World Health Organization

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

Part 1	**General information**
Manufacturers details	
Company information	
Name of manufacturer	**Serum Institute of India Pvt. Ltd.**
Corporate address of manufacturer	Off Soli-Poonawalla Road, 212/2 Hadapsar, Pune- 411 0028, India.
Contact person	Dr. Suresh Jadhav, Executive Director ssj@seruminstitute.com
Unit / block	PCV-10V: SEZ4 & SEZ 7 Line 2, MMR fill and finish: SEZ 3 Ground floor, Quality Control & Microbiology Laboratories: SEZ 3 and SEZ8, Warehouse [Raw materials, Packaging and Labelling]: SEZ 1C Warehouse [Semi-finished & Finished]: SEZ 7.
Inspection details	
Dates of inspection	15 to 19 July 2019
Type of inspection	Initial inspection for Pneumococcal Polysaccharide Conjugate Vaccine (Adsorbed) (10-Valent). [PCV-10V]
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 site And brief summary of the manufacturing activities	Serum Institute of India Pvt. Ltd. (SIIPL) is a producer of Sera, Vaccines and other Biologicals in India. It is located in the extensive Poonawalla Estates of pollution free countryside in Pune. Serum Institute was founded in 1966 by the Poonawalla Family with Dr. Jal Mehta and commenced production in October 1967. Starting with Tetanus Antitoxin, Serum Institute progressively launched DTP group of Vaccine; Polyvalent Anti-Snake Venom Serum; Measles Vaccine; Measles, Mumps and Rubella Vaccine; Hepatitis B Vaccine; Polysaccharide conjugate Vaccines (Men A Vaccine, Hib vaccine); Pandemic Influenza Vaccine (Human Live attenuated); Influenza Vaccine, Live Attenuated (Human) Seasonal, Trivalent; Oral Polio Vaccine; Inactivated Polio Vaccine; Erythropoietin Injection, Rabies Human Monoclonal Antibody, Rabies Vaccine, Rotavirus vaccine, pneumococcal conjugated vaccines and several other products. Since March 1994 SIIPL has started exporting Viral Vaccines and Bacterial Vaccines to WHO / PAHO / UNICEF.
History of the regulatory inspections	The company provided the list of the regulatory authorities' inspections carried out since 2015. The last WHO onsite inspection was conducted in January 2018 and covered Rabies and Rota vaccines.
Brief report of inspection activities undertaken	
Scope and limitations	
Areas inspected	The inspection focused mainly on the production and control of pneumococcal conjugated vaccines and a short visit to MMR fill and finish in SEZ 3 at ground floor. The inspection covered most of the sections of the WHO GMP text, including quality assurance, sanitization and hygiene, qualification and validation, complaints and recalls, self-inspection, personnel, training, personal hygiene, premises and equipment, materials, documentation, materials, production and quality control and utilities.
WHO product numbers covered by the inspection	Pneumococcal Polysaccharide Conjugate Vaccine, adsorbed (10-Valent) is filled in USP type I transparent glass vials, stoppered with 13 mm grey rubber stopper and sealed with 13 mm aluminium flip-off plastic cap (Burgundy). Pneumococcal Polysaccharide Conjugate Vaccine 10V is presented in single dose (0.5 mL) and multi dose (5 dose-2.5 mL) formats. The shelf life of the vaccine at +2°C to +8°C is 36 months. Active ingredients are conjugated with Carrier protein CRM197.
Restrictions	None

Out of scope	Products and vaccines other than PCV-10 vaccines were not inspected during this inspection except the spot check on complaints for MMR, DT and HepB vaccines and a short visit to MMR fill and finish in SEZ 3 at ground floor.

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
CRM197	Cross Reacting Material 197
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
MMR	Measles, Mumps & Rubella
MR	Management Review
NCA	National Control Authority
NCL	National Control Laboratory
NRA	National Regulatory Agency
OQ	Operational Qualification
PAHO	Pan American Health Organization

PCV-10	Pneumococcal Polysaccharide Conjugate Vaccine (Adsorbed) (10-Valent)
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
SIP	Sterilization In Place
SMF	Site Master File
SOP	Standard Operating Procedure
SWFI	Sterile Water for Injection
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

There generally appeared to be adequate resources available for the management of the implemented QMS. Quality assurance and quality control activities were functioning with independence from the production unit. Managerial responsibilities were specified in job-descriptions. Production and control operations were specified in written form and GMP requirements were generally followed. Product and processes were monitored and the results taken into account in batch release; regular reviews of the quality of vaccines were conducted.

