conducted on line (XX) facility, training, gowning practices and cold rooms.

✓ Vendor approval

Vendors for the raw and packaging materials are approved as per SOP which describes the procedure to evaluate the concerned vendor(s) through study on pre-purchase samples and manufacturer's site visit as per requirement. Vendor auditing team includes members from production, QC, QA, Material Management, Finance, Engineering and Administration (for service provider) as relevant. Vendor auditing team select vendor out of a group, for a specific material/service based upon requirement and quality standard.

The "Vendor pre-audit assessment Questionnaire" is sent to vendor (through material management department) to provide the requisite details and other supporting documents. In addition, the pre-purchase samples are requested from vendor for analysis purpose. After evaluation of the questionnaire and results of the samples analysis, Head QA or his designee or a designated team/trained personnel audit the manufacturing location to conduct the site audit of the vendor facility (wherever applicable). Contract testing laboratory is qualified after satisfactory review of assessment questionnaire and certification and site audit (wherever applicable).

Approved vendor from which the company is procuring materials, are re-evaluated every (XX) year to get updated information of the vendor. The frequency of the audit of supplier is defined in the SOP. Every (XX)

years for active raw material and primary packaging material, once every (XX) years for inactive material and for control testing laboratories, (XX) years for secondary packing material.

The list of approved vendors for active raw material, inactive raw material, primary packaging material and secondary packaging material was approved in November 2016.

The schedule of the audit of supplier recorded for 2015 and 2016 was spot checked.

The supplier of the aluminium gel was audited in May 2016. Failures in terms of (XX) and quality controls ((XX) test, (XX) during stability) have been raised. The supplier provided the CAPA and PBL is following up on this.

9. Personnel

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

10. Training

Overall, the trainings are provided to the employees as the following:

- Induction training for new employees to familiarize with the organization, coordinated by human resource department.
- cGMP training for new employee and for existing employee as per cGMP annual plan
- On job training for staff members working in production, quality control, quality assurance, maintenance etc.

The trainings are evaluated by means of questionnaire or by other means. “Individual training record” of the trainings imparted to each individual is maintained. Retraining is done in case of failure to accomplish the training successfully, changes in the documents / equipment / facility or on need basis.

Personnel are trained according to a training individual matrix. For aseptic operations, personnel undergo theoretical and practical trainings. Gowning qualification includes (XX) runs of initial qualification and annual requalification as per the company’s procedure.

The following documents were spot checked:

- Training of QC operators (technical training is performed in (XX) steps for the new employees: For experienced operators the training is imparted in one step;
- Training of an aseptic operator who joined the company in June 2015;
- “Personal gowning qualification report” performed in August 2016;
- SOP “Entry and Exit SOP into clean room of production facility”.

The training of the personnel was considered deficient in the following respects:

- cGMP refreshment was not performed for all the manufacturing operators in 2016.
- Practical training for aseptic filling process in grade A and grade B was not defined and documented.

The company has adequately addressed the raised observations on training by taking the corrective and preventive actions

The qualification of the manual visual inspectors was not considered appropriate. Operators are permitted for breaks for (XX) minutes after (XX) hour performing manual visual inspection. The default kit used for the visual inspection qualification was of (XX) defective vials prepared since 2013. Good vials were not considered during the qualification of the visual operators. The rejection rate was not recorded in the relevant batch processing record according to the criticality of defect types.

The company has taken the acceptable corrective and preventive action (CAPA) for adequately addressing the raised observations.

11. Personal 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. Initial medical examination was conducted at the time of joining (general medical examination, eye test and skin test for personnel working in core area). New employee was being vaccinated with relevant vaccines if required after verification of antibody titer as per relevant SOP. Periodic health checks (on (XX) basis) of all employees are carried out and only the employees who are declared free from any infectious diseases are allowed to work in critical areas. Eye examinations of personnel conducting visual inspections are performed every (XX) months. Skin examination for personnel working in core area is being conducted after specified period. Employees are instructed to report health or medical conditions having adverse effects on the product or its quality before entering Production or QC area. In case of infectious disease like tuberculosis, bronchitis etc., the person is strictly prohibited to enter into the company premises and measures as relevant are in place.

12. Premises and Equipment

PBL, Baddi has a separate and dedicated unit (Unit II-Vaccine Formulation and Filling Plant) for manufacturing of vaccines. The unit has independent manufacturing and quality control facilities, quality assurance, utility block, warehouse, dispatch section and effluent treatment plant. Unit II also includes a separate utility block and effluent treatment plant close to the production block.

