World Health Organization

20, AVENUE APPIA – CH-1211 GENEVA 27 – SWITZERLAND – TEL CENTRAL +41 22 791 2111 – FAX CENTRAL +41 22 791 3111 – WWW.WHO.INT

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

Part 1	**General information**
Manufacturers details	
Company information	
Name of manufacturer	Biological E. Limited.
Corporate address of manufacturer	Biological E limited (BE), Plot #623-H, Road 35, Adjacent line to Neerus showroom Jubilee Hills, Hyderabad-500 033, Telangana. Tel:040-7121 6111 Fax: (+91) 40 7121 6128/6030
Contact person	Srinivas Kosaraju Srinivas.Kosaraju@biologicale.co.in
Inspected sites	
Address of inspected manufacturing site if different from that given above	1. Lot Plot No. 1, S.P. Biotechnology Park, Kolthur (V), Shameerpet (M), Ranga Reddy (Dist.), Telangana, India – 500 078. Manufacturing of Bulk vaccines and Blending, Filling and Packing of final. 2. 7-4-114, Gaganpahad, Rajendra Nagar (M), Ranga Reddy (Dist.), Telangana, India – 501 323. Manufacturing site for Bulk Purified Tetanus Toxoid (BPTT).
Manufacturing license number	Drug License in Form-26-H bearing n°.01/RR/AP/2006/V/R, dated: 21-04-2006 duly renewed for the period from 21.04.2016 to 20.04.2021 and duly approved by the Central License Approving Authority, New Delhi, India.
Inspection details	
Dates of inspection	3 to 7 October 2016
Type of inspection	Routine inspection
Representative from the National Regulatory Authority	The national regulatory authority (NRA) of the country where the inspection took place was informed and Drug Inspector from CDSCO, Hyderabad took part in the inspection.
Introduction	
Brief summary of the manufacturing activities	BE manufactures a range of childhood and adult vaccines, pharmaceuticals (specifically anti-coagulants and anti-infective) and active pharmaceutical ingredients (API). BE has been producing Tetanus Toxoid (TT) vaccine since late 1960's, Diphtheria and Tetanus (DT) and Diphtheria, Tetanus and Pertussis (DTP) vaccines since mid 1970's. BE has been supplying the vaccines to the Extended Program for Immunization (EPI), ever since EPI commenced in India in the late 1970's. In later years, the company has introduced other vaccines like Hepatitis- B Vaccine, *Haemophilus Influenzae type-b* Vaccine (Hib), Tetravalent vaccine (DTP-Hep-B), IPV (Inactivated Polio Vaccine), Pentavalent Vaccine and Japanese Encephalitis (JE) Vaccine.

This WHOPIR is the property of the WHO
Contact: prequalinspection@who.int

	The manufacturing activities at the three different sites are summarized below: **Shameerpet manufacturing site:** ▪ Primary Manufacturing: • Recombinant Vaccine Block: Hepatitis B, • Bacterial Vaccine Block: Whole Cell Pertussis, • Bacterial Vaccine Block: Diphtheria/Haemophilus Influenzae type b (Hib) on campaign basis, • Conjugate Block: Hib Conjugate. ▪ Secondary Manufacturing: • Blending, Filling and Packing. ▪ Raw Material and finished product cold storage rooms **Gaganpahad manufacturing site:** ▪ Tetanus Bulk Antigen Manufacturing Block. **Azamabad Manufacturing Site:** ▪ Japanese Encephalitis Vaccine Antigen and Final Bulk. In order to expand manufacturing capacities and to upgrade facilities to current requirements of various international regulatory, BE has come up with a new facility at Shameerpet to manufacture bulk and finished formulations of existing and new vaccines. The site is also to carry out the blending and filling of all the bulk vaccines produced at this site and also the blending and filling of Bulk Purified Tetanus Toxoid (BPTT) manufactured at one of the facility of BE (Gaganpahad) and Filling of Japanese Encephalitis formulated bulk Vaccine manufactured at one of the facility of BE (Azamabad).
General information about the company and sites	Biological E. Limited (BE) was established in 1953. BE was incorporated in India under the companies Act 1956. Since its inception BE had alliances with several pharmaceutical biotech companies such as Evans, Glaxo, Solvay, ICI, Pasteur Merieux Connaught. In later years, the company had collaboration with companies like Intercell, Merck, NVI (Netherlands Vaccine Institute), Novartis NVGH (Novartis Vaccine Global Health) and GSK. These alliances have allowed BE to expand its product range and incorporate international practices. It is estimated that over 4.3 billion doses of vaccines have been produced by BE till mid of 2016. BE has the list of WHO prequalified vaccines to supply single and multiple dosage presentations as presented in the table below: • TT Vaccine, WHO prequalified in December 2009, • DTwP-rHepB+Hib (Liquid + lyo), WHO prequalified in August 2011, • DTwP-rHepB+Hib (fully liquid), WHO prequalified in May 2012, • Inactivated Japanese Encephalitis (JE) Vaccine (6mcg/0.5mL), WHO prequalified in September 2013, • DTP Vaccine, WHO prequalified in July 2014, • Tetanus Diphteria (Td) Vaccine, WHO prequalified in September 2014, • Inactivated Japanese Encephalitis Vaccine (3mcg/0.5mL), WHO prequalified in August 2016.