➢ ***Product quality review:***

Annual product quality review was conducted on an annual basis for all commercialized products manufactured during particular calendar year. All presentations (dose/strength/formulation/facility) were covered in one product specific APQR. The APQR should be performed and completed within 3 months. Quarterly trends were performed for QC testing reports and were part of APQR. The APQR included the following areas:

- Review of critical in-process controls (based on validation studies),
- Review of significant deviations,
- Review of EM conditions (viable, non-viable),
- Review of starting materials, packaging materials, in-process and finished products results and trend analysis,
- Review of out of specifications,
- Review of stability studies,
- Review of market complaints and adverse drug events (AEFI),
- Review of product returned/recalled.
- Review of corrective actions for regulatory compliance,
- Review of validation (thermal validation, MFT, CSV, PV, CV, three batch concepts was used),
- Review of major/critical change controls,
- Review of dossier variations,
- Review of CAPA,
- Review of post marketing commitments,
- Review of technical agreements,
- Review of qualification of relevant equipment and utilities,
- Review of retained samples.

- **<u>PQR of Rabies:</u>**

The APQR of Rabies Vaccine inactivated (freeze dried) for calendar period January-December 2018 was discussed.

- **PQR of pneumococcal vaccine (or what is available):**

At the time of inspection there was no PQR available for the pneumococcal 10-valent vaccine. To date there had been very limited production of finished product and of mono-valent bulks. Validation had been performed between January and March 2017.

Review of the company's SOPs relating to product review indicated some weaknesses and generally the approach to reviews appeared to fulfil regulatory expectations rather than provide a continuing assessment and history of product manufacture across the product lifecycle rather than use product quality review as an active part of product management and improvement and as a core knowledge management tool.

- **PQR of MMR:**

The annual product quality review of MMR for the year 2018 was prepared by QA, reviewed by QC and production and approved by QA in March 2019. This APQR was briefly reviewed.

The company had provided a CAPA plan adequately addressing the raised issues related to PQR.

Quality risk management:

The company's QRM approach was documented. The procedure on QRM essentially relies only upon the use of the FMEA tool. This tool is not appropriate in all cases and while the SOP mentions other tools this was only by name and gave no guidance on the appropriate selection of tools.

The company's implementation of QRM is relatively mature with assessments being available for many processes although some of these assessments had missed key risks that were discussed with the company.

For pneumococcal vaccine, QRM included a process risk assessment performed for PPVC-10, approved immediately prior to the inspection. Validation lots had been made in 2017 and a commercial lot manufactured in 2019.

A number of processes including the aseptic formulation of bulk vaccine prior to filling is well automated and operates on a recipe basis which mitigates many potential risks however it was noted that several key steps are dependent upon single sterilising filters and that these filters are not tested after sterilisation but before and after the batch is over. In the case of failure of these SIP'd filters then the company would face the destruction of several million doses of the conjugated adjuvanted vaccine at significant cost and delays for replacement.

The company had not yet performed a documented detailed risk assessment against the revision draft of the WHO/EU/PICs sterile products guideline.

The company had provided a CAPA plan adequately addressing the raised issues related to QRM and risk assessment.

➢ ***Deviation management:***

Reporting of deviations procedure was discussed. It was noted that deviations were categorized into critical, major and minor. A soft copy of the deviation form was provided to each department. An initial impact assessment was performed by initiating department and immediate actions were performed. The deviation form was forwarded to QA department for categorization and further recommendations. An investigation and root cause analysis were performed for minor and major deviations whereas for the critical deviations, a separate procedure title "procedure for failure investigation and root cause analysis was referred. The procedure stated that only critical deviations shall be investigated using RCA procedure. The corrective actions and preventive actions procedure was cross referenced, and it is manually tracked using an excel sheet. In general, procedure was found adequate.

The company had provided a CAPA plan adequately addressing the raised issues related to deviations management.

➢ ***Management review:***

Provisions for management review were in place which were confirmed from the executive summaries (e.g. deviations, out of specifications, complaints) prepared for the senior management.

