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

Part 1	**General information**
Manufacturers details	
Name of manufacturer	**GreenSignal Bio Pharma Private Limited (GSBPL)**
Corporate address of manufacturer	Old No. 5, New No. 13/A3, Sai Nikethan, Circular Road, United India Colony, Kodambakkam, Chennai- 600024, India
Inspected site	
Name & address of inspected manufacturing site if different from that given above	No. 49, Pappankuppam Village, Gummidipoondi, Chennai - 601201, India GPS Coordinates: Latitude: 13.417269: Longitude: 80.097202
Unit / block / workshop number	Facility 1 and Facility 2
Inspection details	
Dates of inspection	10-14 June 2024
Type of inspection	Initial inspection for the new application for prequalification of the BCG vaccine (freeze-dried) - Intradermal, 20 doses.
Introduction	
Brief description of the manufacturing activities	GreenSignal Bio Pharma Private Limited has been established as a Vaccine Manufacturer in India since 2005. The products authorized included BCG Vaccine & BCG for Immunotherapy Product. The BCG Vaccine manufactured by GSBPL has been supplied through the Indian Government's Universal Immunization Programme. The manufacturing unit is located at No. 49, Pappankuppam village, Gummidipoondi, Chennai- 601201. It is about 55 Km from Chennai and has a plot area of 1.39 acres.
General information about the company and site	The site's environment is free from pollution and hazardous chemicals. The site has two facilities (Manufacturing facility-1 and Manufacturing facility-2) both dedicated to manufacturing BCG Vaccine and BCG for Immunotherapy. No other manufacturing activities are performed on the site. The built-up area of Manufacturing Facility-1 is 40,669 sq. ft, including a separate area for labelling, packaging, and storage of finished products. The built-up area of Manufacturing Facility-2 is 47,368 sq. ft, including a warehouse, labelling/packing area, and Production office in the same block. Support functions include Quality Control, Animal House, Quality Assurance, Engineering, and Warehouse, located on individual floors. The utility services include a compressor and boiler on the service floor, MV Electrical panels as a separate individual block, and the transformer and Diesel generator are kept outdoors.

History	After the WHO inspection conducted in 2019, the company started a refurbishment project to reduce manual interventions and increase the capacity of the Lyophilizer to meet the demands of the Indian Government's Universal Immunisation Programme and UNICEF.
Brief report of inspection activities undertaken – Scope and limitations	
Areas inspected	Manufacturing facility-1, Manufacturing facility-2, and related QC labs, warehouses, and utilities.
Restrictions	N/A
Out of scope	Products and vaccines other than the BCG vaccine were not inspected, and the manufacturing of the diluent (outsourced) was not covered during this inspection.
WHO products covered by the inspection	BCG vaccine (freeze-dried) - Intradermal, 20 dose The lyophilized active component must be reconstituted with excipient diluent before use (vial and ampoule).

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
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-Spec	Ultraviolet-visible spectrophotometer
WFI	Water for injection

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

1. Pharmaceutical quality system (PQS)

Overall, the principles of Quality Management were in place. A Quality Manual stating the Quality Policy and defining the Quality Management System (QMS) was presented.

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

Management review (MR):

An SOP was in place for Quality Management Review. Management Review Meetings were conducted once every six months. The minutes of the most recent meeting were spot-checked.

Product quality review:

The procedure for preparing the APQR was presented. The SOP and the APQR covered drug substance (DS) and drug product (DP). The data used to prepare the APQR was extracted from the batch records. The APQRs for BCG vaccine for the years 2022 and 2023 were reviewed.

Quality risk management:

Assessment of individual risks related to specific products and starting materials and the recognition of hazards at specific stages of production or distribution was carried out as per approved SOP for Quality Risk Management. This was applicable for both Manufacturing facility-1 & Manufacturing facility-2. According to the procedure, Risk Assessments were performed using the Failure mode effects analysis (FMEA) tool to assess, manage, and reduce risks. The Risk Priority Number (RPN) was determined by multiplying the severity, occurrence, and detection rates. The risk assessment logbook and some risk assessments were reviewed during the inspection.

Contamination Control Strategy (CCS)

A CCS was in place and was presented. The minimum review frequency was defined as yearly.

