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Prequalification Unit Inspection Services
WHO PUBLIC INSPECTION REPORT
(WHOPIR)
Finished Product Manufacturer
(VACCINES)

Part 1	**General information**
Manufacturers details	
Name of manufacturer	**Biological E. Limited.**
Corporate address of manufacturer	Road No. 35, Jubilee Hills, Hyderabad, 500033 Telangana, India.
Inspected site	
Name & address of inspected manufacturing site if different from that given above	**Shameerpet site**: Plot No.1, Biotech Park, Phase II, Kolthur Village, Shameerpet, Medchal-Malkajgiri District, Telangana State – 500078, India Latitude : 17.6650900, 78.6193950 Longitude : 17° 39' 54.32" N, 78° 37' 9.82" E D-U-N-S (Data Universal Numbering System) No.: 65-037-6874 **SEZ site**: Sy. No. 549, 550 & 552 to 556, Kolthur Village, Shameerpet, Medchal-Malkajgiri District, Telangana State – 500078, India Latitude: 17.667635, 78.626586 Longitude: 17°40'03.5"N 78°37'35.7"E D-U-N-S (Data Universal Numbering System) No.: 65-037-6874
Inspection details	
Dates of inspection	24 to 28 February 2025
Type of inspection	Initial inspection for PNEUBEVAX 14®-Pneumococcal Polysaccharide Conjugate Vaccine (Adsorbed) (14 Valent) and Measles Vaccine (Live, Attenuated, Freeze Dried). Routine inspection for Measles and Rubella (MR) vaccine.
Introduction	
Brief description of the manufacturing activities	Biological E. Limited (BE) was established in 1953 and was one of the first Indian pharmaceutical companies to be founded. BE manufactures a range of Childhood and Adult Vaccines, Pharmaceuticals (specifically anti-coagulants and anti-infectives), and Active Pharmaceutical Ingredients (API). BE has been producing Tetanus Toxoid (TT) Vaccines since the late 1960s, Diphtheria and Tetanus (DT), and Diphtheria, Tetanus, and Pertussis (DTP) vaccines since the mid-1970s. BE has been supplying the vaccines to the Extended Program for Immunization (EPI), ever since EPI commenced in India in the late 1970's. Later, the company introduced other vaccines like Hepatitis-B Vaccine, *Haemophilus influenzae* type-b Vaccine (Hib), Tetravalent Vaccine (DTP-Hep-B), IPV (Inactivated Polio Vaccine), Pentavalent Vaccine, Japanese Encephalitis (JE) Vaccine, Measles and Rubella vaccine, Typhoid Conjugate Vaccine, and nOPV2 Vaccine.

General information about the company and site	BE is approved by WHO for various vaccines to supply Single and Multiple Dosage presentations. BE has 4 manufacturing sites surrounding the Hyderabad city area: 1. Shameerpet site - Manufacturing of Bulk Vaccines; Blending, Filling, Testing, Packing and Distribution of Licensed Vaccines. 2. Gaganpahad site - Manufacturing, Testing and Distribution of Bulk Purified Tetanus Toxoid (BPTT) and manufacturing of bulk antitoxins/antivenoms. 3. Azamabad site - Registered office, Manufacturing of JE Bulk Vaccine and finished antitoxins/antivenoms, Testing and Distribution. 4. SEZ Unit - Manufacturing and Testing of Licensed Vaccines, which includes Blending, Filling, Testing, Labelling, Packing, and Distribution. BE's Shameerpet and SEZ manufacturing sites are approximately 40 Km away from Hyderabad city center, in the suburbs towards the north, and very near to each other. The administrative support is taken from the corporate office located at Jubilee Hills (within the Hyderabad city). Shameerpet site was commissioned in 2002 and is licensed for several vaccines from 2006 onwards. The site has several manufacturing blocks/ suites to produce the vaccine antigens and also has several lines for formulation, filling, labelling and packaging. The site is situated in 20.24 hectares of area located in Biotech Park, an industrial park dedicated for biotechnology companies. A new manufacturing site under Special Economic Zone (SEZ) was set up to import antigen and to manufacture (Blending, Filling, Sealing, Testing, Labelling, Packing and distribution) vaccines that are also approved at BE's Shameerpet site, Gaganpahad site and Azamabad site. The SEZ site is situated in an 11.33 hectares area, and the built-up area is 3.4 Hectares, located in a specific sector (SEZ) for Biotechnology and Biopharmaceuticals in Kolthur village, Shameerpet. This is an industrial park dedicated to biotechnology and pharmaceutical organizations. The initial production operations in SEZ site started in 2019.
History	The previous WHO inspection was conducted in January 2024
Brief report of inspection activities undertaken – Scope and limitations	
Areas inspected	• Blending and Filling Lines 2 and 4 of SEZ unit • Block-B at Shameerpet Site • Blending suites 1, 2, 3 and Filling lines 1 and 3 at Shameerpet site • Warehouses, utilities and related QC labs
Restrictions	Due to time constraints and prioritization of other topics, some GMP aspects were not covered during the present inspection (e.g., materials system, and packaging and labelling system at Shameerpet site).
Out of scope	Other vaccines and products not subjected to WHO Prequalification.