➢ ***Change control:***

Change control management procedure was discussed. It was noted that changes were handled manually by logging into a register. Initial risk/impact assessment was performed by the originator department before proposal was forwarded to QA. Change request number issued by the QA and detailed impact assessment was performed covering SOPs, personnel training, IPC test, FP tests, specifications, stability study impact, qualification & validation impact, vendor qualification and maintenance calibration. Regulatory impact assessment was performed. Tracking was handled manually by maintaining an excel sheet. The company is planning to move onto the electronic system. An executive summary report of changes raised in 2018 was reviewed. Summary of major change proposals for 2017-2019 was discussed.

➢ ***CAPA management:***

Procedure for CAPA system management was in place. The procedure covered the internal and external observations, corrective and preventive action from deviation, OOS, OOT, system, product complaint and product recall. The effectiveness check was considered in the procedure.

WHO audit performed in January-February 2018 gave rise to several deficiencies. Accordingly, several CAPAs were raised to address the non-conformities. At the time of this inspection, 2 CAPA were still open.

The closing letter from the last WHO GMP inspection conducted from 29 January to 2 February 2018 was issued stating the GMP compliance of the site with conditions that the company formally committed to implement within agreed and acceptable timelines and mainly related to the filling lines, lyophilisation lines and sterile filtration.

➢ ***Documentation:***

The company has a documentation management system policy, which ensure appropriate control of documents from planning, issuing, and revising till destruction of obsolete & time expired documents.

Each department as well as each product has a unique code for SOP [first three characters in SOP number].

All SOPs are reviewed annually & different type of documents has different retention time with respect to SOP for retention of records.

Preparation of Master batch record (Manufacturing, packaging & consignment despatch record) is done through SAP system by QA & if any change control is done, the obsolete master record was locked in system to lock document file by authorized person.

SOPs for Master test requirement (MTR) of MSL/WSL, pneumococcal purified polysaccharide, pneumococcal monovalent bulk conjugate, final formulated bulk of pneumococcal polysaccharide conjugate single & multi dose, Modified polysaccharide & CRM 197 are established with respect to test methods & specifications.

Batch numbering systems for bulk antigens, finished products & development and experimental products (non-commercial batches) were revised.

Master batch manufacturing records for preparation of MSL/WSL of different serotypes, fermentation, purification, modification, conjugation, formulation, filling – stoppering & sealing were revised.

Sanitization of cassette &TFF system was mentioned in BMR of purification of PPCV (as per SOP).

Hold time validation study for dirty equipment as well as hold time validation study for sterilized equipment used for PPCV production were revised.

The company had provided a CAPA plan adequately addressing the raised issues related to documentation management.

➢ ***Complaints:***

Procedure for handling of product complaints was in place. Complaints can be received from different sources (regulatory authorities, wholesaler, customers, HCP…). Upon reception, all complaints are forwarded to QA for login into the database. They are classified as critical, major or minor. In case of confirmed quality defect with a product which may result in the recall of the product or an abnormal restriction in the supply, the regulatory affairs department, in coordination with QA department shall inform the concerned regulatory authorities within two business days. An investigation is launched to find out the root cause of the complaint, resulting, where relevant, in CAPA and an investigation report. The conclusion may be either justified or unjustified. A response is sent to the complainant and the procedure is closed.

Since PCV is not yet distributed, no complaint has been, reported yet. Therefore, the 2017 and 2018 reporting of complaints of other vaccines, MR and MMR, HepB, and DT, was reviewed.

Complaints related to MR and MMR vaccine:

The complaints recorded in 2017 and 2018 were spot checked.

In 2017, 6 general complaints mostly related to poor quality of the gum of immunization label. The preventive action consisted of replacing the label paper with PET/PP film. In 2018, 4 general complaints were reported for rubella OOS in Mexico.

WHO PQT Vaccine Assessment team received a complaint about batches of prequalified MR and MMR vaccines from Serum Institute of India for which potency test results for rubella component was reported as out of specification. Several mails were exchanged with the company to clarify this issue. This inspection provided an opportunity to discuss details with the QC staff members and to review the associated documentation.

The procedures for testing on final products of Measles and rubella vaccine and Measles, Mumps and Rubella vaccine were reviewed. The Rubella titre is performed on Rk-13 cells by determining the $Log_{10}CCID_{50}$ following CPE induced by serial dilutions of the vaccine, using the Spearman-Karber formula (the validation of these assays is addressed below, under "Method Validation"). The Indian NCL uses a similar method and a same cell line, displaying similar results to those observed at SIIPL.

