

**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	PT BIO FARMA (Persero)
Corporate address of manufacturer	Jalan Pasteur 28, Bandung 40161- Indonesia
Contact person	Jeni Tresnabudi Quality Assurance & Regulatory Affairs Division jeni.tresnabudi@biofarma.co.id
Inspected site	
Address of inspected manufacturing site	Jalan Pasteur 28, Bandung 40161- Indonesia GPS number: -6.8994264,107.6003 or 6°53'57.9"S 107°36'01.1"E
Inspection details	
Dates of inspection	18 to 22 March 2019
Type of inspection	Initial inspection for mOPV2 Routine inspection for Measles prequalified vaccines.
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	PT Bio Farma is a full state-owned Enterprise and the sole Vaccine & Antisera manufacturer in Indonesia. PT Bio Farma is licensed to manufacture vaccines and antisera using biotechnological processes.

company and site And brief summary of the manufacturing activities	PT Bio Farma vaccine products are used in more than 130 countries worldwide. Currently, 10 of Bio Farma's vaccine products have been WHO prequalified. Bio Farma supplies vaccines to international organizations, such as United Nations Children's Fund (UNICEF), Global Alliance of Vaccines and Immunization (GAVI), and Pan American Health Organization (PAHO) and to countries that requested assistance for their domestic immunization programs. Vaccines, antisera, and diluent manufactured by Bio Farma are as follow: ✓ Vaccines: • DTP - HB vaccine • DTP vaccine • Adsorbed DT vaccine • Adsorbed Td vaccine • Tetanus vaccine • Measles vaccine • DTP-HB-Hib • Hepatitis B Recombinant vaccine • BCG vaccine • Bivalent Oral Poliomyelitis Vaccine Types 1 & 3 • Monovalent Oral Poliomyelitis Vaccine type 1 • Seasonal Flu Vaccine • Inactivated Poliomyelitis Vaccine (IPV) ✓ Diluents for freeze-dried vaccines ✓ Antisera: • Tetanus antisera • Diphtheria antisera • Polyvalent snake venom antisera
Brief report of inspection activities undertaken	
Scope and limitations	
Areas inspected	The inspection focused on the production and control of mOPV2 and Measles 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 mOPV2 and prequalified vaccines were not inspected during this inspection.
Vaccines covered by the inspection	Initial inspection for mOPV2 vaccine Spot check for prequalified vaccines mainly focusing on Measles 20 dose and Measles 10 dose 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
	MR	Measles vaccine
	NCA	National Control Authority
	NCL	National Control Laboratory
	NRA	National Regulatory Authority
	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
	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
	WFI	Water for Injection
	WHO	World Health Organization

Part 2: Brief summary of the findings and comments

1. Pharmaceutical quality system

The Quality Department and the Production Department were managed and operated independently. Employees involved in GMP activities were qualified and trained. The manufacturing processes were validated and regularly reviewed. The company has premises with suitable equipment and services, appropriate materials, containers and labels. Approved procedures, instructions and batch records were implemented and followed. Suitable storage and transport conditions were provided. A system for recall and complaints management was in place.

In general the current Pharmaceutical quality system and all of the elements were in place however these elements varied in their maturity and some need further attention and improvement.

The company has provided adequate corrective and preventive action plan to address the issues related to the quality system.

Product quality review:

Provision for the product quality review was in place. The procedure covered the finished products and active pharmaceutical ingredients as per the requirements of WHO GMP guideline. Furthermore, the company was using a procedure for statistical analysis of the relevant quantitative data. There were separate statistical analysis reports performed for starting materials, intermediate and drug substances. However, these reports were not mentioned and reviewed in the annual product quality review exercises.

In general, the PQR were performed on annual basis on rolling plan. Over 40 PQR were performed annually. One person was assigned to gather the PQR reports from relevant subject matter experts through the site.

The PQRs of the following vaccines were reviewed during this inspection:

Measles, bOPV, Tetanus and Pertussis.