Deviation management:

The SOP for Event Reporting System and Failure Investigation, described the guidelines for identifying, reporting, initiating, taking immediate actions, conducting initial impact assessment, categorization, investigating, identifying root causes, tracking, conducting final impact assessment and review, approving, and closing quality events. A trend investigation was initiated when a recurring pattern was identified. Some deviation records were spot-checked.

CAPA management:

The company's procedure for Management of Corrective Action and Preventive Action covered the initiation, review, CAPA plan, approval, tracking, CAPA implementation, verification, effectiveness, and closure. This procedure was applicable to all relevant GMP activities at GSBPL. Based on the investigation findings or quality events, the quality system could identify and implement an appropriate corrective and preventive action plan. Depending on the findings of the investigation/ quality events, an appropriate corrective and preventive action plan could be identified and triggered from the quality system. Some examples were reviewed during the inspection.

Change control (CC):

Changes in the approved facility, equipment, material, process, formula, analytical, and/or controls were routed through the change control system. Change control was initiated by the user (owner of the activity) and reviewed by qualified representatives from appropriate disciplines, including quality and regulatory discipline (if applicable). The review evaluated the impact of change on the validated status of the facility and equipment and purity, safety, and efficacy of the final product and/or regulatory compliance, including the registration status by cross functions, and finally, it was approved by the QA Head. Some change control records were spot-checked.

Complaints:

Product complaints were handled as per the approved SOP entitled "Handling, Investigation of Product Complaints (Quality Related and Adverse Events) and Control of Recalled Product". All product complaints received by GSBPL were registered in QA. Based on the nature of the complaints, they were categorized into two types: Adverse Drug Event Report (ADER) or Quality-related complaints (e.g., variation of fill volume, improper labeling, compromised container/closure system). Adverse events complaints were evaluated by a medical doctor and categorized as per ICH-E2E pharmacovigilance guidelines. A multidisciplinary team led by QA evaluated quality-related complaints. If any deviation was found, a deviation report was opened to conduct the investigation, root cause analysis, and CAPA definition. Since 2021, no complaint has been recorded.

Product recalls:The circumstances under which a product recall was considered were handled per the recall procedure. Recalls were classified as class I (wholesaler/distributor, retail, and customer), II (wholesaler and retail), and III (wholesaler). They could be voluntary or statutory. For export products, based on a product recall notice issued by QA, responsible personnel in the international marketing department shall pass on the information to relevant regulatory authorities, applicant agents, and distributors located in exporting countries. According to the procedure, a mock recall should be performed annually for the longest distribution chain and maximum number of distributors.

Self-inspection:

As per current SOP for audit program (Self-inspection), the site performed internal audits regularly, at least biannually. The quality assurance department prepared a self-inspection plan presented during the documentation checking. Based on incidents, market complaints, external audit observations, OOS, and repetitive failures upon the Quality Head's recommendation, unscheduled internal audits may also be carried out at the site. The schedule was organized, and the annual plan was issued for the 2024 fiscal year was presented. The findings related to the self-inspection execution were typically classified as critical, major, and minor observations. Based on the report's issuance and reported findings, a timeframe was established for CAPA completion. However, the deadline could be extended. Designated and qualified auditors had minimum and required experience in the relevant pharmaceutical industry and QMS. Some internal audit reports were spot-checked.

Quality audits and suppliers' audits and approval:

The quality unit approved specifications for all critical raw and packaging materials used in production and quality control. All materials required for manufacturing and testing were procured from qualified vendors or wholesalers. Critical vendor qualification involved site visits and testing of representative samples, wherever applicable. An approved procedure was also in place for service vendor.

Vendor qualification was carried out by conducting onsite inspection or obtaining a filled vendor evaluation questionnaire, reviewing the results of evaluation samples by QC and production suitability.

After receiving a satisfactory compliance report, the QA included vendor's name in the material management control system, and the approved vendor list was amended and communicated to the purchasing warehouse and QC departments. Suppliers and contract services were categorized as critical and non-critical based on the material category criticality. Critical vendors were reaudited at least once every two years for performance assessment, while non-critical vendors were audited once every three years.

A list of contractors and testing laboratories, including addresses and contact information, was provided. Some supplier audit records were spot-checked.

Contract production, analysis and other activities and Quality agreements:

The responsibilities shared between the contract giver and the contract acceptor were defined through a quality agreement. The QA team and the user department drafted the agreement conditions, which outlined the roles and responsibilities of the contract agency/supplier and GSBPL. Third-party or external service providers were identified, evaluated, and qualified based on an approved procedure.