The qualification of the new in-house reference standard was also reviewed. To establish the titre of the proposed reference standard, several vials of the selected vaccine lot were titrated on duplicate. At the same time, the titer of the NIBSC international standard was established and found almost identical to the assigned value. The conclusion of this study is that the Rubella in house reference standard displays an established reference titer and that it can be used in routine testing.

The provided explanations and details are considered adequate and substantiated by sound, scientific and appropriate data.

There was a complaint regarding 2 vials of MR missing from each box of 50 vials for one lot. The corrective action was the awareness training imparted to all concerned in packing and the preventive action that the procedure shall be revised to elaborate procedure for vigilance in process check by officers/supervisors. An automatic line with weight checker is used only if the batch size for packing is more than 30000 vials as per the company representative. However, this was not clearly defined in the procedure in force. There should be the same control measures for both automatic and manual packing process.

Complaints related to HepB vaccine:

Three complaints were reported in 2017. The first related to the extractable volume and classified as "unjustified". The second related to the Q-tag device which recorded an elapsed time of 25 hours whereas 222 hours actually elapsed. This device was inadvertently switched off. The corrective action consisted of changing the form of the button from convex to flat to avoid such switching. The third related to snowflakes like substance that may be seen in the vials. This was classified as unjustified since this observation results from vaccine freezing. In 2018, 9 market complaints were received, both unjustified (particles or crystal-like matter following subzero temperature during storage…) and justified (particles stuck in the cavity of rubber stopper release during subsequent storage, accidental stoppage of Q-tag due to component failure, leakage of coolant pack…).

Complaints related to DT vaccine:

In 2017, only 2 complaints were reported, namely one missing vial (a corrective action aimed at increasing awareness was implemented) and an unjustified complaint related to the result of OOS potency of diphtheria component. Based on re-verification of quality and quantity of raw materials used in the manufacture, quality parameters etc… no process abnormality could be identified from the company side. Hence, the complaint was concluded as unjustified. Of note, information was requested by SIIPL to the complainant, but no information was eventually received. In 2018, 2 failures of visual inspection test were reported. In both cases, black particles could be seen in the sample. The complaint sample from one country was not received by SIIPL and therefore, it could not be analysed. As a consequence, the complaints were closed with conclusion as unjustified. As for the other country sample, considering the size of the particle (94-100 µm), according to a report of the Parenteral Drug Association, the probability of detecting of such particle is 40%. Moreover, the possibility of particles stuck in the cavity of rubber stopper and released during subsequent storage and transport cannot be nullified. The complaint concluded as justified and relating to the intrinsic nature of the vaccine.

The company had provided a CAPA plan adequately addressing the raised issues related to the complaints management.

- ***Pharmacovigilance (PV):***

The procedure related to the handling of individual case safety reports (ICSR) is applicable for all vaccines (including PCV), biological and other pharmaceutical products for human use manufactured by SIIPL. Safety reports can be received from different sources (spontaneous reports from NRA, customers, patients, HCP…). Upon reception, all the adverse events are forwarded to QA for login into the log book. If they fulfil some criteria, the adverse events are validated as AEFI. If not, follow-up actions are initiated to get additional information. The adverse event is categorized as serious or non-serious by SIIPL pharmacovigilance department. In case of valid fatal death(s)/report(s), the regulatory affairs department shall inform the concerned regulatory authorities (RA) / WHO, within 07 days from receipt of the adverse event. A quality investigation conducted by QA & QC or a clinical investigation performed by an audited service provider, namely Lambda Therapeutics Limited (UK), will be initiated. Observation and conclusion are classifying the adverse event into 6 groups, i.e. vaccine product related reaction, vaccine quality related reaction, immunization error related reaction, coincidental event, immunization anxiety related reaction and indeterminate/unclassifiable. A SAE report will be submitted to applicable RA, if applicable, a reply will be addressed to the reporter and, finally, the report will be closed.

Since PCV is not yet distributed, no AEFI has been, reported. Therefore, the 2017 and 2018 reporting of AEFI of other vaccines, HepB, MMR and DT, was reviewed.