Water and environmental monitoring & Annual Critical Services review:

The company prepares annual reviews of critical services including water and environmental monitoring. These indicated a generally satisfactory level of overall control. The company however stated that it is not performing interim reviews on a monthly and quarterly basis and decisions on batch release are based upon only the daily batch monitoring from production without taking a wider view of the overall level of control on the days before and following the aseptic activities that potentially could be indicative of a problem that was not detected on the actual production day. The implementation of more frequent trending is recommended.

EM monitoring locations were based upon a risk analysis to select the locations for routine monitoring. The most recent re-assessment was performed on 7 March 2019, shortly before this inspection. The original risk assessment was performed in 2014 and the recent assessment was part of the preparations for the mOPV2 project. The annual review process did not include a periodic reassessment of the continuing applicability of routine monitoring locations.

In addition to the routine QA patrol monitoring the company also performs additional monitoring after incidents. It was noted that swabs are not used except in these special occasions and it was recommended that the routine monitoring should not be solely reliant upon contact plate monitoring for surfaces.

Quality risk management:

The company was able to provide ample evidence of quality risk assessments being performed and demonstrated a broad understanding of many of the procedural, organizational and technical risks raised during the inspection of operations. It was noted that:

- (i) there was no formal risk register for the site and its variety of operations, listing those risks that had been assessed, when they had been assessed and when they should be re-assessed.
- (ii) There was no formal holistic process that required a plan for the consideration and identification of gaps where an existing assessment was either absent, have gaps identified during investigations or required improvement.
- (iii) There was no formal longer-term plan or outlook to identify and document those topics where future initial RA should be performed to mitigate residual risk.

Procedures in place for monitoring of regulatory changes and regulatory intelligence and identifying potential risks to continuing compliance were weak. In general, the procedures in place looked only to implemented finalized guidance and did not include a surveillance of guidelines in preparation. This omission may lead to a situation where the company is unable to continue in compliance with new guidance if major work is necessary to meet the new guidance. For example, to date the company has not performed a gap analysis of its existing operations versus the draft EU-PICs-WHO consolidated draft for revision to the GMP for sterile products. Furthermore, it appeared that the company was only reviewing documents prepared by the WHO ECBS and appeared ignorant of other WHO GMP updates and had not updated its systems in line with the recent new and revised GMP standards issued by WHO applicable to all medicines such as the revised guidance on validation and those for HVAC systems.

The company has provided an adequate corrective and preventive action plan to address the raised issues related to the quality risk management as outlined above.

Deviation management:

Procedure for deviation handling was in place. This procedure classifies deviations according to perceived risk into critical, major and minor classes.

The register of deviations recorded in QA system during 2018 and 2019 to date were requested and provided as translations. Some major deviations were selected for spot check.

Change control:

Procedure for change control was in place.

The register of change control was spot checked.

CAPA management:

Procedures for CAPA management was in place. Most but not all CAPA is managed routinely as part of the quality system elements from which the specific CAPA issues arise e.g. deviations and generally not as a standalone QMS subsystem.

In general terms the individual specific investigations reviewed were substantive and had good scientific rigor however the procedures were lacking in that there was no formal requirement for documented review of other areas and operations where similar issues may lie and CAPA also needed, and in some cases additional trainings and details of processes were changed without formal update to include these details and enhancements in the relevant SOPs.

Management review:

This section was not inspected in detail. Provisions for periodic management review were in place.

Documentation:

Overall, the production activities are recorded in the form of batch manufacturing records, equipment logbook and/or general control records. Procedures, operating conditions and specifications related to the manufacturing processes are established. The quality control activities are recorded in the respective documents of record including laboratory control records, equipment logbooks and general control records. Procedures, operating conditions and specifications related to the quality control activities are established.

The following procedures were reviewed:

- Gowning procedures in QC department. Weaknesses were found during review regarding the maximum capacity or equipment to be found in gowning rooms;
- Procedures for data plotting, definition of action and alert limits, trend analysis and the parameters to be followed.
- Frequency and maintenance of equipment. Necessity of outsourcing maintenance is also addressed.
- Company policy regarding management of out of specification results.
- Calibration procedures of micropipettes.
- OPV titration. Validity criteria were found insufficient as specificity of CPE or evaluation of assay confidence interval ($P=0.95$) were not considered, though for the latter specifications were taken from TRS980 annex 2.