Personnel

Organization, organogram, independence of production from quality control:

The current site organogram, key personnel information, and the total number of qualified employees working in various departments and roles were presented. The site appeared to have sufficient personnel trained in applicable GxP/job-specific functions required to manufacture, release, and distribute vaccines in accordance with GMP principles.

- ***Training:***

Site management was responsible for implementing a training program for each employee, and the respective manager/team leader was responsible for defining training needs in addition to QS-defined mandatory training. HR was responsible for establishing, maintaining, and assessing employee performance and QA was responsible for overall/specific training program for all employees on the site. The needs for retraining or refreshing training sessions were identified if the employee gets new responsibilities, a new job position, returning to the site after leave, or as part of a deviation. Training records consisted of several documents described in the procedure for GMP training and the employee training file history. The site's training program also covered any contractors or temporary staff. Some relevant training records were reviewed.

- ***Personal hygiene:***

Changing rooms were provided, and toilets were placed at the entrance to the manufacturing area. As per internal rules, food or drinks were prohibited inside the manufacturing facilities and associated compartments. When entering a restricted area, the employee changed clothes from private to site-manufacturing clothes according to gowning procedures. Procedures were in place to establish the hygiene standards. There were approved procedures for entering the classified manufacturing workshops and QC areas. Gowning requirements were clearly defined in a SOP. Only authorized personnel could enter the manufacturing and testing facilities.

- ***Health Requirements for personnel engaged in production.***

Health monitoring of personnel and visitors/auditors, all personnel engaged in production and working in critical manufacturing operations were regularly submitted to medical checkups (eye check, chest X-ray, routine tests), including vaccination shots. They must be healthy and cannot enter the manufacturing facilities if they have open wounds or other health abnormalities. All employees were responsible for reporting sickness to their manager, and individuals with infectious diseases were not allowed to work in the manufacture of products. Visitors must also report sickness or other relevant health conditions to their host. Some medical records were spot-checked.

- ***Qualification of aseptic operators in Grade B areas:***

Approved procedures were in place for aseptic behavior and technique in the aseptic area. Gowning requirements for entry into classified areas were defined in a SOP. Based on acceptable personal hygiene practices, the operators wore appropriate gowning according to the relevant area classification. Measures were in place to qualify the aseptic gowning techniques and retrain operators frequently. The operators followed proper cleanroom behavior as per training guidelines and gowning procedures. As noticed during the plant walk-through, the operators working in Grade A or B cleanrooms were adequately trained and certified in gowning procedures. They showed satisfactory knowledge and skills in aseptic procedures.

Documentation:

According to the Quality Manual, the Quality System document organization was organized into four levels. GSBPL had a document management system consisting of written procedures to control creating, issuing, revising, handling, archiving, and obsoleting GMP documents. The GMP documents were maintained in an entirely paper-based documentation management system. Effective and obsolete versions of SOPs and the subset of documents were marked and provided with an effective date. Each document had a unique document number and was version-controlled. Overall, the documents were available as paper copies in controlled binders. Records were stored in an access-controlled archive room located on-site. Document archival and retrieval followed the instructions, and they were under the control of Quality Assurance at the site. The retention period for documentation associated with the product's manufacture was defined in compliance with GMP regulation.

Batch Release Process and Lot Summary Protocol (LSP):

After the production of a batch, the BMRs and BPRs were reviewed by QA for correct entries, calculations, yields, analysis, and deviations, if any. Samples were submitted to Central Drug Laboratory (CDL Kasauli), with the LSP after satisfactory verification of the batch according to product specifications. Upon receipt of the release certificate from CDL, Kasauli, the head of QA, or his designee, undertook the product's final release through a release order. Responsible QA personnel issued a separate batch release certificate for each batch. A typical lot summary protocol was presented and found to be in compliance with what the PQ applicant submitted as part of the vaccine prequalification application. It was also aligned with the WHO recommendations.

2. Production system

The BCG vaccine is a freeze-dried vaccine derived from the live attenuated strain of *Mycobacterium bovis*, originally generated by Calmette and Guerin at the Pasteur Institute, France, through in vitro attenuation of a strain of *Mycobacterium bovis*. The *Mycobacterium bovis* strain, which has been attenuated over time, is demonstrated to be non-pathogenic and used for the prevention of tuberculosis. The GSBPL vaccine is based on the Danish 1331 BCG strain.