WHO products covered by the inspection	- PNEUBEVAX 14®-Pneumococcal Polysaccharide Conjugate Vaccine (Adsorbed) (14 Valent) - Measles Vaccine (Live, Attenuated, Freeze Dried) - Measles and Rubella Vaccine (Live, Attenuated, 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
PUPSIT	Pre-Use Post-Sterilization Integrity Test
PW	Purified water
QA	Quality assurance
QC	Quality control
QCL	Quality control laboratory
QMS	Quality management system
QRM	Quality risk management
RA	Risk assessment
RABS	Restricted Access Barrier System
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**

1. Pharmaceutical quality system

An appropriate quality system was established and implemented across the inspected sites. The firm's commitment to quality was clearly articulated in its Quality Policy. A Quality Manual, approved in August 2023, was available and maintained. Overall, the principles of a Quality Management System were in place, and the responsibilities of senior management were defined. The Quality Control (QC) and Quality Assurance (QA) functions operated independently from production activities. The QMS was consistently applied throughout the vaccine manufacturing sites, collectively referred to as the Biologics Division.

Some deficiencies were identified during the inspection; however, corrective and preventive actions (CAPAs) were proposed and accepted to address these issues.

Management review

Management reviews were conducted to ensure the continuing suitability and effectiveness of the Quality System and to serve as a communication mechanism regarding its overall health. These reviews were held quarterly in accordance with the company's procedure for Management Review Board meetings, effective since January 2024.

Key Quality Indicators (KQIs) were established and presented during these meetings to assess opportunities for improvement. The indicators included audit results, customer feedback, process performance, product conformity, the status of corrective and preventive actions, new or revised regulatory requirements, and organizational structure, including adequacy of staffing and resources.

Minutes and presentations from the most recent meeting, conducted in January 2025, were reviewed and found to be appropriately documented.

Product quality review

Annual Product Quality Reviews (APQRs) were conducted in accordance with the company's procedure for product quality review. The 2023 APQR for PCV14 was reviewed. The review included trend analysis of product quality attributes using statistical and process control tools, supported by electronic trending software.

Corrective and preventive actions (CAPAs) were proposed and accepted to address the noted deficiencies.

Quality risk management

The process for applying Quality Risk Management was defined in the site procedures. Annually, a quality risk assessment plan was prepared by QA, designating a QRM team. Tools used included FMEA, HACCP, FTA, and HAZOP.

For the SEZ Site, the list of risk assessments for PCV (formulation and filling, visual inspection, and contamination control strategy) was presented. For Measles vaccine, risk assessments covered bulk manufacturing and processes from blending through packing.

For Shameerpet Site, a list of risk assessments for Pneumococcal Polysaccharide Conjugate (drug substance and drug product) was available.

Deficiencies were identified, and CAPAs were proposed and accepted.

Contamination Control Strategy

A procedure was in place for Contamination Control Strategy. The following CCS documents were spot-checked:

1. CCS for Pneumococcal Polysaccharide Conjugate Vaccine (Adsorbed) (14 Valent) with preservative (multidose) manufactured at SEZ site.
2. CCS for Measles and Rubella Live Vaccine (freeze-dried).
3. CCS for Shameerpet site blending and filling, including an annexure related to PCV.

Deficiencies were noted, and CAPAs were proposed and accepted.

Deviation management

A procedure for handling deviations was in place. Deviations were defined as departures from approved instructions or established standards, and all GMP-related incidents were managed as deviations. Deviations were required to be reported immediately and recorded in the electronic system within one working day.