- ***Product recalls:***

Procedure for product recall was revised with respect to responsibilities & system to conduct recalls at different levels of supply chain, Also SOP for mock recall was revised where a mock recall should be done once per year and the mock recall of year 2018 which was done on a TT vaccine distributed in 9 countries was reviewed.

➢ ***Self-inspection:***

Internal audits procedure was reviewed. It was noted that internal audits were performed at least once per year covering all departments. Internal auditors were identified from QA, QC and production department and a list of qualified auditors was maintained. Annual internal audit schedule for calendar year 2019 was in place. It was noted from the schedule that all the departments were randomly assigned to be inspected between January and December. An external consultant audited QA. A list of trained and qualified auditors was in place. A checklist was used for internal audit whereas a separate template was used for reporting observations. The observations were categorized into critical, major and minor. The CAPA were raised and tracked using the same observation template.

➢ ***Quality audits and suppliers' audits and approval:***

The company has a program of supplier audit and review. A number of key materials such as stoppers are purchased in a ready to use format and the control of these materials and supporting audit of the manufacturers were reviewed to determine the extent of the possible variability of materials were well understood by the company and whether robust indicators were embedded in the company quality control systems that would be capable of detecting an unexpected change had it occurred. Review of the supplier audits of rubber stoppers provided information on the audit of the processes for the selection of side samples on which the company's testing was performed.

Follow up lead to the conclusion that the checks of the grades of rubber formulation and the glass tube from which vials were manufactured should be strengthened. Checks necessary to control for variation need to be robustly embedded in the QC systems in Pune. A spot check on pyrolysate spectra of FTIR for analytical report of Rubber Stopper revealed discrepancies between actual testing and reporting. There was also no reference IR spectrum run on the same FTIR available and no system in place to label each wave numbers and compare against the reference standard wave numbers. These issues highlighted the deficiency in the current controls to avoid mix up and for this reason the controls over checks of certificates should be strengthened.

The management of the primary packaging material and associated data integrity was found deficient. The company had provided a CAPA plan adequately addressing the raised issues related to the data integrity issues.

➢ ***Procedure for batch review and release***

The batch release procedure was in place. Production and QC department forward the BMRs and testing reports respectively to the QA Department, which will review the provided information for compliance with standards, including compendial requirements, WHO requirements and national control requirements. After completion of this review, batch shall be released for forwarding to NCL and summary lot protocol along with the samples shall be forwarded to NCL for obtaining batch release certificate. After receiving the batch release certificate from the NCL, the batch is released for dispatch as a complete batch or in parts, based on the market requirements. If everything is found streamlined and satisfactory, the batch is released for distribution through computerized system by head of QA.

The procedure for batch release in SAP is laid out in the above-mentioned SOP.

The batch release process is closely tied to the dispatching procedure, as described below under "Distribution and shipping".

➢ ***Summary lot protocol and NCL release.***

The summary protocol for production and testing of 10 valent pneumococcal polysaccharide conjugate vaccine is established as per WHO requirements and encompasses information on the seeds, production details on fermentation; purification, conjugation, testing of the intermediates, drug substances, final bulk and drug product, filling and sealing, authorization for labeling and packing, certificate for final product signed by director production and director QC, certificate of quality assurance signed by director QA and, finally, the batch release certificate signed by director QA.

➢ ***Personnel:***

The manufacturer had an adequate number of personnel with the necessary qualifications and practical experience. Specific duties were recorded in written job descriptions for responsible staff. Personnel met were aware of the principles of GMP and received initial and continuing training, including hygiene instructions, relevant to their needs. Steps were taken to prevent unauthorized people from entering production, storage and QC areas. The manufacturer had provided a breakdown of permanent and contractual employees in their site master file.

Job description:

Procedure and records for job description of the personnel was in place. Some records were spot checked and found acceptable.

Training:

Firm established standard procured for imparting training. Per SOP the head of department (HOD) or section head will identify the training needs. There were three types of training imparted viz. Induction training, technical training (specifically for SOPs) and general training (specifically for cGMP and Quality system) for management staff and operators. The training SOP also has procedure for the assignment of job description of staff and operator. The HOD or his nominee shall prepare JD of new employee after reviewing the completed training records as per the training need identification.