The plant has been commissioned in April 2008 and it has (XX) different filling lines ((XX) filling lines for vial and (XX) filling line for PFS).

The vaccine-manufacturing comprises (XX) separate facilities, Line (XX) and Line (XX). Line (XX) facility is used for (XX) presentation (Line (XX)) and for vial presentation (Line (XX)) operated on campaign basis. Line (XX) and Line (XX) are equipped with sterilizing and decontaminating autoclaves respectively.

Line (xx) and Line (XX) are used for the manufacturing of bOPV on campaign change basis. The facility has primary change rooms, day material storage area, disinfectant preparation room, dirty and clean laundry areas, utilities and service areas. The facility has separate quality control laboratories and quality assurance department. Warehouse and cold storage block is located in a separate building adjacent to vaccine manufacturing block. Dedicated areas for receipt of raw materials, active ingredients, packaging materials and dispatch of finished goods under cold chain, sampling and dispensing are provided in the warehouse. Separate areas for storing the finished product (under quarantine and approved stage) are also in place. Procedures for shipments for domestic and international destinations are in place. The ice packs are stored in appropriate conditions.

Ventilation systems, details of AHUs with room-area identification, classification and environmental conditions in manufacturing facility Line (XX) and Line (XX) and quality control area were provided in the Site Master File. Line (XX) is designed to have a sink with negative pressure through the personnel changing room so that minimizing the risk of escape of live microorganisms to surrounding areas. Line (XX) is designed as having positive pressure cascade with the maximum protection of the aseptic rooms.

The environmental monitoring program is in place at PBL, Baddi and includes the following parameters which are controlled on routine basis: 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.

Water system (PW and WFI) showing storage tanks, loops, point of use, sampling points, quality testing, sanitation procedures and schedules were spot checked.

Bore well raw water is tested monthly. WFI and PW loops are sanitized as per approved frequencies. TOC, conductivity and temperature are monitored on line at return for WFI system.

14. Materials

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.

Provisions are in place for water systems sampling and testing according to the pharmacopoeial specifications. 3 QC operators are in charge of sampling including the sampling point in aseptic areas during the campaign of the manufacturing of bOPV. The trend analysis of the water test results was performed monthly and yearly.

15. Documentation

The documentation system in place includes elements like preparation, revision, approval, issue, controlled distribution, review, updating, change control & archiving of documents.

The documents including SOPs, master formulae are prepared by the concerned department and by the authorized personnel who are directly involved in the activity. The documents are reviewed by the department-in-charge. The final approval of the document is done by Head QA. Periodic review of the document is done at a minimum of once every two years or on need basis. There are SOPs and standard format for preparation and review of the documents. The distribution of the documents is done by QA and records are maintained.

Approved specifications for raw materials and packaging material and final product are available with QA. Master documents and master copies of all documents are kept with QA. Only updated and approved master documentation is being used.

A change required in the documents need the prior approval from appropriate departments through a change control procedure. ‘Change History Log’ is maintained for any changes in the documents. After approval and authorization of revised document, QA retrieves all the obsolete formats and issues new version of master documents and obsolete master copies are kept with QA. QA maintains the records of preparation, control, retrieval, issuance and destruction of documents.

The BPRs of all the vaccine batches manufactured are archived with QA.

16. Good practices in production

✓ bOPV vaccine:

The manufacturing activities of bOPV Type 1 and Type 3, at PBL, Baddi involves the formulation, filling and packaging operations. At VFP Baddi, (XX) consistency lots have been manufactured in line (XX) and are considered of standard quality.

The vaccine is a sterile suspension of live attenuated poliomyelitis virus Type 1 & Type 3 (Sabin strains) formulated with diluent, stabilizer, antimicrobial agents and buffer.

1. Manufacturing formula is well established and followed;
2. Manufacturing processes comprises the following steps:
 - Preparation of solutions/additives
 - Thawing and dispensing of (XX) bulks
 - Blending of (XX) product
 - Preparation of primary packaging materials for use in filling process
 - Filling, stoppering and sealing of the vaccine in vials
 - Visual inspection
 - Labeling
 - Packaging
 - Storage and release of the vaccine

✓ Easyfive-TT[®]

Easyfive-TT[®] is a pentavalent vaccine manufactured by utilizing the (XX) bulk antigens from a WHO prequalified manufacturer and (XX) & (XX) bulk antigen from (XX) Manufacturer. Easyfive-TT[®] has been re-prequalified by WHO prequalification team in October 2013

The flow chart for the production process including the formulation and the filling of Easyfive[™] were provided and presented in details.