<table>
<tr><td>History</td><td>The previous WHO inspections are presented in the table below:
<table>
<tr><th>Audit Date</th><th>Scope of Audit</th><th>Compliance Status of Observations</th></tr>
<tr><td>13 to 17.10.08</td><td>WHO Pre-Approval Inspection-TT Vaccine</td><td rowspan="6">All observations are closed.</td></tr>
<tr><td>25 to 27.05.09</td><td>WHO Follow up audit for Pre-Approval Inspection-TT Vaccine</td></tr>
<tr><td>05 to 09.07.10</td><td>Audit for Recon- Liquid Pentavalent (LPV) Pre-Qualification</td></tr>
<tr><td>30.05 to 01.06.11</td><td>Follow up audit of Recon Penta Prequalification</td></tr>
<tr><td>24 to 27.09.12</td><td>JE Vaccine Pre-Qualification</td></tr>
<tr><td>27 to 29.09.12</td><td>Liquid Pentavalent sterility investigation</td></tr>
</table>
The company indicated a plan to submit a Measles-Rubella vaccine for prequalification in 2017. Licensing in India is pending. There was also a partnership with Glaxo Smith Kline (GSK) to develop a hexavalent vaccine (DTwP-HepB-Hib-IPV), with IPV provided by GSK and use of preservative (in the 10-dose presentation).</td></tr>
<tr><td colspan="2">Brief report of inspection activitiesundertaken</td></tr>
<tr><td>Scope and limitations</td><td></td></tr>
<tr><td>Areas inspected</td><td>The inspection focused on the production and control of the following vaccines:
• Diphtheria-Tetanus-Pertussis (whole cell), Hepatitis B, Haemophilus influenzae type b (2, 5 and 10 doses fully liquid),
• Diphtheria-Tetanus (reduced antigen content, 1 and 10 doses),
• Diphtheria-Tetanus- whole cell Pertussis (1 and 10 doses),
• Tetanus Toxoid (1, 10 and 20 doses).
The inspection was limited to the production areas used for the above mentioned commercial vaccines.</td></tr>
<tr><td>Restrictions</td><td>• There has been no liquid-lyophilized pentavalent vaccine (Diphtheria-Tetanus-Pertussis (whole cell)-Hepatitis B-Haemophilus influenzae type b) supply to UNICEF since 2012. The preferred presentation of pentavalent vaccine for supply through UN agencies has been the fully liquid type. The company indicated that experience with the manufacture of lyophilized Hib vaccine is maintained through supply of this monovalent preparation for local Indian supply.
• There has been no supply of Japanese Encephalitis Vaccine (JEV) (Inactivated) through UN agencies since the prequalification. It was indicated that 4.5M doses (adult and pediatric) of JEV was produced. The company indicated a plan to produce 5 dose JEV (containing thimerosal as preservative).</td></tr>
<tr><td>Out of scope</td><td>The following manufacturing areas and activities were not visited during this inspection:
• Azamabad manufacturing site for JE bulk vaccine
• Shameerpet site:
o Hepatitis B manufacturing block,
o Blending suites,</td></tr>
</table>

	○ Vial Filling Lines-1 and the vial filling Line-4 equipped with lyophilizer, ○ The PFS line for commercial manufacturing.
Vaccines covered by the inspection	• Diphtheria-Tetanus-Pertussis (whole cell), Hepatitis B, *Haemophilus influenzae* type b (2, 5 and 10 doses fully liquid), • Diphtheria-Tetanus (reduced antigen content, 1 and 10 doses), • Diphtheria-Tetanus- whole cell Pertussis (1 and 10 doses), • Tetanus Toxoid (1, 10 and 20 doses).