The initial impact assessment was performed by Quality Assurance (QA), followed by a formal investigation. All deviations were expected to be closed within 30 days of initiation, with any extensions requiring approval from QA leadership. The procedure also included a specific tool for assessing human error through structured interviews.

Quality Risk Management principles were applied during the generation of corrective and preventive actions (CAPAs). The reviewed deviations demonstrated compliance with these requirements, and CAPAs were proposed and accepted to address identified issues.

CAPA management

Corrective and Preventive Actions were handled as per the respective SOP, which applied to all sites. CAPAs were tracked electronically. Investigation methodologies described in the procedure included the Six-M Framework, the Five-Why technique, and Fishbone analysis. CAPAs were prioritized as high, medium, or low based on risk. Effectiveness checks were mandatory for critical deviations, while for major and minor deviations, the need for effectiveness checks was assessed by QA.

During the inspection, several CAPAs were reviewed. While most were implemented as required, some effectiveness checks were found to be inadequate. Corrective actions were proposed and accepted to strengthen CAPA verification and ensure consistent application of effectiveness checks.

Change control (CC)

Change control was managed through an electronic system in accordance with the company's procedure. The process covered changes to facilities, equipment, materials, manufacturing processes, formulas, analytical methods, and controls.

Each change was initiated by the responsible activity owner and reviewed by qualified representatives from relevant functions, including quality and regulatory. The review assessed the potential impact on validated status, product purity, safety, efficacy, and regulatory compliance, including registration requirements.

Lists of change controls related to PCV14 and CRM197 were presented for the relevant periods. Several changes were spot-checked during the inspection, including adjustments to process parameters, raw material trials, removal of certain tests, process validation activities, and revisions to cleaning procedures. Most changes were appropriately documented and closed.

Complaints

Complaints were managed according to the company's procedure for handling product complaints. The process required immediate communication to Quality Assurance (QA) and submission of related documentation and samples to the designated responsible person. Complaints were categorized into two types: medical events and quality-related issues.

For serious adverse events, a meeting with the complainant was organized within one working day, and regulatory authorities (including WHO/UNICEF) were notified within 15 calendar days of initial receipt of information. If investigations revealed any safety or quality concerns, product recall was initiated as per the established recall procedure. Investigations were expected to be completed within 45 working days, and complaint trends were prepared on a semi-annual basis.

During the inspection, the complaint trend report for January–December 2024 and a recent complaint record were reviewed.

Product recalls

Recalls and mock recalls were managed according to the company's procedure for product recall. Mock recalls were performed annually for the domestic market and every two years for the international market. Selection criteria included the longest distribution chains, the largest number of units supplied, and territories where product retrieval posed challenges.

The most recent international mock recall conducted in January 2025 was spot checked. The protocol for this exercise was reviewed during the inspection and found to be appropriately documented and implemented.

Self-inspection

Self-inspections were conducted according to the company's internal audit procedure, applicable to all manufacturing sites. The audit plan was managed electronically, and each area was inspected at least annually, with increased frequency in case of issues or deviations.

The procedure defined criteria for selecting Lead Auditors, including minimum experience requirements and prior participation in audits. QA personnel were part of the audit team and prepared checklists, reviewed previous observations, and assessed CAPA compliance. CAPA implementation and compliance with audit findings were the responsibility of the concerned department, while QA monitored progress and reviewed critical and major observations quarterly. Trends of recurrent deviations were prepared on a quarterly basis.

Audit plans for 2024 and 2025 were reviewed during the inspection and found to be appropriately documented and in progress for the current year.

Quality audits and suppliers' audits and approval

Supplier qualification was managed according to the company's procedure for selection, evaluation, approval, and qualification of vendors. The process began with vendor identification through a questionnaire, followed by evaluation steps including the review of sample batches, suitability assessment, audit, and establishment of a Quality Technical Agreement (QTA). Some QTAs were spot checked, including the manufacturer of the adjuvant Aluminium Phosphate.

A disqualification process was in place based on annual performance reviews. Audit frequency was defined as every three years for suppliers of critical materials and every five years for major materials. During the inspection, the qualification of the aluminium phosphate supplier was reviewed and found inadequate. Corrective and preventive actions were proposed and accepted to address the identified gaps.