Each department prepare its own training schedule viz. schedule for technical training was prepared once in two years by the HOD and the same was approved by QA, schedule for general training i.e. cGMP & quality system training schedule prepared and approved by QA. The trainee attendance was recorded vide training program attendance sheet. Training was imparted by different methods like class room training, on job training or demonstration, read and understand and other method like e-learning, case studies, quiz etc. Post training, evaluation was done based on training questionnaire or quiz or group discussion or written feedback. The trainer will decide the mode of training to be used for the training of staff or operator. SOP defined the training frequency; each employee shall be given refresher GMP training conducted by QA at least once every year. Per SOP, the cGMP and quality system training of new employee shall be completed within defined period of time from joining date. SOP have defined procedure for retraining and reassessment.

Training schedule for Pneumococcal Polysaccharide Conjugate Vaccine department for year 2018 -2020 was reviewed and found acceptable.

The company has a formal training program for aseptic area operators that is linked to gowning qualifications and the involvement in routine media fills before being qualified for routine working in the aseptic area. The review of aseptic training and how this is linked to the performance of set up critical tasks was reviewed. There was inadequate tracking of set up operators and the detailed tasks they are required to perform in routine production in media simulation plan. As the set-up teams are greater than the number of times available for the performance of that task by each individual operator it is not clear how the company plans to requalify the set-up teams for each authorized task once in a year.

The training of visual inspectors was spot checked. AQL inspection of inspected product containers was done by QA specialist. The last qualification of the visual inspector in charge of AQL conducted in October/November 2018 for DTP-HeB-Hib 1 dose in 2 ml vials was spot checked. The Knapp batch of vials including defective samples were used for this qualification. This qualification was performed as per the procedure "Qualification of visual inspector for physical inspection". The critical, major and minor defects were appropriately defined.

Personal hygiene:

The procedures for gowning and access to the comfort zones and classified manufacturing areas were in place.

The authorized personnel who complied with the monthly medical examination, half yearly gowning qualification and vaccinated can access the manufacturing areas. Access card to be used to enter the area and personnel is required to enter the details like name, entry and exit time with signature in the clean room entry and exit record of respective area found maintained at the entry as per SOP driven format.

Medical Examination:

The procedure for the vaccination requirements of employees of SIIPL was in place. The immunization record card was maintained.

Firm have occupational health center (OHC) with four medical doctors for taking care of the occupational health hazards or medical check-up and related control governed by different SOPs, which briefed hereunder:

Monthly medical check-up for clean area personnel and animal house personnel was reviewed. Per SOP the employees are examined for any infection/disease of hair, skin, nails, general hygiene, treatment if any prescribed etc. The medical health care recorded and signed by doctor and office in charge of the concerned employee's department. The clean area monthly health card data was verified/cross referred with the Occupational Health Centre (OHC) log sheet maintained by the OHC doctor. The monthly clean area medical records entries were verified with their access card punching data and found satisfactory.

For yearly medical check-up, physical examination, and systemic examination (CVS, respiratory, vascular) were conducted. Per SOP the pathology test and ECG were done in every alternate year for each of employee. Pre-employment medical examination was done as per SOP, where all systemic, pathology, X-Ray were done, medical history and vaccination details of the new employee/staff. Firm also perform exit medical health check-up of its employees who leaving or separating from SIIPL or employment.

2. Production system

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. Procedures for qualification and validation of equipment, manufacturing processes and quality control testing methods were in place. Qualifications and validations were performed. Systems were in place for handling complaints and recalling batches of product from sale or supply.

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 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.

➢ ***The following manufacturing procedures and processes were reviewed during the inspection:***

CRM197

- Bacterial seed lots:
- Upstream process
- Downstream process

Streptococcus pneumoniae:

- Bacterial seed lots;
- S. pneumoniae upstream process;
- PnPs downstream process;
- Conjugation;
- Monovalent bulk conjugates;
- Final bulk;
- Filling.

Process validation:

The general process validation strategy consisted of monitoring each process parameters, IPC and specification test at each step for at least 3 batches, verifying consistency and, where applicable, conformity to acceptance criteria. Data were spot checked, displaying consistency and, where relevant, compliance with the acceptance criteria. The process is deemed to be adequately validated.

