World Health Organization

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Prequalification Unit Inspection Services
WHO PUBLIC INSPECTION REPORT
(WHOPIR)
of the Vaccine Manufacturer

Part 1	**General information**
Manufacturers details	
Name of manufacturer	**Serum Institute of India Pvt. Ltd.**
Corporate address of the manufacturer	Soli-Poonawalla Road, 212/2 Hadapsar, Pune- 411 0028, India.
Inspected site	
Name & address of inspected manufacturing site if different from that given above	**Serum Institute of India Pvt. Ltd.** 1. 212/2, Hadapsar, Pune, 411 028 India 2. S. No. 105-110, Manjari Bk. Pune, 412 307 India
Inspection details	
Dates of inspection	13 to 17 and 20 to 24 February 2023
Type of inspection	Initial WHO inspection for: 1. MenFive® (Meningococcal (A, C, Y, W, X) Polysaccharide Conjugate Vaccine) 2. R21 Malaria vaccine (Recombinant, Adjuvanted) 3. HEXASIIL® (Hexavalent Vaccine (DTwP-HepB-IPV-Hib) 4. BCG Vaccine (freeze-dried) at the new additional facility (Manjari site)
Introduction	
Brief description of the manufacturing activities	Production and quality control of Sera, Vaccines, and other Biologicals.
General information about the company and site	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. The manufacturing activities are performed in two sites, namely Hadapsar and Manjari, which are connected by a private road. Serum Institute commenced production in October 1967. Starting with Tetanus Antitoxin, Serum Institute progressively launched the DTP group of Vaccines: 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 Polysaccharide Conjugate Vaccine, COVID -19 Vaccine, Meningococcal (A, C, Y, W, X) Polysaccharide Conjugate Vaccine, R21 Malaria, and several other products. Since March 1994, SIIPL has been exporting viral vaccines and bacterial vaccines to WHO, PAHO, and UNICEF.
History	The company provided the list of the regulatory authorities' inspections carried out since 2020. The last WHO onsite inspection was conducted in July 2019 and covered the Pneumococcal Polysaccharide Conjugate Vaccine (Adsorbed) (10-Valent) [PCV-10V].
Brief report of inspection activities undertaken – Scope and limitations	
Areas inspected	**Facilities at the Hadapsar site:** - Meningococcal Purified Polysaccharide(s) Drug Substance (DS) production and Formulation of MenFive® vaccine. - Manufacturing of *Haemophilus influenza* type b conjugated bulk - Recombinant CRM197 (for conjugation with meningococcal polysaccharides) production. - Filling, Lyophilization, Stoppering, and Capping of MenFive® vaccine. - R21 Malaria bulk DS production. - Blending and fill-finish of Hexavalent vaccine. - Manufacturing of B. pertussis (whole cell) bulk. - Manufacturing of Diphtheria and Hepatitis B DS bulks production. - R21 Malaria vaccine filling line. - Microbiology Quality Control laboratory for Hadapsar site. **Facilities at the Manjari site:** - BCG vaccine production, Labelling and Packaging. - Animal House. - Warehouse. - Warehouse. - BCG Quality Control laboratory. 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.
Restrictions	None
Out of scope	Products and vaccines other than those described below were not covered during this inspection.

WHO products covered by the inspection	1. MenFive® (Meningococcal (A, C, Y, W, X) Polysaccharide Conjugate Vaccine) 2. R21 Malaria vaccine (Recombinant, Adjuvanted) 3. HEXASIIL® (Hexavalent Vaccine (DTwP-HepB-IPV-Hib) 4. BCG Vaccine (Freeze Dried)
Abbreviations	**Meaning**
AHU	Air handling unit
ALCOA	Attributable, legible, contemporaneous, original and accurate
API	Active pharmaceutical ingredient
APR	Annual product review
APS	Aseptic process simulation
BMR	Batch manufacturing record
BPR	Batch production record
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
FPP	Finished pharmaceutical product
FTA	Fault tree analysis
GMP	Good manufacturing practices
GPT	Growth promotion test
HEPA	High efficiency particulate air
HPLC	High performance liquid chromatography (or high performance liquid chromatography equipment)
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
NC	Non conformity
NRA	National regulatory agency
OQ	Operational qualification
PHA	Process hazard analysis
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
URS	User requirements specifications
UV	Ultraviolet-visible spectrophotometer
WFI	Water for injection

Part 2	**Summary of the findings and comments (where applicable)**

1 Pharmaceutical quality system

The quality management system was generally well-established, documented, and implemented. The quality assurance department was independent of production. The persons authorized to release products were specified. The PQS was defined and documented in the Quality Manual.