Abbreviations

AHU	Air Handling Unit
ALCOA	Attributable, Legible, Contemporaneous, Original and Accurate
APR	Annual Product Review
APS	Aseptic Process Simulation
BE	Biological E Limited
BMR	Batch Manufacturing Record
BPDT	Bulk Purified Diphtheria Toxoid
BPR	Batch Production Record
CA	Compressed Air
CAPA	Corrective Actions and Preventive Actions
CC	Change Control
CCID	Cell Culture Infective Dose
CFU	Colony-Forming Unit
CIP	Cleaning In Place
CoA	Certificate of Analysis
CPE	Cytopathic Effect
DQ	Design Qualification
DT	Diphtheria and Tetanus
DTP	Diphtheria, Tetanus and Pertussis
EDI	Electronic DeIonization
EM	Environmental Monitoring
EPI	Extended Program for Immunization
FMEA	Failure Modes and Effects Analysis
FTA	Fault Tree Analysis
GMP	Good Manufacturing Practices
GPT	Growth Promotion Test
HDPP	High Density Polypropylene
HEPA	High Efficiency Particulate Air
Hib	*Haemophilus influenzae type b*
HVAC	Heating, Ventilation and Air Conditioning
IQ	Installation Qualification
LAF	Laminar Air Flow
LIMS	Laboratory Information Management System
MB	Microbiology
MBL	Microbiology Laboratory
MCB	Master Cell Bank
MEM	Minimum Essential Medium
MF	Master Formulae
MFT	Media Fill Test
MR	Management Review

MWB	Master Working Bank
NCA	National Control Authority
NCL	National Control Laboratory
NRA	National Regulatory Agency
OOS	Out Of Specification
OQ	Operational Qualification
OOT	Out Of Trend
PHA	Process Hazard Analysis
pH	(-ve) logarithm of H^+ concentration
PLC	Programmable Logic Controller
PM	Preventive Maintenance
PQ	Performance Qualification
PQR	Product Quality Review
PQS	Pharmaceutical Quality System
PW	Purified Water
QA	Quality Assurance
QC	Quality Control
QCL	Quality Control Laboratory
QMS	Quality Management System
QRM	Quality Risk Management
RA	Risk Assessment
RCA	Root Cause Analysis
RO	Reverse Osmosis
SIP	Sterilization In Place
SMF	Site Master File
SOP	Standard Operating Procedure
TAMC	Total Aerobic Microbial Count
TT	Tetanus Toxoid
UF	Ultra Filtration
UN	United Nations
UNICEF	United Nations Children's Fund
URS	User Requirements Specifications
UV	Ultraviolet-Visible Spectrophotometer
VVM	Vaccine Vial Monitor
WFI	Water for Injection
WHO	World Health Organization
WHOPIR	World Health Organization Public Inspection Report

Part 2: Brief summary of the findings and comments

1. Pharmaceutical quality system The pharmaceutical quality system (QMS) and all of the elements were in place. The quality management organizations of the company include quality assurance department (QA) and quality control department (QC). The production is independent from the quality control department.

The company has provided the corrective and preventive actions (CAPAs) adequately addressing the raised issues regarding the pharmaceutical quality system.

Quality Risk Management

The procedure for the QRM in place refers to ICH Q9 and PDA TR 44. The ranking system used combines the qualitative (high, major, minor) and the quantitative approach from 1 to 9 reduced to the 3 middle values. It was recommended to start with a simple qualitative ranking system and to apply a detailed quantitative one when unwanted events come in the same category of risks and need to be discriminated for prioritization.

The FMEA template model used should be modified since after the first evaluation the operations with non-acceptable risks need recommended action(s) before the risks could be re-evaluated. It is not possible to appreciate the risk for a lot of different events together in the same line and the justification of the criticality for each parameter (severity, occurrence, detection) for each individual unwanted event was not indicated (PDA TR 44).