The successive steps of the manufacturing process were validated as per the process validation protocols and validation reports:

- CRM197 Manufacturing process (both upstream and downstream process);
- Pneumococcal bulk (PS) Manufacturing process;
- Pneumococcal polysaccharide modification (Conjugation) manufacturing;
- Pneumococcal Conjugation Manufacturing Process;
- Formulation of pneumococcal polysaccharide conjugate vaccine (10-valent) (adsorbed);
- Vial filling, sealing and physical inspection of PPCV10 vaccine.

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Continuous Process Verification and process validation:
Procedure for process validation was in place. The company has also recently established a new procedure dealing with continuous process verification. This SOP requires quarterly reviews of key indicators.

Validation of aseptic process (Media simulations):
The company has a general SOP on media simulations. This procedure is supported by specific study specific protocols, media fill BMRs and summary reports. The most recent media simulations were performed in February-March 2019.

There have been no media fill positives in the filling validations. The protocols and reports of the finished formulation media simulations of pneumococcal formulated product fills were satisfactory and the interventions well documented in the batch documentation.

Pneumococcal review of existing data and questions raised by quality assessors as relevant:

During this inspection, the questions raised during the quality assessment were briefly reviewed with SIIPL. The SIIPL experts had the opportunity to present what they intend to answer and to justify their position. The message got through and will be considered when assessing the responses to questions at WHO PQT.

3. Facilities and equipment system

PCV polysaccharide and conjugated are manufactured in a fully dedicated facility. The facility is adequately designed, equipped and maintained. The live area has its dedicated AHU separated from the other processing areas. The live area was self-contained, physically and by dedicated AHU along with adequate differential pressure design with negative pressure in the fermentation room and a bubble point at the changing room.

Critical areas are continuously monitored for differential pressure with alarms in place.

Waste management:
The disposal of waste for fermentation activity was in place. The fermentation room is equipped with a decontaminating autoclave. Load patterns for contaminated material and solutions are decontaminated through this autoclave. The fermenters and centrifuges are sterilised after fermentation. The containment of spills was in place. The preparation and use of disinfectant procedure was in place. An efficacy study of disinfectant on *S. pneumoniae*/serotype 5 was conducted.

- ***Qualification and validation:***

Provisions for qualification and validation were in place and covered 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.

The validation master plan was in place. Annual validation plan shall be prepared for existing production facility to track various validation activities to be carried out in the facility in a calendar year.

The qualification and validation report of the following was reviewed:

- Depyrogenation Tunnel;
- Autoclaves;
- Cleaning and Sanitization;
- Cleaning process verification;
- Vial washing machine;
- Capping machine;
- Visual inspection;
- Air Handling Units;
- Environmental monitoring;
- Water systems.

4 Laboratory control system

Entry to all QC buildings/areas and rooms was restricted to authorised personnel (list of authorized personnel is given at entrance) and was controlled by access code. Visitors and guests have to sign in before entering the QC area or animal housing.

Management of OOS test results

Out of specification (OOS) investigation procedure was discussed. A checklist was used for the laboratory investigation. Hypothesis testing was described in the procedure like dilution error, pipetting error, instrument malfunction, power failure etc. The procedure described retesting plan and minimum determinations required to be performed. Both first analyst and experienced second analyst perform retesting. The acceptance criteria were based on respective test described in the analytical method validation report. Resampling was performed if it was confirmed sampling was an issue. Following the Phase-I laboratory investigation, Phase-II investigation was performed using failure investigation and RCA procedure.

The list of OOS was spot checked.

Qualification of reference/standard material:

One monovalent bulk conjugate per serotype was selected as reference standard. It should be emphasized that these conjugates were formulated into a vaccine which was used in a phase II clinical trial. These standards are stored at low temperatures, as are the conjugates to be used in the manufacturing process. A certificate of analysis was spot checked, namely i.e. the bulk conjugate of serotype-5.

PnPs reference standards are stored at low temperature.

The documentation of other references standards (thiomersal, CRM197…) was not reviewed during this inspection.

The following method validation were reviewed:

- Potency of MR and MMR;
- ELISA;
- Sterility test method validation;
- Bacterial endotoxin test.

Stability Studies:

- CRM197;
- PnPs;
- Modified/size reduced PnPS;
- Monovalent bulk conjugates (DS);
- Drug product.

As per GMP requirements, one commercial scale batch will be placed on the long-term stability study annually if manufactured.

5 Materials system

Each consignment of materials after receipt by Warehouse department is initially inspected. Different batch materials are segregated.