Management review (MR):

Quality management review was managed as per SOP. Management review was performed quarterly. Meeting minutes and the presentations prepared for the meeting were reviewed and found to be generally acceptable.

Product quality review:

The Annual Product Quality Review (APQR) SOP was reviewed and found acceptable. The APQRs for the Hexavalent vaccine, MenFive, BCG (Manjari site), and R21 Malaria vaccine were reviewed.
An SOP describing the tools for trend analysis and reporting of OOT results was in place. Trend analysis was performed quarterly for each product presentation, and a cumulative trend for APQR was performed at the end of the last quarter.

Quality risk management:

The company´s QRM approach was documented in a SOP. The document was based on ICH Q9. A SOP for Contamination Control Strategy (CCS) was in place. The CCS for filling and lyophilization of BCG was spot checked.

Deviation management:

A SOP for reporting of deviations was in place. Deviations were manually tracked; however, qualification of a computerized system was ongoing at the time of inspection. Deviations were categorized into critical, major, minor based on risk. The adoption of CAPA was based on the investigation. Recurrence was checked manually in a logbook. A root cause investigation was performed according to a specific procedure.

The deviation list of BCG manufacturing for 2022 and 2023 was presented and discussed. Some deviations were selected for review.

Change control (CC):

The SOP for Change Control Management was in place. Changes were classified as Minor, Moderate, and Major. A computerized system was used to track changes. Impact assessment included SOPs, training, tests, specifications, stability studies, qualification & validation, vendor qualification, maintenance, and calibration. The regulatory impact assessment was also performed.
The list of major changes since the last PQ inspection (2019) was presented.

CAPA management:

An SOP was in place for the Management of the CAPA system. The company used a manual system. However, the implementation of a computerized system was planned for June 2023. The procedure covered the internal and external audit observations, corrective and preventive action from deviations, OOS, OOT, product complaints, and product recall. An effectiveness check was considered in the procedure.
Follow-up on observations made by WHO during the inspection that took place in July 2019 was reviewed.

Complaints:

An SOP was put in place for handling product complaints (Corporate procedure). Complaints received by SIIPL by any means (telephonic communication, e-mail, media etc.) were logged in a logbook by QA department. Implementation of a computerized system was planned for Q3 of 2023. QA, in co-ordination with cross functional department carried out the investigation. Whenever applicable, the QC department performed the necessary tests on the retained samples or complaint samples. Depending on the outcome of the investigation, root cause/probable root causes were identified and accordingly CAPA was recommended. The findings of the investigation and recommendations were communicated to the complainant. Complaints were classified as critical, major, and minor.
The list of WHO PQ Products complaints for 2022 was presented, and some records were spot-checked.

Product recalls:

An SOP was put in place for product recall. Recalls were categorized into classes I, II, and III based on risk. The SOP established the need to communicate with regulatory authorities and WHO, as applicable. For mock recall, the company adopted a procedure establishing that recall should be simulated once a year. The mock recall was challenged as Class I (higher risk), and within 3 years, 2 mock recalls should be for international markets and one for the Indian market. The tracking was manual. However, the implementation of a computerized system was planned for Q3 2023.

Since the last WHO Inspection (2019), the company informed a class II voluntary recall conducted in 2021 for the Indian market related to the Rotavirus vaccine (live attenuated oral). Investigation was completed, probable root cause identified and CAPA implemented.
The last mock recall for the international market conducted in 2021 was briefly reviewed. The mock recall summary report was approved.

Self-inspection:

An internal audits SOP was in place. All departments were audited at least once a year. However, the frequency can increase depending on the risk assessment, considering the number of deficiencies found in the previous year. QA prepared an annual/monthly schedule. Provision for the qualification of internal auditors was described in the procedure. Observations were categorized into critical, major and minor. Deviations and CAPA were initiated and tracked, as applicable. The annual Internal Audit Schedule for Hadapsar and Manjari sites was presented, as well as the Annual Executive Summary for Internal Audit for the year 2022.