The company has provided the corrective and preventive actions (CAPAs) adequately addressing the raised issues regarding the quality risk management.

Annual Product Review (APR)

Provisions for APR were in place according to the new approved procedure (September 2016) which includes parameters of MCB and WCB storage location, effectiveness of CAPAs and review of previous CAPAs, list of OOT, stability studies trend, review of technical agreements and review of previous actions of APQRs.
The following APR were spot checked:

- Hepatitis B bulks for the year 2015
- Whole cell pertussis bulks for the years 2014 and 2015
- For Diphtheria bulks for the year 2015
- Pentavalent vaccine for the year 2015.

In general terms, the APR were considered lacking the comparison with previous reviews and failing to achieve the objective of verifying the consistency of the existing process and the appropriateness of current specifications for both starting materials and finished product, to highlight any trends and to identify product and process improvements.

The company has provided the corrective and preventive actions (CAPAs) adequately addressing the raised issues regarding the APR management.

Deviation Reporting and Failure Investigation

The unexpected events that occur in non-compliance with the designed system or procedure during the receipt, storage, manufacture and/or analysis of a product are registered as deviation. The deviations are handled in Track Wise (Software) as per the implemented procedure. Deviation Report (DR) is initiated and reported to QA by the person, who is observing/deviating. The investigation is carried out under the supervision of QA for identifying the root cause of deviation and the corrective and preventive actions are initiated to rectify the deviation and to avoid the reoccurrence, wherever applicable. The deviations are reviewed for their impact and closed by the batch release group of QA prior to release of the batch.

The company reported that the deviations trending reports are presented during the quarterly management board. The deviations have been spot checked.

The company has provided the CAPAs adequately addressing the raised issues regarding the deviation management.

Change Control management

Changes in the approved facility, equipment, material, process, formula, analytical and/or controls are managed through the implemented change control procedures. Change control is initiated by the owner of the activity and reviewed by qualified representatives from relevant disciplines, including quality and regulatory. The review evaluates the impact of change on validated status of the facility and equipment and purity, safety and efficacy of the final product and/or regulatory compliance including the registration status. Changes are implemented only after the approval by QA. Trackwise has been introduced to manage the change control and deviation management system. In general, the company was able to rapidly provide information from the system and adequately documented processes involved.
The list of change controls has been spot checked.

Major changes since previous inspection and planned future changes are presented as the following:

Enterprise Quality Management System

- Sparta Systems Inc. TrackWise 8.4.2 implemented in December 2013.
- Deviation and change control systems were implemented.
- Extended to cover internal audit along with major enhancements to existing processes.
- QMS metrics and trends.

Laboratory Information Management System (LIMS)

- Caliber Technologies Ltd, LIMS implemented in November 2015
- Sample management, i.e., from sample registration to CoA generation
- Inventory management of chemicals and test solutions
- Stability management from protocol preparation to stability reports.

Calibration and Preventive Maintenance System

- Pharma Soft Sol, CAL-PM-BM implemented in July 2016
- Calibration management, from schedule preparation to execution
- Preventive Maintenance of equipment and facility
- Reports on calibration dues and overdues.

Primary Manufacturing

- CS-III facility modification for introduction of Grade B for sterile filtration activity
- Hep B facility modifications to accommodate Fermenter, continuous centrifuge (Westfalia) and Ultra Centrifuge
- Fermenter and meat block introduction for preparation of Diphtheria bulk antigen
- Pertussis – fermenters and centrifuge.

Secondary Manufacturing

- Filling Line-4 modifications for usage of bacterial and viral vaccines.
- New blending suite – IV for development products.
- New filling line – 3
- New PFS line (Line –2).

Quality Control

- Animal house expansion
- New QC Lab –II.

Development Blocks

- Block A for Measles and Rubella bulk antigen
- AIC Pilot plant for R&D.

Changes anticipated in next two years

Facilities:

- Pertussis expansion block
- Block –B for Pneumococcal conjugate vaccine.
- Animal breeding facility (close proximity to Shameerpet site).

QMS:

- LMS - Learning and Management Systems
- DMS - Document Management System
- LIMS - Laboratory Information Management System for utilities (EMP and Water).