Separate areas have been allocated for storage of raw materials, packing materials. Materials are stored at controlled temperature depending on the storage requirement of the materials.

Standard operating procedures for sampling of the raw material and packaging materials were in place. The raw materials are approved or rejected by QC Department based on the results of analysis.

As exemplified during the visit, incoming raw materials are received in the warehouse. They are quarantined, sampled, tested by QC and eventually approved or rejected. Appropriate tags affixed on the materials and dedicated storage area allow to unambiguously assign the status of the materials. When sampling is to be performed, the company applies the rule $\sqrt{n} + 1$. Rejected material is stored in a dedicated room. Identification test of excipient is performed on each container of received material.

Labels & inserts were stored securely as well as rejected materials.

Finished products are stored under appropriate storage conditions and controlled status before the release and shipment.

6 Packaging and labelling system

Printed packaging materials like labels and cartons are stored under lock and key with restricted entry for authorized personnel.

As incoming raw material, VVM are received in the warehouse. The SOP specifies that materials that need to be maintained under specified temperature should be checked for actual maintenance under appropriate temperature conditions. In the case of VVM, the operator must check that dry ice is still present in the shipment packaging of VVM. Several units are received per order. They are quarantined and, following approval, stored, at -20°C in cold room. Boxes are randomly selected for testing. One roller. Several VVM units are analyzed. The available densitometer, is calibrated. A QC operator showed a demonstration. The difference between the reference circle and the active square surface met the acceptance criteria.

During packaging & labelling, density test for VVM was performed again in packaging area and recorded in packaging batch record.

Packaging material:

SIIPL has developed a specialized cold chain packaging for its vaccines which ensure safe temperatures during transportation. Vials of vaccine (both single dose and 5 dose presentations) are packed in 3-ply corrugated box along with a direction slip. Inner corrugated boxes, containing vials, are packed in one 3-ply outer corrugated box. Outer corrugated boxes, containing vials, are then packed inside the expanded polystyrene (EPS) box along with ice packs. The EPS box is then placed in a 7-ply corrugated box/shipper box, after which it is further wrapped in a plastic bag and strapping is completed. Every shipper box will have a Type 1 temperature monitoring device. Photos of the packaging material were made available.

The described packaging configuration was approved by WHO PQT as acknowledged in a WHO letter of 26 April 2012 that concludes: "We have reviewed the validation testing at 43 °C (class B packaging) and 43 °C and -5 °C (class C packaging) for the above presentations, and the results have found meeting the WHO requirements for international packaging and shipping. Therefore, new packaging configuration for these two products have been approved."

7 Distribution and shipping

The procedure for export consignment, packing and dispatching was in place.

The export department plans the shipment, specifying the vaccine, product quantity, data, final destination, possible specific requirements of the customers etc… and addresses a request to the shipping department.

The shipping department carries out the process in 3 steps.

Firstly, the shipping line department proceeds to the line clearance, prepares the material (shipping box, ice packs, temperature monitoring devices) and verify all these components,

Secondly, the shipping department shall pack the vaccines. The necessary entries are to be made in the consignment dispatching record. Prior to shipping, the QA officer verifies the consignment packing and the dispatch activity,

Thirdly, the vaccine is sent to the airport in refrigerated truck.

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, **Serum Institute of India Pvt. Ltd.*, Pune, 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.

DEFINITIONS

Critical deficiency
A *critical* deficiency may be defined as an observation that has produced, or may result in a significant risk of producing, a product that is harmful to the user.

Major deficiency
A *major* deficiency may be defined as a non-critical observation that:

- has produced or may produce a product that does not comply with its marketing authorization and/or prequalification application (including variations);
- indicates a major deviation from the GMP guide;
- indicates a failure to carry out satisfactory procedures for release of batches;
- indicates a failure of the person responsible for quality assurance/quality control to fulfil his or her duties;
- consists of several other deficiencies, none of which on its own may be major, but which together may represent a major deficiency and should be explained and reported as such.

Other deficiency
A deficiency may be classified as other if it cannot be classified as either critical or major, but indicates a departure from GMP. A deficiency may be other either because it is judged as minor or because there is insufficient information to classify it as major or critical.

Classification of a deficiency is based on the assessed risk level and may vary depending on the nature of the products manufactured, e.g. in some circumstances an example of another deficiency may be categorized as major.

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