Personnel

- ***Organization, organogram, independence of production from quality control***

The organizational structure of the vaccine and biologics division was presented and found to be approved and current. Quality Assurance (QA) and Quality Control (QC) departments were independent from production activities, in line with GMP requirements.

- ***Training:***

Personnel interviewed during the inspection demonstrated good knowledge of GMP principles and were cooperative throughout the process. Key staff were competent and appropriately qualified for their roles. Training activities were conducted according to established procedures, and newly recruited personnel received training relevant to their assigned duties.

During the inspection tour, operators in aseptic areas were observed performing tasks with a high level of awareness, including slow, controlled movements and frequent hand sanitization, consistent with aseptic behavior requirements.

- ***Personal hygiene:***

Operators entering aseptic areas wore appropriate sterile garments and protective goggles. Garment changing was documented and traceable. Washing and sterilization of garments were performed in-house, and each garment was tracked for the maximum number of wash and sterilization cycles. Visual inspection of garments was conducted prior to use. Handwashing and sanitization procedures were in place and observed during the inspection.

- ***Qualification of visual inspectors:***

The qualification process for operators performing visual inspection was reviewed and found to be comprehensive. The qualification of manual visual inspection of suspension products included fatigue qualification. Annual visual eye examinations were performed and documented for all inspectors.

Documentation

Documentation was managed through an electronic Document Management System (DMS) implemented across all manufacturing sites. The system defined roles for employees, document controllers (DC), and initiators responsible for document creation.

The DC was responsible for issuing documents and was the only role authorized to print controlled copies using the DMS print tool. Each procedure included a barcode containing key information such as requester, approver, and recipient.

The DMS provided automated notifications 60 days before document expiration and ensured traceability of effective issuance following completion of training. Any modification to a document required initiation of a change control process through the electronic system.

Batch Release Process

The batch release process was managed according to the company's procedure for review of executed batch production records (BPR) and batch release. After completion of all required testing by Quality Control (QC), Quality Assurance (QA) performed an internal release based on a comprehensive review of production, filling, testing, and environmental monitoring results.

Following internal release, samples and the summary protocol were sent to the Central Drugs Laboratory (CDL) in India for official approval. Final release for dispatch and distribution occurred only after CDL approval. Batches were packed and shipped exclusively after this external release step.

QA reviewed all executed BPRs for accuracy of entries, calculations, yields, analytical results, environmental monitoring data, and any associated deviations. The review included verification against product-specific checklists and assessment of related Quality Management System (QMS) elements such as deviations, change controls, out-of-specification (OOS) results, out-of-limit (OOL) and out-of-trend (OOT) data. Audit trail review was implemented as part of the process.

The list of authorized QA personnel for batch certification was presented during the inspection. Deficiencies were noted in the batch release procedure; corrective and preventive actions (CAPAs) were proposed and accepted to address the identified gaps.

2. Production system

In general, resources required for production were available, including qualified and trained personnel, suitable premises, equipment and services, materials, containers and labels, documented procedures and instructions, as well as laboratories and equipment for in-process and other controls. Procedures for qualification and validation of equipment, manufacturing processes, and quality control testing methods were established and implemented. Production operations were conducted according to defined procedures and master formulas. Deviations from procedures were documented and investigated in line with the quality system.

Cell and Seed Banks

Working cell banks for *Streptococcus pneumoniae* are stored in a qualified deep freezer within the Cell Bank Room at the Shameerpet site. The freezer is subject to annual requalification and defrosting. Access is restricted to authorized personnel under QA oversight, with temperature control managed automatically and verified manually. An inventory is maintained, and all activities are logged. Additional master and working cell banks are stored at another Biological E site in dedicated equipment, while WSL cell banks are kept in a freezer in the production area prior to inoculation. The procedure for cell bank management was reviewed and found satisfactory.

Drug Substance

PCV14 monovalent conjugated bulks are produced at the Shameerpet site in Block B.

The process flow was explained and observed during the visit to the production area. Media is transferred through dedicated transfer lines to fermenters. A segregated area is available for fermentation and purification processes. During the inspection, the fermentation stage of a batch of pneumococcal polysaccharide was observed. Fermentation occurs in a dedicated room equipped with two fermenters.