Quality audits and suppliers' audits and approval:

All raw materials and packaging materials were required to be sourced from approved vendors. Vendor Management System SOP and Preparation and Management of Quality Agreements were checked and found acceptable. Vendor approval was a corporate function.

Contract production, analysis and other activities and Quality agreements:

No manufacturer was contracted out, and only garment laundry service was contracted out.

Personnel

Organization, organogram, independence of production from quality control:

There was the adequate number of personnel suitably qualified by education and training to perform and supervise the manufacture of the vaccine products. The personnel met during the inspection appeared to be knowledgeable about GMP.

Organization charts were available and reviewed. Key personnel responsibilities were required to be defined in job descriptions. The job descriptions and responsibilities of some employees were reviewed and discussed.

Training:

The training was performed according to the status of the trainee: new employee or existing employee (retraining or new assignment). For a new employee, after basic induction and subsequent general training on GMP and quality, the training need identification (TNI) was issued in accordance with a specific list of job roles, each linked to a specific technical SOP. Update or retraining for existing employees was notified in a computerized system.

Personal hygiene:

The company had several written procedures to manage personal hygiene and regular health examinations of staff appropriate to their responsibilities to ensure personnel did not become a source of contamination to the products.

Washing and changing areas were provided. Each employee entering the production area was required to follow the gowning procedure before entering the manufacturing areas.

Qualification of aseptic areas operators:
Gowning qualification SOP was presented. Initial qualification was performed with 3 runs, each with 8 sampling locations. Requalification was performed with one run once every 6 months for grade B operators. In case of failure during monitoring, an intimation report was sent to the department. After investigation, the operator should perform 3 runs before returning to grade B operations. Gowning qualifications of two aseptic operators were checked.

Documentation:
The documentation system was managed by both a computerized electronic system and paper-based manual system and controlled by the QA department at the corporate level and site level. The quality management system and relevant procedures have not been fully harmonized at both sites at the time of this inspection. The company explained the harmonization process had been initiated and was ongoing. The documentation management followed in-house approved procedures for SOP's initiation, revision, review, approval, obsolete, and distribution.
In general, documentation was designed, prepared, reviewed, and distributed according to a documented procedure. Approved, signed, and dated testing procedures and specifications were available for starting and packaging materials and for finished vaccine products. Documentation retention time was defined. The batch numbering system was defined in a SOP.
Batch manufacturing records (BMRs) were retained for each batch processed.

Batch Release Process:
The batch release was performed through the SAP system following 2 different release cycles: non-CDL cycle for some therapeutic products or vaccine bulks for commercial use/finished products for clinical trials, both without the release of NCL, and CDL cycle for any commercial vaccine. The information presented was aligned with the one submitted in product dossiers.

The deficiencies noted in this section were adequately addressed and will be verified during future PQ inspections.

2 Production system

The manufacturing processes were performed and recorded according to instructions in the batch production records. Production related SOPs were in place and followed. 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.

Production of MenFive, BCG and Hexavalent vaccine products were in operation at the time of inspection. Production of the R21 malaria vaccine was not in operation.

Cell banks:

BCG

The details of Master Seed Lot (MSL) and Working Seed Lot (WSL) used for the manufacturing of BCG bulk vaccine in Year 2022, were spot checked.

MenFive

Cell bank details for *Neisseria meningitidis* serogroups A, C, Y, W, and X were provided. Cell bank vials were stored at appropriate conditions at two different and distant locations.

Hexavalent

Master, pre-working, and working seed lots for *B. Pertussis* (whole cell) bulk production were stored in appropriate conditions. Access was controlled with a key available for authorized persons, for which there is a list affixed on the freezer. Back-up MC and WC banks for several antigens (HepB, Hib) development projects and reagents were stored in the QC lab. Temperature was monitored with a centralized system. Access was controlled with a padlock on the opening system, and authorized personnel, listed on a controlled document affixed on the freezer, were in possession of the keys. Replenishment of stock was assured through a fraction of the production of new MC and WC banks.

R21 Malaria

Storage of R21 MCB/WCB was conducted on the vapor phase of liquid nitrogen. Room access was controlled with badge and padlock. Tank lid was opened with a code. Temperature was monitored via centralized system. In case of problem, alarm was picked up by personnel from maintenance, always present, even during holidays. An oxygen sensor system was present.
Alternative storage was in place in another building. Room access was controlled with a fingerprint. An adequate level of nitrogen was maintained through an automated filling system from another tank. Temperature was monitored via a centralized system.