- Decontamination procedure in case of mOPV2 spillages. It is addressed mainly to production operators, QA personnel and supervisors. If product is spilled, liquid is covered with several layers of tissue paper. Hypochlorous acid is added and a physical barrier is erected around the zone. The whole operation is repeated. Then waste is collected, put in a plastic bag and sent to decontamination autoclave.
- Transport of reaction mixes for mycoplasma detection by PCR between buildings. No validation of the procedure and its impact on assay results was performed though.

Complaints:

Procedures for complaints management were in place. Complaints were adequately discussed in the PQRs that were reviewed. No specific observations made however see the related comment on CAPA above.

Product recalls:

Procedures for recall management were in place. No recall related to quality issues was recorded in the last five years.

Self-inspection:***➤ Self-inspection:***

Internal audits were controlled and performed according to the procedure in place. They were required to be performed a minimum of three times per year in each facility. There was evidence that self-inspection teams were led by trained and certified auditors and performed by a team with the requisite expertise according to the area under audit. The programme appeared to be according to the published schedule.

In addition to the audits performed by internal staff, the company retains several external auditors to provide additional training and oversight. This includes a number of experts that have previously conducted audits on behalf of WHO PQT.

➤ Vendor quality audits and suppliers' audits and approval:

The procedure for Vendor qualification was spot checked. The suppliers of the critical material were site audited. There was provision for regular onsite audit or desk review audit. The list of planned audits for 2019 was spot checked.

Contract production, analysis and other activities

The company manufactures several bulk virus and concentrated antigen for supply to other vaccine manufacturers. This aspect of the site operation was not inspected in detail during this inspection.

The Hepatitis B component of the Penta vaccine was currently sourced from another manufacturer of prequalified vaccines and is the same bulk used in the formulation of the prequalified Hepatitis B containing vaccines from that company.

Personnel:

Organizational charts indicating key personnel involved in manufacturing, quality control, quality assurance, warehouse and distribution, engineering and department wise organograms were presented. Individual responsibilities were defined and described through personnel job descriptions. All departments at the site have sufficient number of personnel with appropriate qualifications with respect to education, experience and training to perform their functions. There was organizational separation of responsibilities for production and quality matters. The QA unit reports directly to the President Director of the company and was responsible for QA Operations.

➤ Training:

The gowning qualification of the aseptic operators was in place. It is required to perform 3 runs at the initial qualification and the gowning verification was on annual basis. The personnel clothing and Garb action limits established by the company were 5 cfu for grade A with the background of grade B and 20 for the areas of grade B. The test results of the annual verification from 2016 to 2018 for the aseptic operators were spot checked and found all with nil cfu.

The test results of the monthly verification at rest from 2016 to 2018 for the aseptic operators were spot checked and found all with nil cfu.

The procedure for aseptic gowning was illustrating how to wear goggles and allowing the forehead skin to be uncovered. This was seen for one operator during the visit of the manufacturing building of Measles on Tuesday 19 March 2019.

The production operators conducted the sampling. The training was theoretical, and no microbiological training or recovery studies were considered for contact agar sampling method.

The company has provided an acceptable corrective and preventive action plan addressing the above-mentioned observations.

➤ Personal hygiene:

Procedures for health requirements of personnel were in place.

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.

1. mOPV2:

mOPV2 vaccines are produced on primary monkey cells, issued from foetal kidneys. After preparation of cell suspension, cultures are propagated to gain enough cells for viral inoculation at a determined multiplicity of infection with a diluted, well-established, and characterized type 2 working seed lot.

Upon incubation, viruses are harvested and pooled into unique polio single harvest (PSH). This PSH can be temporarily stored under temperature and time conditions as per validated procedure. Several PSH are then pooled into a unique monovalent bulk which will be subsequently clarified via filtration and distributed into small volume containers. These can be put into long time storage under temperature and time conditions as per validated procedure.