The labeled claim was 2 - 8 x 10^6 CFU. The vaccine is reconstituted with 1.0 mL ampoule of sodium chloride injection (0.9%w/v). Each 1mL of reconstituted vaccine is equal to 20 doses (0.1 to 0.4 million CFU/dose) and equal to 10 doses (0.2 to 0.8 million CFU/dose). The standard dose of reconstituted BCG vaccine is 0.05 mL of the reconstituted vaccine for children up to 1 year, equivalent to 0.1 to 0.4 million CFU and a dose of 0.1 mL for children over 1 year and adults, equivalent to 0.2 to 0.8 million CFU.

The vaccine shelf-life is 24 months from the date of manufacturing, which is considered the date of the initiation of the viability test.

The production process of the BCG vaccine was presented during the inspection.

The vaccine was filled in amber-colored vials, half stoppered and then lyophilized.

After lyophilization was finished, vials were fully stoppered inside the Lyophilizer and unloaded for sealing.

The BCG vaccine (lyophilized product) vials were 100% inspected after the freeze-drying and sealing steps were completed. The vials were observed under a white background followed by a black background. Defects were categorized as critical, major, and minor. Rejection rates were established to identify atypical lots. The rejection was trended and classified. Following the 100% manual visual inspection, a statistically valid sample was taken from the units accepted by the inspection process (Acceptance Quality Limit - AQL). Operators were qualified and eye tests were conducted. During the visual examination of the finished product vials and had breaks according to the defined procedure. Defective vial photos were displayed or available for reference to the defects that could be encountered during the revision.

Process Validation

The policy on process validations was outlined in the Validation Master Plan. Process validation studies were conducted in accordance with the pre-approved validation protocols. The specifications used during validation were consistent with the commercial specification, and the methods of analysis were also validated.

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

Batch manufacturing record review (BMR):

Some selected batch records were reviewed during the inspection.

3. Facilities and equipment system:

The facilities at GSBPL included Manufacturing Facility-1 and Manufacturing Facility-2. Both facilities were dedicated to BCG products (Vaccine and BCG for Immunotherapy) and were visited during this inspection.

The site had a dedicated Effluent Treatment Plant (ETP) and Sewage Treatment Plant (STP) setup as per the CPCB norms.

The layouts of production areas were reviewed, including material flow, personnel flow, and general flow charts of manufacturing processes. Room finishes were smooth, cleanable, chemically resistant, and non-flaking. Support area finishes were GMP compliant.

The refurbished premises were designed and renewed to permit effective cleaning and maintenance, avoid cross-contamination, and meet the GMP expectations for vaccine production.

Both Facilities 1 and 2 production areas were of similar design, including the culture room with the respective supporting areas (media preparation, sterilization, cool zone, incubation rooms, airlocks, etc.), the bulk pooling room (formulation), and the filling and lyophilization room with the respective supporting areas (vial washing, washing and sterilization, cool zone, airlocks, etc.). All the open activities (culture, harvesting, pooling, formulation, and filling) were conducted in grade A/B environments since all the production was performed as an aseptic process.

The filling line was fully integrated with washing, depyrogenation, filling, and Lyo loading/loading under oRABS. The filling machines were equipped with an automatic statistical weight check system and no vial, no filling system. The lyophilizers were fitted with an Auto Loader, Unloader, Automatic CIP and SIP. Continuous monitoring of all critical areas was performed through BMS.

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

Qualification and validation:

The Validation Master Plan was in place to ensure facilities/ Equipment are qualified, and all systems, processes, and analytical test methods are validated. Qualification was performed in the phases of URS, impact assessment, risk assessment, DQ, FAT, SAT, commissioning, IQ, OQ, and PQ. The VMP included cleaning, process, analytical method, and shipping validation.

Revalidations/Re-qualifications were carried out at defined frequencies. The validation activities were planned according to a matrix. The 2024 Validation Matrix for Manufacturing Facility 1 was presented.

QA in coordination with Engineering /user departments executed the qualification/validation activities /Users through approved protocols. Results generated during the qualification/ validation activity were reviewed and approved by QA to ensure compliance with pre-determined specifications and acceptance criteria. Changes in the qualified facility, equipment, process, formula, analytical, and/or controls were routed through the change control system. During the change control review, the impact of the change on validated status and regulatory compliance was evaluated.