Drug substance

BCG

The production of BCG Vaccine bulk at a new building located on the Manjari site was inspected.

MenFive

Polysaccharide bulk manufacturing, conjugation, and formulation of the vaccine were performed at the SIIPL Hadapsar site. The company informed that a new additional manufacturing facility was planned for Drug Substance(s) manufacturing and Formulation and was already approved by the NRA under Marketing Authorization in India however at the moment of this inspection, no batch of MenFive Bulk DS or Formulated bulk had been manufactured in this area. Purified Tetanus Toxoid is manufactured at the SIIPL Hadapsar site. CRM-197 is also manufactured at the SIIPL Hadapsar site.

Hexavalent

The Bulk Drug Substances of the Hexavalent vaccine were the same as those of the already prequalified Pentavalent vaccine and IPV vaccine (bulk produced by Bilthoven Biologicals B.V., The Netherlands),

except for the Pertussis component, which for the Hexavalent vaccine did not use thiomersal during inactivation.

The following production areas at SIIPL Hadapsar were visited:

- Diphtheria bulk
- Pertussis (whole cell) bulk
- Hepatitis B bulk
- Hib conjugated bulk

As no activities were performed at the time of visits in most of the areas or visibility from the CNC corridor was limited, an *in-situ* overview of the manufacturing process was dispensed in each area. Additionally, clarification on personnel/material/reagents flows, and cleaning/sterilization procedures were provided in each facility. No observation was reported.

R21 Malaria

R21 DS bulks were produced at the SIIPL Hadapsar site. As no R21 malaria vaccine related activities were performed at the time of visits, an in-situ overview of the manufacturing process was provided. The bulk was dispensed in sterile bags in grade A in grade C configuration. Though there was a final 0.2µm filtration, there was no sterility claim.

Drug product:

Hexavalent

Manufacturing of the drug product Hexavalent Vaccine at the SIIPL Hadapsar site was inpected, including the process of blending, filling, inspection, and packaging operations.

MenFive

Formulation of Drug product, performed at the SIIPL Hadapsar site was observed. Filling, Lyophilization, Stoppering, and Capping can be performed at 2 separate facilities within SIIPL Hadapsar premises.

BCG

The BCG vaccine (freeze-dried), manufactured in a new building at the SIIPL Manjari site, was inspected.

R21 Malaria

A multi-product filling line located at the SIIPL Hadapsar site was used for the R21 malaria vaccine. Other products manufactured in this line were Covid vaccine and HPV. The filling line was in an isolator in Grade C room condition.

Process Validation

Process validation was performed according to the process validation SOP. Documents of media simulation for the filling line and blending process for the Hexavalent vaccine were available.

Batch manufacturing record review (BMR):

Some of the batch records were reviewed during the inspection.

Reprocess

The Policy on re-processing activity was spot-checked. It was limited for bulks in the case of OOS (not related to sterility and bioburden). Decisions on reprocessing should be made by QA. The policy described that stability studies should be considered in the reprocess plan.

The deficiencies noted in this section were adequately addressed and will be verified during future PQ inspections.

3 Facilities and equipment system:

BCG

BCG Facility located at the SIIPL Manjari site was inspected. The facility was access controlled by biometry. The list of authorized people for entering the filling area was presented. Vials were washed and depyrogenated in a tunnel. The filling line was installed with a restricted protected barrier (oRABS). Non-viable and viable monitoring were performed. Materials were sterilized in an autoclave in double-layer packaging and transferred from the autoclave room (grade B) to the filling line with grade A trolleys. BCG Bulk was transferred to the filling area in a Stainless-Steel Vessel. The tank is connected to a filling line with aseptic connectors.

Lyophilization was performed in 2 lyophilizers. Only one lyophilizer was used per batch. Lyophilizers and trays were sterilized before each batch. Transfer to lyophilizers was performed with grade A trolleys. The loading areas of the lyophilizers were protected with a barrier system, and the trays were loaded semi-automatically. Environmental monitoring for viable and non-viables was performed. Nitrogen, used for initial vessel pressurization and for lyophilization process, was filtered through 0.2 µm filters. Filters were tested for integrity in every batch.