Following fermentation, the broth undergoes treatment with DOC, continuous centrifugation, low pH incubation, a second centrifugation, deep filtration, and transfer to downstream processing according to the validated manufacturing process. Activated polysaccharides are conjugated to CRM197 and stored in glass containers at 2–8 °C.

For conjugated bulk filled at the SEZ site, transport validation and temperature-controlled conditions are in place.

Fill and finishing operations

Measles and Measles/Rubella (MR) vaccines at SEZ site

Measles bulk antigen was received frozen in sealed containers, while Rubella antigen was manufactured on-site (Shameerpet). Formulation and filling were performed in a controlled environment at the SEZ site. Antigens were thawed and combined with a stabilizer solution, which was prepared in a closed single-use system under Grade C conditions, sterilized by filtration, and transferred to a Grade B blending room. PUPSIT was implemented.

Pooling and blending of antigens occurred under Grade A laminar airflow within a Grade B background, with environmental monitoring performed during operations. Filters underwent sterilization and integrity testing pre- and post-use, with results documented. The formulated bulk was transferred via closed single-use systems to the filling station. Filling was conducted aseptically; vials were depyrogenated, stoppers and caps autoclaved, and lyophilizers sterilized before each batch.

Pneumococcal Polysaccharide Conjugate Vaccine (PCV14)

SEZ Site:

Antigens were received at controlled temperature and stored in a cold room until use. Formulation was performed in a Grade B blending suite. Sodium chloride solution was prepared in Grade C and sterilized by filtration. Antigens and excipients were pooled under laminar airflow using single-use systems. Sterile filtration was conducted with PUPSIT in place. Aluminum phosphate adjuvant was aseptically added, pH adjusted, and batch volume completed. Final bulk was stored at controlled temperature and transferred aseptically to the filling line. Filling was performed under Grade A conditions using a peristaltic pump, followed by stoppering and capping. Vials were depyrogenated, and intermediate storage was at 2–8 °C. In-process controls included volume checks every 30 minutes.

Shameerpet Site:

Formulation was conducted in Grade A/B blending suites. Aluminum phosphate adjuvant was added aseptically. Filling was performed aseptically in controlled conditions, with depyrogenation and sterilization of components prior to use.

Deficiencies were noted, and corrective actions agreed upon.

Visual Inspection

Visual inspection at the SEZ site was observed. Inspection rooms were equipped with calibrated lighting and panels, and line clearance procedures were verified. Defects were categorized and recorded according to established procedures, with AQL applied. Inspector breaks and TOR were managed per SOP. Logbooks and defect kits were checked and found satisfactory.

Process Validation

A Master Validation Plan was in place and approved. Process validation was conducted in three phases: Design, Process Performance Qualification (PPQ), and Continued Process Verification (CPV). The procedure for process validation covered both bulk (from pre-seed to drug substance) and drug product manufacturing to ensure consistency in meeting predefined specifications.

For Pneumococcal Monovalent Bulk Conjugate, validation was performed on three consecutive batches at different scales. All batches met the predetermined Critical Quality Attributes (CQAs), demonstrating that the process was controlled and reproducible across scales.

At the SEZ site, a process validation study was conducted in one scale for PCV14 with preservative. The study confirmed that blending, filling, capping, vial filling, visual inspection, and storage operations were consistently performed under controlled conditions. Holding times between blending and filling were defined and validated. Time-out-of-refrigerator limits were established and found satisfactory.

Validation of Sterilizing Filtration

Sterilizing filtration for PCV14 at the SEZ site was validated. Filters used for pre-blending underwent compatibility, extractables, and bacterial retention studies. PUPSIT was implemented.

At the Shameerpet site, integrity and compatibility testing were completed; however, bacterial retention testing was pending at the time of inspection. During CAPA review, the complete filter validation was presented and accepted.

Aseptic process simulation (APS)

Media fill and aseptic simulation studies were conducted at both sites for blending and filling operations. No contamination was observed in completed studies. A bracketing approach was applied for different batch sizes and products. APS protocols and reports were reviewed and the deficiencies noted during APS were addressed through corrective actions.

Reprocessing/ reworking

Reprocessing was permitted under controlled conditions according to established procedures.

Batch manufacturing record (BMR)

Batch records for selected lots were reviewed. Records included complete documentation of processing parameters, in-process controls, and component quantities. Printouts of measurements were attached to the records. Documentation was found accurate and compliant with requirements.