Calibration and Preventive Maintenance

Calibration of instruments in Manufacturing facility-1 and Manufacturing facility-2 was carried out according to the respective SOP. The instruments in the facility were categorized into two groups. The instrument calibration categorization was based on the criticality of their usage in the process, and the calibration frequency was based on criticality. Master Calibration Planner and a master list of the year were prepared by Engineering personnel, reviewed by the Engineering head, and finally approved by QA.

Preventive maintenance was performed in accordance with the QA-approved program, the annual planner oversight, and documented service frequencies. Overall, it consisted of part/material replacement, certification, and calibrations.

Qualified personnel or qualified vendors performed maintenance, calibrations, and repair activities per controlled procedures and programs. Records of maintenance, calibration, and service performed on the equipment were securely stored and maintained per the established record retention policy.

Maintenance methods and intervals for maintenance and calibration of equipment were performed as described in an approved procedure. They were developed in accordance with the manufacturer’s recommendations, qualification and process requirements, industry standards, risk assessments, and maintenance performed on similar or similar equipment.

During the plant walk-through, it was noticed that all major equipment was clearly labeled with the corresponding PM/calibration status and assigned an expiration date.

Aseptic process simulations:

Aseptic Process Simulations (APS) were performed according to the respective SOP. Initial validation with 3 consecutive successful media fill runs was performed, and after that, the APS were conducted once every 6 months.

Water systems:

Purified water (PW)

The schematics for generation and distribution system were reviewed. The PW was fully qualified as per validation report. The qualification phases demonstrated that the system operates within established ranges as per test protocol. No deviations were noted.

Water for Injection (WFI)

The schematics for generation and distribution system were reviewed. The plant 1 floor specific WFI generation & distribution system were qualified and validated as per respective protocols and reports presented during the inspection. The results obtained from this comprehensive qualification exercise provided stable quality indicators in the system's capability to generate, store and distribute WFI according to the required standards and was deemed to be fit and qualified for routine usage during GMP operations.

Pure Steam (PS)

Pure steam was generated by the evaporator principle. Pure steam condensate was routinely tested as per WFI specifications. Pure steam was also tested for non-condensable gases, dryness fraction, and degree of superheat according to a defined frequency. Qualification protocols and reports were spot-checked. Based on the raw data obtained and its statistical evaluation outcome, the installed PS met all the quality requirements. Annual reports were presented.

HVAC

The HVAC for Manufacturing Facility-1 was reviewed. The drawings for the AHUs were presented. Appropriate Ventilation and Exhaust arrangements were provided for areas such as Production, Stores, Quality Control, and Animal Testing Facilities. The drawing describing the pressure cascade was presented. Differential pressures were continuously monitored.

The Requalification Protocol and the Requalification Report for the HVAC System were spot-checked.

4. Laboratory control system

The Analytical Quality Control and Microbiology laboratories were part of the quality department. The Quality Control department comprised the Chemistry testing group (Biochemistry), the Animal House group and the Microbiology group. The main functions of the Quality Control department were summarized as: sampling, inspection, testing and release of raw materials against written specifications describing acceptance and release criteria; managing the environmental monitoring program, including air, water, process gases and surface monitoring; testing of in-process, bulk Drug Substance and final

product samples, testing of samples to support validation activities, coordinating testing by external contract testing companies as required, storage of retention sample, management of stability program.

Retain samples were stored in cold chambers. Retention samples were tracked in the respective Logbook.

Animal House Breeding & Testing Facility

A plant walk-through was conducted in the animal house breeding facility, which includes the breeding room, testing room, stabilization room, post-mortem room, and support rooms. The animal house has been accredited according to Indian regulations. During the tour, the sample workflow and sample preparation for the absence of virulent Mycobacteria (safety test) for the intermediate product was followed. No abnormalities were found.

Out-of-specification (OOS) management

A SOP for Handling and investigation of out-of-limits (OOL)/out-of-specification (OOS) was in place and was applied to any out-of-limits (OOL) or out-of-specification (OOS) incidents reported in the QC department in relation to any raw material, packing material, water, or product (including intermediates and finished products) for Manufacturing facilities -1 and -2 of GSBPL. The procedure outlined the responsibilities, identification and classification of OOS results, handling of OOS and OOL results during different investigation phases, tracking and numbering, reporting methods, guidance for the investigation, and applied methods for Laboratory Investigation (Phase 1) and Phase II. Specific sections addressed the handling of sterility failures, out of Alert/Action limit incidents, and BET failure investigation guidance.