MenFive

The Polysaccharide bulk manufacturing, conjugation, and formulation were performed at the SIIPL Hadapsar site.

Purified Tetanus Toxoid can be manufactured at different facilities at the SIIPL Hadapsar site. The facilities were not visited since the areas were already prequalified for other vaccines.

CRM-197 was manufactured at 2 separate facilities at the SIIPL Hadapsar site.

The filling and Lyophilization area were visited during the filling of the Rabies vaccine. The assembly of the filling line and the start of filling were observed. An additional fill and finish line facility within the SIIPL Hadapsar site was visited during the blending and filling of MenFive.

Hexavalent

The following production areas at the SIIPL Hadapsar site were visited:

- Diphtheria bulk.

- Pertussis (whole cell) bulk.
- Hepatitis B bulk.
- Hib conjugated bulk.
- Blending and fill-finish of Hexavalent vaccine. The filling line operation was observed from the CNC corridor, including vial washing, tunnel dry/sterilization/cooling, filling machine setup, and filling operation in oRABS. PW, WFI, and steam facilities on the terrace floor and HVAC/compressed air on the second mezzanine floor were spot-checked.

R21 Malaria

R21 Malaria DS bulk manufacturing area located at the SIIPL Hadapsar site were visited during the inspection. However, no malaria-related activities were being performed at the time of the inspection, so an overview of the manufacturing process was provided. Clarification on personnel/material/reagents flows and cleaning/sterilization procedures were provided. A multi-product filling line was used for the DP R21 malaria vaccine. The filling line equipped with an isolator in Grade C room condition was used for the production of other products, including Covid vaccine and HPV. The filling operation of HPV production was observed at the time of inspection.

- ***Waste management:***

The SOP for Decontamination of Used Material (BCG Manufacturing Facility) was reviewed. All decontaminations were performed in Autoclave.

- ***HVAC***

The SOP for HVAC Qualification, Routine Monitoring Continued Compliance, and Requalification Guidelines was spot-checked. The procedure described the initial IQ, OQ, and PQ. Requalification (named continued compliance) was performed every six months for grades A and B and yearly for grades C and D.

- ***Water system***

Hexavalent

The water system at the SIIPL Hadapsar site, including PW, WFI, and steam facilities, was spot-checked. P&ID was available for review. The clean steam sampling points were not specified and were corrected by the company during the inspection.

MenFive

The water system at the SIIPL Hadapsar site was visited and found in accordance with the P&ID available.

The SOP describing the sampling of water and pure steam condensate (Hadapsar) was reviewed. The Water and Pure Steam Monitoring Summary Report for 2022 was presented. The SOP for Trend analysis of microbial results was spot-checked. Trending of EM and the Water system data, performed quarterly, was reviewed.

BCG

PW, WFI, and PS systems were visited and checked according to the P&ID. The Procedure for Operation of Water for Injection Storage and Distribution System (Manjari Plant) and the Trend Analysis and

documentation of trend summary report for water testing, Quarterly summary report for water testing results, and Trend review report of water and pure steam (micro testing) were spot-checked.

- ***Compressed air system***

The compressed air system generated at the SIIPL Hadapsar site was supplied for formulation and filling areas. Its P&ID and annual summary 2022 of compressed air were reviewed and discussed. The compressed air distribution system was checked during the inspection.

- ***Nitrogen***

Nitrogen was procured in cylinders. The distribution system for the BCG facility was checked. The quality of the Nitrogen cylinder was tested on every consignment. The farthest point was sampled and tested quarterly. All user points were tested annually (for assay and micro). The schedule for the year 2023 of the BCG facility was checked.

Qualification and validation:

The Validation Master Plan for the Manjari Site was documented and approved. The matrix for BCG was spot-checked. The Hadapsar Site Validation Master Plan and the matrix for the filling line were checked, as was the report for 2022.

Computerized systems validation (CSV)

Computerized systems were used in the warehouse and production. There was a LIMS in QC. Analytical instruments such as HPLCs were networked with a computerized system. A summary of all activities, a list of standalone systems, a summary of CSV, a List of SOPs related to CSV, and data life cycle management were provided for review.

Aseptic Process Simulations:

BCG Facility

SOP for Aseptic Process Simulation (Manjari Plant) was spot-checked. The facility was initially validated with 3 bulk runs. Requalification was performed every 6 months with one run. No contamination was ever noted for the BCG process simulation. Bulk APS and Filling APS for the BCG vaccine in the Manjari site were reviewed.