During the visit of the line (XX), Easyfive-TT[®] batch XX was being filled, sealed, visually inspected, labelled and packaged.

Broken vials have been seen at the exit from the depyrogenation tunnel on the accumulation table of the vials and on the conveyor of the filling line. The procedure for handling the breakage of vials of vaccines during the packaging operations was in place however, no SOPs were implemented regarding the instructions and the measures to be taken in case the vials of vaccines are broken during the aseptic filling and during the vials washing.

The monitoring of environmental parameters in production area including pressure, temperature, humidity and non-viable particles was in place. The relative humidity and temperature are recorded manually every (XX) minutes in the BMR. The pressure is recorded manually every (XX) minutes in the batch record. Non-viable

particles are recorded continuously under grade A areas. Visual and audible alarms are triggered when exceeding the alert levels. A print-out of the environmental monitoring is attached to the BMR.

During the packing of the vaccine vials into boxes, a tray of the same color of the accepted vials and without identification was used for rejected vials.

TOR (Time out of refrigeration) was not measured during the filling, visual inspection, labelling and packaging operations where the product was at the room temperature. This was not documented and nor justified.

The company has addressed the raised observation by taking the acceptable corrective and corrective action.

17. Good practices in quality control

A dedicated set up of QC laboratories for all vaccines was situated at site separate from production areas. The laboratories are designed to perform different tests as per compendial requirements. Cold room, refrigerator and deep freezer are provided 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 according to the SOP. A separate microbiology laboratory was available for carrying out microbiological work. 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. For the other samples, they are destroyed when testing QC results are declared pass.

The Out of Specification (OOS), out of trend (OOT) and out of limit (OOL) handling

SOP for OOS describes the process of OOS and out of trend (OOT). As part of OOS investigation, the OOS report form Annexure 4 for Phase (XX) is initiated as per investigation between the analyst and the QC supervisor and further reviewed by the QA personnel. The report of Phase (XX) should be completed within (XX) days. If Phase (XX) investigation was unsuccessfully identifying the root cause then Phase (XX) (annexure 5) will be initiated and investigation team from QA/QC should be involved. Phase (XX) report should be finalized within (XX) days. Accordingly, CAPA will be implemented.

In case of sterility failure there will be a separate OOS checklist (Annexure 6) that investigates in depth the reasons behind the failure. The following parameters are included in the investigation namely; identification of isolates, personnel monitoring including garment, culture media, testing method, environmental monitoring and qualification/validation/ calibration aspects.

Handling of OOT has also been explained in the SOP in an Annexure. This Annexure contains general information and description of OOT. Investigation team may involve personnel from QA, QC and other related departments. The OOT should be finalized before the release of a batch. The investigation team plus the QA are involved in the signing off the investigation.

The OOL procedures describes the investigation required in case of failure in water system which is explained Annexure 1 of the SOP. The Annexure contains the essential parameter for OOL description, investigation and date of initiation and completion.

The timeline for complete the phase (XX) investigation is within (XX) days from the day of initiation of the investigation and the timeline of completion for phase (XX) is within (XX) days.

Method validation of potency test has been reviewed by the inspection team and deemed in compliance with ICH Q2 requirements. The QC lab uses 6 vials of final container and 2 vials are combined in one container for testing step; hence perform potency testing on 3 replicates not 6. The validity criteria comply with WHO method

except it lacks for the criterion that the variation between two samples under test should not be more than 0.5Log.

The company has addressed the raised observation by taking the acceptable preventive and corrective action

Reference standard material

Provision for establishing and monitoring the reference standard materials were in place.

Stability studies

Stability data at 2 – 8°C for the above 3 lots at specified time points have been reviewed and found within the acceptance criteria. Stability data at -20°C for the above 3 lots at (XX) month time points were also spot checked and found within the acceptance criteria.

The stability test result for the time point 6 months at 2 – 8 °C was not yet finalized.

18. Distribution and dispatching

Warehouse is secure and environmentally controlled area. Supervisory Control and Data Acquisition (SCADA) system is installed for regular recording of temperature. Duly labeled finished product received from Production is kept in defined cold room on pallets as per SOP. After receiving of Central Drug Laboratory release letter, QA release order is prepared and simultaneously QA release label is put over the finished product. Through approved cold chain procedure, the product is dispatched along with complete documents and records are maintained. Retained samples are also kept for records.

PART 3: CONCLUSION

Based on the areas inspected, the personnel 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, Panacea Biotec Limited was considered to be operating at an acceptable level for 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.