Next step in production is the blending of the monovalent bulk with stabilizer and dilution media to reach the assigned viral activity of the vaccine. This final bulk is sterile filtered and filled into glass vials under aseptic conditions. The vials are finally packaged, labelled and stored at appropriate temperature until final shipping to destination, according to WHO guideline on international packaging and shipping of vaccines.

Batch manufacturing record review (BMR):

Batch records of lots mOPV2 10 doses were reviewed. These documents covered blending and filling processes. The records were found lacking details on the rejection rate of vials during filling and capping.

Validation of thawing of polio single harvest (PSH) and monovalent bulks:

Thawing of PSH for pooling or monovalent bulks for blending is performed in a water bath. Validation was conducted and documented in relevant reports. Maximum thawing times were defined.

Validation of Time out of Refrigerator (ToR) of Polio Final Bulk (PFB):

Validation of time out of the cold chain for Polio final bulk (PFB) between start of filling until packaging was documented in relevant report.

Validation of holding time of Polio Final Bulk (PFB):

Sampling for validation was performed directly on the PFB production vessel and the samples were stored at 2-8°C for defined times in the same room as PFB for production. The samples were then transferred to QC department. Statistical analysis of titres was performed using t-Test and all experimental t values were below theoretical t value, confirming the defined maximum holding time.

2. Measles:

Media preparation:

The prepared media were sterile filtered, or steam sterilized when relevant and stored in glass bottles or plastic bags as appropriate. The media used for Measles vaccine were stored in glass bottles for defined period of time. Some media for OPV vaccines were stored in plastic bags for a defined period of time. A risk assessment report for leachable and extractable was presented and found acceptable for the media used for OPV vaccines. There was no integrity test of the containers used for storage of media. This is particularly critical for the full aseptic manufacturing process such as for Measles vaccines.

The possibility and feasibility of addition of buffers, media and excipient through filters during the aseptic manufacturing process was not discussed and justified.

Culture, inoculation, single harvest and bulks:

The production of measles bulk takes place in class B clean room, under laminar air flow cabinet of class A. Chicken embryo fibroblast (CEF) are prepared by removing the old embryonic Specific Pathogen Free (SPF) chick from its egg, after disinfection of shell, under laminar air flow cabinet of class A. The embryo is then dissected to remove the head and the internal organs, which are discarded. The chicken embryo fibroblast (CEF) cell culture is made from a defined chick bodies of defined days old embryonic Specific Pathogen Free (SPF) chicken by digestion with trypsin in PBS. The cell culture in MEM with new born calf serum growth medium is incubated at defined temperature for defined period. When the cell culture is confluent, Measles virus seed is inoculated. The virus culture is incubated at defined temperature in MEM with new born calf serum medium. After a defined period of incubation, the growth medium is changed to M-199 serum free medium and continue the incubation for defined period.

The culture is harvested as single harvest if the cytopathic effect (CPE) has achieved the required grade. The minimum titer to be harvested is not less than the required specification. The single harvest contains glucose and gelatine as stabilizer.

Samples are taken for in process control tests. The cell culture is tested for control observation, hem-adsorbing virus, and non-hem-adsorbing extraneous agents. The single harvest is tested for potency and sterility to bacteria, fungi, and mycoplasma. Batches of single harvests are pooled and clarified as bulk or clarified virus pool.

Samples are taken from both virus pool and bulk for QC tests. Virus pool is tested for potency, sterility, and extraneous agents. The clarified bulk is tested for potency, identity, and sterility against bacteria, fungi and mycoplasma. The bulk is kept at low temperature.

Formulation and filling:

Final bulk and aseptic filling process are conducted in class B clean room, under laminar air flow cabinet of class A. During the thawing of the bulk, the stabilizers, buffer and diluent are mixed in stainless steel vessel through filters. A required amount of bulk is added to the targeted titer for measles vaccine 10 doses or 20 doses. The pH of the bulk is checked and adjusted.

Samples are taken for QC tests. The final bulk is tested for potency, sterility and residual serum protein.

The mixing vessel is interconnected aseptically by silicon tubing and connected to the vial filling machine. The filling nozzles are adjusted before use. The final bulk is filled into vials and half stoppered. The filling quantity is checked at the beginning, middle and before the end of filling process. The filled vials are manually transferred into the freeze dryer chamber. The product is lyophilized and capped with aluminium caps.