Hadapsar Site

An SOP for Media Fill Process Simulation was in place. The Protocols and Reports were spot-checked.

Equipment qualification

The equipment installed was multi-purpose, and each piece of equipment had a unique identification number.

Autoclaves

The SOP for the Validation of the Autoclave and autoclave requalification report for the Autoclave was spot-checked. Autoclave loading patterns were validated and documented in SOP. Bowie Dick test was

routinely performed. The requalification report of the autoclave, used MenFive filling parts, vessel, product filter, and rubber stoppers was reviewed.

Depyrogenation Tunnel:

The SOP for a validation study of the depyrogenation tunnel defined that initially, 3 runs were performed for each vial size, and requalification was performed every year with one run for each vial size. The requalification of the depyrogenation tunnel was spot-checked.

Lyophilizer

The requalification of Lyophilizers performed yearly was checked. The report regarding the yearly SIP cycle requalification was also presented. An assessment for sterilization of lyophilizers after every batch was presented, describing the company's plan to implement sterilization of the lyophilizers before every batch.

Filling and stoppering machine:

The filling line 1 used for the Hexavalent vaccine was visited, and the HEPA Filter Integrity test and Air velocity document were reviewed.

Disinfectant Validation:

Validation protocols and reports for disinfectant efficacy were spot-checked.

Fumigation or decontamination of the manufacturing facility:

Fumigation was performed when there was a major shutdown or for product changeover. The protocol for the fumigation effectiveness study and the respective report were spot-checked. Representative coupons of each surface of the clean area were exposed to the area during fumigation.
Fumigation performed for the isolator in the filling area was reviewed and found acceptable.

Cleaning validation:

The SOP for the Cleaning Validation of the Hadapsar Plant was spot-checked. For product contact parts, 3 runs were initially validated. Cleaning verification was performed monthly and during the changeover. The cleaning validation protocol for MenFive contact material was reviewed and found acceptable. As per the validation protocol, all the materials used for this product are dedicated to each group of vaccines, including the tubing, needles, blending vessels, and pumps. MenFive parts were shared with other polysaccharide-conjugated vaccines (Hib and MenA). This was verified in the assignment of equipment for products, where a coding system was established for each of the dedicated materials (e.g., pumps, blending vessels).

Campaign changeover procedures were spot-checked.

The deficiencies noted in this section were adequately addressed and will be verified during future PQ inspections.

4 Laboratory control system

BCG quality control located at the SIIPL Manjari site was inspected. The BCG testing, specifications, media and reagent preparation were explained.
During this inspection, the micro lab located on the SIIPL Hadapsar site, which is responsible for EM, Sterility, and Bacterial Endotoxin tests, was also inspected.
The animal facility hosting a nursery and testing room for several *in vivo* QC tests was visited.
Documents regarding QC sample receiving and distribution, receipt, storage, and usage of biological indicators, microbial identification, and Container Closure Integrity test (CCIT) were spot-checked.
Potency and antigen content tests for some of the components of the HEXASIIL vaccine were observed during the inspection.
R21 malaria vaccine identity and antigenic ratio tests were also demonstrated during the inspection.
Instruments calibration was spot-checked.

Out-of-specification (OOS) management:

The SOP for handling OOS in microbiology, SOP for sterility testing, SOP for handling OOS (Manjari site), OOS Electronic e-log system, and some OOS records were spot-checked.

Analytical method validation

The analytical methodology used in the testing and release of the drug substances and drug products were properly validated.

Validation of Excel spreadsheets

Excel spreadsheets to calculate QC results were validated against WHO, EU, or GAMP 5 requirements. Spot checking on site assured that the reviewed spreadsheets were fit for purpose and ensured data integrity.

Reference Standards

In-House Reference Standard (IHRS) qualification was spot-checked.

Stability:

The SIIPL Hadapsar site, where several stability chambers were located, was visited. Some stability studies and results were spot-checked.

Retention Samples

Retention Samples storage at SIIPL Hadapsar and Manjari sites were visited. A SOP for the management of quality control samples, retention samples, reference samples (drug substance), and CDL Samples was in place. The SOP defined the amount for retention as 2 times the amount needed for full test. Samples are stored for 1 year after the expiration date.