3. Facilities and equipment system

Shameerpet Block-B

Block-B is a multi-product manufacturing facility designed for the production of pneumococcal polysaccharides, CRM197, pneumococcal monovalent bulk conjugates, purified Vi polysaccharide (Typhoid), and RBD antigen (COVID-19). The facility comprises dedicated suites for polysaccharide production, media preparation, CRM197 production, and conjugation, as well as walk-in cold and freezer storage areas. Each suite is equipped with separate air handling units (AHUs) and distinct personnel and material airlocks with access control systems. Personnel entry for live and non-live areas is segregated, and access is restricted to authorized staff. Unidirectional flow of materials and personnel is maintained throughout the facility. Media preparation is performed in a dedicated suite for use in polysaccharide and carrier protein production.

Shameerpet Blending & Filling Block

The blending and filling facility is multi-product, comprising five blending suites and multiple filling lines. Suites 1–3 are used for bacterial vaccines and PCV14 formulation, Suite 4 is dedicated to viral vaccines, and Suite 5 is used for sterile manufacturing of TT and Td products. Filling lines are located on the ground floor, with lines 1–3 for inactivated vaccines and line 4 for viral vaccines. For PCV14, blending is performed in glass bottles due to batch size, and transfer to filling is carried out under controlled conditions using sanitized trolleys and dynamic pass boxes. Surface disinfection procedures are in place; however, deficiencies related to sanitization during transfer from Grade B to Grade A were noted and corrective actions agreed.

SEZ site

The SEZ facility occupies a large area and includes blending and filling suites, a warehouse, and QC laboratories. Four blending/filling lines are available, with lines 2 and 4 inspected during this visit. Classified areas are equipped with airlocks, gowning procedures, and differential pressure cascades to maintain segregation. Blending was performed in fixed stainless steel vessels and the sterile bulk was transferred through single-use silicon tubes to the filling line. Autoclaves for sterilization and decontamination are installed in each department. Blending and filling operations are performed under controlled conditions, including laminar airflow units (LAFU) and RABS systems for aseptic processing. Filling lines are equipped with vial washing machines, depyrogenation tunnels, and lyophilizers with automated loading/unloading systems. PCV14 manufacturing is conducted in Blending Suite 4 and Fill-Finish Line 4 under Grade A/B conditions. Environmental monitoring and material transfer procedures were reviewed and found satisfactory.

Water systems:

Only water systems at the SEZ site were inspected. The purified water (PW) generation system was supplied by borewell water and included reverse osmosis, EDI units, storage tanks, and distribution loops serving blending and filling lines. Sanitization was performed monthly at 80 °C. Water for Injection (WFI) was produced by a multi-effect still and maintained at >80 °C in the distribution loop, with online TOC monitoring. Sterilization of the WFI system was performed monthly at 121 °C. Pure steam was generated from PW and tested annually for dryness, non-condensable gases, and superheat; recent results were compliant. Quarterly water system reports showed no out-of-limit results for PW, WFI, or pure steam.

Other gases

Nitrogen was supplied via cylinder yards for lyophilizers. Monitoring included bioburden, oil, and moisture content. A deficiency related to cylinder maintenance was noted; corrective actions were agreed. Compressed air was generated by two compressors, filtered through a multi-stage system, and tested quarterly for oil, moisture, and microbial contamination. All results for Q4-2024 were compliant.

Qualification and validation

A Master Validation Plan was in place, covering facilities, equipment, utilities, processes, and analytical methods. Qualification followed the standard sequence (URS, DQ, IQ, OQ, PQ), and requalification was performed at defined intervals. Validation protocols were prepared by the execution team, reviewed by validation, and approved by QA. Documentation was archived appropriately.

Requalification of critical equipment, such as fermenters, included heat distribution and biological studies; frequencies were defined and adhered to.

Calibration and preventive maintenance

Calibration and maintenance were managed electronically. Preventive maintenance schedules included monthly, quarterly, semi-annual, and annual tasks. Calibration certificates and standards were reviewed and found satisfactory.

HVAC

Requalification of Grade A/B areas was performed every six months, and Grade C/D annually. Protocols and reports for HVAC and laminar airflow units were reviewed, including smoke studies for airflow patterns. Deficiencies noted during HVAC qualification were addressed through corrective actions.