Some records of OOS/OOL were spot-checked.

Reference Standards

The procedure for standardizing in-house reference standards (IHRS) was in place. Every six months, the QC performed the trending of quality attributes of the material in use. The last review conducted was presented. The stability of the standard appeared to be on trend and well monitored during the studied period. Values between testing batches and the in-house standard were verified and cross-checked.

Stability

The report presented the stability protocol and ongoing stability data. The data suggested the vaccine was stable for 24 months when stored at 2 - 8°C. Additionally, the stability data, which supported the hold time for intermediates, was examined and deemed satisfactory.

Environmental monitoring:

An Environmental Monitoring Program was in place. The sampling locations were defined based on a risk assessment. Action and alert levels were defined. The Trend Analysis Summary and Conclusion Report for Manufacturing Facility 1 for April 2024 was spot-checked. The quarterly summary record for the identification of microorganisms was also presented.

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

5 Materials management:

Relevant standard operating procedures documented the GMP materials receipt and handling procedures. Raw materials were received into the goods receiving area. Raw materials were received from approved vendor/supplier and the items were checked against the supplier's delivery note to ensure that material conformance, quantities, descriptions, and suppliers' batch/lot numbers were agreed upon and that the external packaging was not significantly damaged. Information regarding the item was recorded in a paper-based inventory system. Raw materials that required inspection and testing were inspected against written specifications, sampled as per sampling plans, tested by Quality Control, and either released or rejected by the Quality Unit following standard operating procedures.

Approved materials were placed into stock using a paper-based warehouse management system. Different rooms were designated for materials in various status. Procedures for handling rejected materials were in place. There was a dedicated room for the weighing of materials upon request from the manufacturing department. Storage condition for seed lots, VVM labels, and filled vials were also checked. The temperature was monitored in real-time via BMS and was also manually checked on-site thrice daily.

Preparation for dispatch activity, with requirements for cold chain packaging, equipment, storage, and handling requirements were handled through specific SOP. Additional requirements for the distribution of temperature-sensitive vaccines were followed as per respective SOP. The shipping validation was performed.

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

6 Packaging and labelling system:

Visual inspection, packaging and labelling activities were carried out in the same area. Procedures for line clearance were in place. After labelling, samples were collected and sent to CDL, Kasauli. The packaging process was semi-automated. The vaccine boxes were transferred to the cold room of the Dispatch Department. Packed vials were stored in a cold room. The respective number of diluents were packed with batches of BCG vaccine. The BCG vaccine was shipped at 2-8^{0}C. A temperature logger was placed in the shipper to monitor the temperature constantly during shipping.

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, **GreenSignal Bio Pharma Private Limited (GSBPL)**, located at **No. 49, Pappankuppam Village, Gummidipoondi, Chennai - 601201, 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-eighth Report Geneva, World Health Organization, 2014 (WHO Technical Report Series, No. 986), Annex 2. ***Short name: WHO TRS No. 986, Annex 2***

2. WHO good manufacturing practices for biological products. WHO Expert Committee on Biological Standardization. Sixty-sixth Report Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 999), Annex 2. ***Short name: WHO TRS No. 999, Annex 2***

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***

4. Good manufacturing practices: guidelines on validation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-third report. Geneva, World Health Organization, 2019 (WHO Technical Report Series, No. 1019), Annex 3. ***Short name: WHO TRS No. 1019, Annex 3***

5. 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***

6. WHO Good Practices for Pharmaceutical Quality Control Laboratories. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-seventh Report. Geneva, World Health Organization, 2024 (WHO Technical Report Series, No. 1052, Annex 4.
   Short name: WHO TRS No. 1052, Annex 4

7. 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 3.
   Short name: WHO TRS No. 957, Annex 3

8. WHO good manufacturing practices for sterile pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-sixth Report Geneva, World Health Organization, 2022 (WHO Technical Report Series, No. 1044), Annex 2. ***Short name: WHO TRS No. 1044, Annex 2***

9. 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***

10. 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**

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***

12. 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***

13. 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***

14. 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***

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***

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***

17. WHO general guidance on variations to multisource pharmaceutical products. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fiftieth Report* Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 10. ***Short name: WHO Multisource guidance*** or ***WHO TRS No. 996, Annex 10***

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