Environmental monitoring results:

The Environmental Monitoring Plan for the Manjari Site and related risk assessments for EM locations definition were reviewed. Alert and action levels were established. Trends were evaluated monthly, six-monthly, and yearly. The Trend Review Report for the BCG Bulk and Filling area was spot-checked. The report concluded that no adverse trend was detected. An SOP describing the selection of microbial flora for microbial identification was in place. A summary of environmental monitoring isolates was used to define the representative EM isolates. The protocol for evaluation of the impact on recovery of the microorganisms after completion of environmental monitoring and incubation and respective reports were reviewed.

A procedure for Microbiological Monitoring of Cleanrooms at the Hadapsar site, including the definition of alert and action limits, was in place. Some EM excursion investigations were selected for review.

The deficiencies noted in this section were adequately addressed and will be verified during future PQ inspections.

5 Materials management:

Seven warehouse facilities were available at the Hadapsar site, and two warehouses were available for the Manjari site.

Incoming materials and finished products were quarantined after receipt until they were released for use or distribution as per SOP for receipt, registration, and testing of quality control samples, reporting, and review of analytical data.

Starting materials and packaging materials were purchased from approved suppliers and stored in different warehouse rooms under the specified conditions. Materials were managed by a hybrid system, including a computerized and manual system for material status labels. Some warehouses were briefly inspected, and no objectional comments were made.

6 Packaging and labelling system:

<u>BCG Labelling and Packaging</u>

Labelling, Packing, and dispatch activities were performed at the SIIPL Manjari site. A flow chart of the packing process was explained. Labeling and packing operations were not in progress at the time of the visit.

Labeling lines were separated by physical barriers or divisions. There were two main lines, and another was dedicated to labeling and packing a combo (vaccine vial + diluent) for the domestic market. The packing line was semi-automatic. There was no labeling or packing activities at the time of the visit.

The BCG leak test was performed on 100% of BCG batches. The leak testing machine was not in operation at the time of the visit. The machine could discriminate and separate vaccine vials with structural defects from those that failed the pressure vacuum by laser spectroscopy. This leak-testing machine was installed in 2018 and validated (IQ, OQ, and PQ).

In the cold room where BCG batches were stored at 2 - 8°C, batches were properly identified as per the label system in place by QA. Several batches were already packed and samples sent to CDL, Kasauli, for final release.

Dispatch activities diagrams were available for the staff who prepared the shipping boxes. No activity was executed during the time of the visit.

7 International shipping

Following the publication of the 6th edition of the WHO shipping guidelines, SIIPL launched a program to meet WHO requirements. The company has collected ambient route data by including external data loggers in each shipment of UNICEF, PAHO, and private customers on various shipping lanes and routes across all continents of the world. Eight routes were identified (Asia - Southeast and Middle East; Oceania; Africa - North / Desert – Central / South / East; Europe; America – North / South). A total of 14 profiles were created. With the help of a thorough comparative analysis of profile data and mean kinetic temperature values and transit elapsed duration of the journey, two profiles were selected to represent all 14. Profiles were in step graph format. All shipping solutions were qualified operationally.

The Cold Chain Validation Protocol - Transport Route Profiling Study and Qualification of Packaging Solutions for International Packaging and Shipping of Vaccines was reviewed. The Cold Chain Validation Protocol and report on the qualifications of various shipping solutions were provided. The data generated was huge, and based on the same, SIIPL supported the use of different packaging solutions depending on the vaccine class, as defined in the most recent review of the WHO vaccine shipping guidance document.

Part 3	**Conclusion – Inspection outcome**

Based on the areas inspected, the people met and the documents reviewed, and considering the findings of the inspection, including the observations listed in the Inspection Report, **Serum Institute of India Pvt. Ltd.**, located at **212/2, Hadapsar, Pune, 411 028 India** and **S. No. 105-110, Manjari Bk. Pune, 412 307 India** was considered to be operating at an acceptable level of compliance with WHO GMP Guidelines.

All the non-compliances observed during the inspection that were listed in the full report, as well as those reflected in the 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 WHO 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-eight Report Geneva, World Health Organization, 2014 (WHO Technical Report Series, No. 986), Annex 2. ***Short name: WHO TRS No. 986, Annex 2***
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http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

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http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_981/en/

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