Cleaning Validation and Product Changeover

Cleaning validation was established through a documented procedure describing the methodology and acceptance criteria. Most equipment in the blending suite was equipped with automated CIP systems, including sequential rinses with purified water, basic and acidic solutions, and a final rinse with WFI. Conductivity checks were performed on the final rinse. Cleaning verification studies for blending vessels used in PCV14 manufacturing were reviewed and found satisfactory. Manual cleaning was limited to non-product contact items such as buffer solution bottles, using purified water and WFI. Decontamination of other equipment and tools was performed by autoclaving.

Disinfectant Validation:

Disinfectant validation was performed for all disinfectants used at the site, including ATCC strains and in-house isolates. Surfaces tested included stainless steel, glass, epoxy, PVC, and HEPA filter materials. Studies demonstrated that Bacillocid and Minncare were effective after a 10-minute contact time, achieving the required log reduction. Validation of 70% IPA confirmed efficacy and defined a hold time of six days. Additional verification studies for sanitization of materials transferred from lower to higher classified areas were conducted and found effective, although these were not considered full disinfectant validation studies. Deficiencies noted were addressed through corrective actions.

Computerized System

A list of computerized systems was maintained, detailing equipment, software, GAMP classification, audit trail review frequency, and backup procedures. Audit trail management and data integrity controls for selected systems, including laboratory instruments and autoclaves, were reviewed and found satisfactory. Backup and restore procedures were implemented at defined intervals, and audit trails captured all relevant events with appropriate time stamps and user attribution.

4. Laboratory control system

QC operations at the Shameerpet site were reviewed. QC is responsible for testing all incoming raw and packaging materials, intermediates, and final products, as well as monitoring critical utilities (PW, WFI, pure steam), environmental conditions, and stability studies. Raw materials are sampled in a dedicated warehouse area under controlled procedures. Testing is performed according to approved specifications, and materials are released or rejected based on compliance. A full analysis is conducted

for the first consignment of each calendar year; deficiencies noted for incomplete testing were addressed through corrective actions.

During the inspection, an analysis for molecular size of PCV14 was observed. Samples were logged in LIMS and stored at 2–8 °C until testing. The test was performed by a qualified analyst using validated equipment. Results met acceptance criteria; however, deficiencies were noted, and corrective training was agreed upon.

Analytical methods

Analytical methods for monovalent bulk, final lots, and filled products are based on established specifications and supported by validated SOPs. Validation covered identity, content, adsorption, residuals, pH, endotoxin, sterility, and other critical attributes for both bulk and final products. The method for determining average molecular size was reviewed and confirmed as validated. Reference standards for each serotype are prepared from commercial lots, verified by biochemical assays, and stored at -20 °C.

Environmental monitoring (EM):

SEZ Site:

An environmental monitoring program was in place for viable and non-viable particulates. Monitoring included RABS gloves, air sampling, and personnel checks. Trend reports for Q4 2024 showed no out-of-limit results. Alert limits were justified and set at 60% of action limits. Non-viable monitoring trends were also reviewed and found satisfactory.

Shameerpet Site:

Environmental monitoring was performed during batch activities, including air sampling and surface checks. Trend reports for Q4 2024 showed no out-of-limit results. Deficiencies noted during monitoring were addressed through corrective actions.

5 Materials system:

The SEZ warehouse was inspected. Temperature-sensitive raw materials were stored in controlled rooms at 21 ± 3 °C, monitored by an electronic management system (EMS). Packaging materials were stored separately. Freezers operating at -30 °C were available, with alarms set for deviations and verified during the inspection. Cold rooms and freezers were connected to the EMS for continuous monitoring, and alarm systems for high temperature were in place.

The sampling and dispensing area was equipped with ventilated pass-boxes and a laminar airflow unit under Grade C conditions. Differential pressure was maintained to ensure a positive cascade for product protection. Procedures for sampling and retesting of raw materials were reviewed and found satisfactory, allowing retesting up to the expiration date where applicable.

International shipping

Dedicated packaging areas were available for each production line, with temperature-controlled conditions appropriate for the specific vaccine. For PCV14, packaging and storage areas on Line 4 were inspected, including secondary and tertiary packaging. Procedures for storage, packing, and distribution complied with WHO requirements. Shipping validation previously performed for similar vaccines was applicable to PCV14, ensuring compliance with international standards.