Samples are taken for QC tests. The final product is tested for potency, identity, sterility, residual moisture content, abnormal toxicity. Each vial is inspected. The defective vials are disinfected before discarded.

Visual inspection, labelling and packaging of Measles Vaccine:

The visual inspection of mOPV2 is conducted with automated machine. The visual inspection of the other products was performed manually. Each vial is inspected visually for particles, fibers, broken/cracked vials, colour, volume, and capping. The visually inspected vials are stored in the cold room waiting for the next step of labelling. The labelling of the vials is automated. Relevant checks and line clearance of the lines were in place. During labelling, batch number and expiry date are printed on each label.

Labelled measles vaccines are brought to an adjacent room to be packed into boxes. Packaging is done manually. Each box is weighed by means of a counting balance to affirm the quantity of the vials in each box. The boxes are stored in crates; once filled, the crates are immediately stored in cold room.

3. Facilities and equipment system

The premises were generally maintained at an acceptable level of cleanliness. The company had provisions for personal hygiene and sanitation in its production facility. Dedicated manufacturing facility were provided to contain and prevent the risk of cross contamination.

Manufacturing areas were 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.

In general operations were seen to be performing in an orderly, calm and well-designed manner with adequate process and man and material flows. All areas, including the older designed areas, visited during the inspection appeared generally well ordered and cared for suggesting that they were generally “well owned” and supervised. The premises and equipment were considered adequately maintained however deficiencies were raised and should be adequately addressed. These are discussed as outlined under Part 3 “List of Deficiencies” of this report.

Many of the company’s facilities lack good direct observational access for routine supervision and audit without directly entering the clean rooms. It was noted at the previous inspection that there were no cameras used in the filling suites to monitor performance or provide records during media simulations. The company was at the time strongly advised to consider the videoing of at least its media simulations to assist investigation in the case of contamination being detected and in general to allow peer review and coaching of aseptic practices and techniques. Since the last inspection a relevant procedure has been established and media fills and routine production operations are now recorded. However, for media fills the company does not keep the original files and SD cards from the recording devices. In terms of the daily CCTV data the system over writes the video files dependent upon the storage capacity. It was stated that there is storage for approximately one month’s data. The SOP described the necessity to keep the data longer if required but gave no specific guidelines as to the GMP status of the video records and minimum time for the retention time for the archived files.

Site tour of Measles manufacturing facilities:

Measles vaccine production facility was fully dedicated to the upstream and downstream manufacturing of the Measles vaccines.

Waste management:

Procedures for decontamination and disposal of used contaminated materials and waste management were in place. There was a decontamination autoclave dedicated for the material from virus culture facility and a decontamination autoclave for the aseptic filling rooms.

The procedure to deal with spillage of biological material was in place. There was an efficacy study for the decontamination of OPV virus.

A four-month rotation of disinfectants was in place as per the relevant procedure.

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.

No rework was recorded at the company.

Reprocessing can be conducted after investigation of OOS. The product can be released if meet the specification of the product. Reprocessing procedures are foreseen as occasionally necessary for biological medicines and, in such cases, are validated and pre-approved as part of the marketing authorization.

The qualification and validation of the following systems and equipment was spot checked as the following:

- ✓ UPS;
- ✓ Lyophilisation;
- ✓ Pooling tank used for the formulation of Measles vaccine;
- ✓ HVAC qualification;
- ✓ Autoclaves;
- ✓ Depyrogenation Tunnel;
- ✓ Cleaning validation;
- ✓ Fumigation of manufacturing facility;
- ✓ Validation of aseptic process through media simulations;
- ✓ Measles;
- ✓ Visual appearance.

4 Laboratory control system

Management of OOS test results:

Handling of out of specification (OOS) results is conducted as per the relevant procedure.