6 Packaging and labelling system

The labelling department was equipped with automated labelling machines. Line clearance and sensor functionality checks were performed prior to operations. Secondary packaging activities were carried out manually in designated areas.

Packaging of the final lot was conducted in controlled packaging zones. Dedicated cold rooms were available for storing finished products during optical inspection, post-inspection, and prior to dispatch. Vaccine Vial Monitors (VVM) were stored in qualified freezers located in the SEZ warehouse, maintaining temperatures between -25 °C and -35 °C. Freezers were initially qualified through temperature distribution, door opening, and power failure studies, and annual requalification was performed as per approved protocols. Spot checks confirmed satisfactory conditions during the inspection.

Inventory management was controlled electronically, with stock movements tracked through a validated system. VVM stickers inspected during the visit were within their expiry date. Overall, packaging and labelling operations were found to be organized and compliant with established procedures.

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, **Biological E. Limited**, located at Sy. No. 549, 550 & 552 to 556, Kolthur Village, Shameerpet, Medchal-Malkajgiri District, Telangana State – 500078, India (**SEZ unit**) and Plot No.1, Biotech Park, Phase II, Kolthur Village, Shameerpet, Medchal-Malkajgiri District, Telangana State – 500078, India (**Shameerpet site**) were 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 1. ***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***

18. Stability testing of active pharmaceutical ingredients and finished pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-second Report Geneva, World Health Organization, 2018 (WHO Technical Report Series, No. 1010), Annex 10. ***Short name: WHO TRS No. 1010, Annex 10***

19. Production of water for injection by means other than distillation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fourth Report. Geneva, World Health Organization, 2020 (WHO Technical Report Series, No. 1025), Annex 3. ***Short name: WHO TRS No. 1025, Annex 3***

20. Good chromatography practice. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fourth Report. Geneva, World Health Organization, 2020 (WHO Technical Report Series, No. 1025), Annex 4. ***Short name: WHO TRS No. 1025, Annex 4***

21. Good storage and distribution practices for medical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fourth Report. Geneva, World Health Organization, 2020 (WHO Technical Report Series, No. 1025), Annex 7. ***Short name: WHO TRS No. 1025, Annex 7***

22. Points to consider for manufacturers and inspectors: environmental aspects of manufacturing for the prevention of antimicrobial resistance. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fourth Report. Geneva, World Health Organization, 2020 (WHO Technical Report Series, No. 1025), Annex 6. ***Short name: WHO TRS No. 1025, Annex 6***

23. WHO Recommendations, Guidelines and other documents related to the manufacture, quality control and evaluation of biological products. WHO Expert Committee on Biological Standardization. Seventy-first Report. Geneva, World Health Organization, 2021 (WHO Technical Report Series, No. 1028), Annex 1. ***Short name: WHO TRS 1028, Annex 1***

24. New and replacement WHO international reference standards for biological products. WHO Expert Committee on Biological Standardization. Seventy-first Report. Geneva, World Health Organization, 2021 (WHO Technical Report Series, No. 1028), Annex 4. ***Short name: WHO TRS 1028, Annex 4***

25. Points to consider when including Health-Based Exposure Limits (HBELs) in cleaning validation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fifth Report. Geneva, World Health Organization, 2021 (WHO Technical Report Series, No. 1033), Annex 2. ***Short name: WHO TRS 1033, Annex 2***

26. WHO good manufacturing practices: water for pharmaceutical use. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fifth Report. Geneva, World Health Organization, 2021 (WHO Technical Report Series, No. 1033), Annex 3. ***Short name: WHO TRS 1033, Annex 3***

27. Guideline on data integrity. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fifth Report. Geneva, World Health Organization, 2021 (WHO Technical Report Series, No. 1033), Annex 4. ***Short name: WHO TRS 1033, Annex 4***

28. Procedure for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies. WHO Expert Committee on Biological Standardization. Sixty-first report. Geneva, World Health Organization, 2013 (WHO Technical Report Series, No. 978), Annex 6. ***Short name: WHO TRS No. 978, Annex 6***

29. WHO good manufacturing practices for excipients used in pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-seventh Report. Geneva, World Health Organization, 2024 (WHO Technical Report Series, No. 1052), Annex 2. ***Short name: WHO TRS 1052, Annex 2***

30. WHO Guidelines for the International Packaging and Shipping of Vaccines, 6th edition. Geneva, World Health Organization, 2020.