Qualification of in-house reference standard:

Bivalent reference 202-REF-STD-WRBOPV is currently in use. The specifications were established in a collaborative study between PT Biofarma and BPOM. These limits are evaluated annually based on the data from current and previous year. When a new reference is available, bridging study with the current reference is made over 20 tests at PT Bio Farma and 6 at BPOM.

Method Validation:

The validation report of OPV titration was reviewed. The following criteria were evaluated:

- Precision: repeatability of final product and monovalent bulk were assessed as well as intermediate precision;
- Linearity;
- Specificity by use of antisera;
- Robustness
 - cell age by evaluation of time-lapse after passage in days for virus inoculation;
 - Incubation temperature after viral inoculation;
 - Incubation time after viral inoculation.

Validation of reagents used for polio titration:

Validation of serotype 1 antiserum and foetal bovine serum (FBS) were reviewed. No functionality test by bridging study was envisaged for these 2 reagents or any new critical reagent (antisera, FBS, trypsin, ...).

➤ Environmental monitoring results:

The procedure for the environmental monitoring was in place. The personnel clothing and Garb action limits established by the company were 5 cfu for grade A with the background of grade B and 20 for the areas of grade B. For gowning of personnel, sampling points at mouth, chest, left and right hands were monthly tested.

The EM in the manufacturing building for Measles was based on the risk assessment report. Internal action limits based on trend data were established for microbial as per relevant report.

The media used for EM were prepared in-house and subcontracted for gamma irradiated. The COA of a batch of contact surface plate was spot checked. The contact surface media contained polysorbate and lecithin as neutralizer. Formaldehyde was used for the decontamination in the manufacturing building of Measles. Shelf life were used media were defined.

Identification provision was in place for detected contamination in grade A and B.

The annual environmental monitoring review of the manufacturing building of Measles covering the data from 2017 to March 2018 was spot checked.

➤ **Water system:**

Details of the water system production, capacity and sanitization were provided in the site master file.

The procedure for water monitoring was in place. Sampling, testing and frequency for all sampling points were mentioned.

Water source was a mix of city water and bore well water. There was a dedicated WFI loop for Measles and another dedicated WFI loop for mOPV2. Conductivity was continuously monitored in both loops. There was no sampling point in the WFI that was sampled and tested on daily basis such as the return loop. Water was tested as per USP 38. There was no heavy metals testing of water system in place.

Sanitation program for water system was in place. WFI was steam treated twice a year and PW loop chemically (H₂O₂) once a year.

The trend results for 2015-2018 was spot checked.

5 Materials system

Overall, provisions for incoming materials including raw and packaging material, intermediates and finished products were in place for reception, quarantine and release processes. Appropriate storage conditions were provided. Rejected and returned material procedures were in place. All incoming raw materials, including packaging materials, were examined and stocked in the warehouse

Raw and packing materials are procured from qualified vendors. The incoming materials are verified on receipt and are stored at appropriate storage conditions. Materials are received, sampled and tested according to implemented procedures. Packaging materials and finished products are sampled as per the sampling plan. Rejected materials are stored in segregated rejected material area.

Labels are stored under locked area in the warehouse. Labels are printed out on line during labelling operations.

The list of the raw material in contact with the product and that can be found at the finished product was established and the sampling for identification test was performed on all received containers. However, few raw materials were not 100% sampled for identification testing due to hygroscopic nature or due to sterility attribute (Aluminium hydroxide gel and chloride, gelatine, Natrium carbonate and bicarbonate).

Procedure for verification and testing of optical density was in place for VVM dot received with labels of mOPV2.

6 Packaging and labelling system

The labelling machine, automatic visual inspection machine and package machine were inspected. The automated visual machine was installed and undergoes operational qualification.

Packaging/Labelling store was visited. Labels are well segregated and locked.

Only the staff in charge of materials management can have access to the warehouse and hazardous materials warehouse.

7 International shipping

International shipping of mOPV2 vaccines was reviewed during visit of shipping facilities. Though currently preparation for shipping procedure is manual, an automated shipping line was under testing for future use. Description was in compliance with the information submitted for prequalification, currently under review.

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, ***PT Bio Farma (Persero)***, located at ***Jalan Pasteur 28, Bandung 40161, Indonesia***, 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
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