Batch record review

Batch production record for filling of liquid pentavalent vaccine (LPV) was spot checked. The filling date was on 4/7/2016 and first potency testing was initiated on the 7/10/2016. The batch record was found satisfactory.

2. Good manufacturing practices for pharmaceutical products

Resources were available, including qualified and trained personnel, premises, equipment and services, materials, containers and labels, approved procedures and instructions, laboratories and equipment for in-process and other controls. Manufacturing processes, instructions and procedures were generally defined and available. Qualification and validation of equipment, manufacturing processes and quality control testing methods were considered. Operators were trained to carry out procedures, and records were considered for production. The operations were essentially compliant but a number of areas with examples need further improvement to be in full compliance with WHO good manufacturing practices and guidelines.

The company has provided the corrective and preventive actions (CAPAs) adequately addressing the raised issues regarding the good manufacturing practices.

3. Sanitation and hygiene

The company had provisions for personal hygiene and sanitation in its production facility and quality control laboratories. Smoking, eating, drinking, chewing, and keeping plants, food, drinks, smoking was not permitted in production, laboratory and storage areas. Wrist-watches, cosmetics and jewelry were not observed as being worn in clean areas. Manufacturing areas are provided with airlocks for personnel and materials entries and exits. Gowning procedures for access to the classified manufacturing areas were in place. Changing rooms were provided instructions describing the gowning procedures. In general terms, the level of hygiene observed and the measures taken to maintain this were considered satisfactory.

The disinfection program in aseptic rooms of grade A within grade B background includes the daily use of two commercial sterile sporicidal disinfectants Minncare® and Baccilocid®, 70% sterile IPA and fumigation.

The fumigation was performed, however the fumigation process was not validated to demonstrate its effectiveness in the concerned areas. The bulk manufacturing block for Diphtheria and Hib was used on campaign basis. Occasional contaminations have been observed.

The company has provided the corrective and preventive actions (CAPAs) adequately addressing the raised issues regarding the sanitization and hygiene management.

4. Qualification and validation

Provisions for qualification and validation were in place and covered premises, equipment, utilities and processes and procedures at defined frequencies. Results generated during the validation/qualification activities were reported to be independently reviewed and approved by QA to ensure the compliance to pre-determined specifications and acceptance criteria. Overall, protocols and reports of the validation and qualification were in place.

Validation and qualification protocols and reports were spot checked and deficiencies were raised. The company has provided the corrective and preventive actions (CAPAs) adequately addressing the raised issues regarding the qualification and the validation.

Preventive Maintenance (PM)

The preventive maintenance was implemented as per procedure and the frequency was based on the SLIA (System Level Impact Assessment) of each equipment indicated in the Validation Master Plan (VMP). The table indicating the dates of the preventive maintenance activities for 2016 was spot checked and found satisfactorily managed.

5. Complaints

Product complaints were handled as per procedure. The SOP indicates that the suitable response shall be sent to complainant and appropriate corrective action shall be taken after a thorough investigation. The SOP describes all types of complaints (Quality/safety, AEFI), the receipt of the complaints, the responsibilities, record and handling the complaints, response timeline and any further follow up might require during or after the investigation. The SOP was also categorizing the type of the complaints which may be based on quality related investigation or the seriousness of the adverse event. In case of any complaints the SOP indicates that investigation should be closed within 7 working days. Serious/unexpected events shall be informed to QA by pharmacovigilance section within 48hours from the registration date. QA shall inform the RA within 48 hours. The disposition of the product during and after the investigation has been described. Depending on the outcome of the investigation the product may be recalled from the markets as per procedures. Flowchart for handling of the complaints was available in the SOP. The SOP indicates that the QA personnel were responsible for preparing the trend of events once every 6 months.
Contact details including phone number and email address of the personnel that was handling of the product complaints has been provided and reviewed as satisfactory.

The trend of product complaints for the period of January to June 2016 has been spot checked.

Safety logbook record from January 2016 up to date was spot checked.

The company has provided the corrective and preventive actions (CAPAs) adequately addressing the raised issues regarding the complaints and AEFI management.

6. Product recalls

The procedure for recall handling was implemented. It describes the required steps for any decision (i.e. recall domestic and or international, inform the regulatory authority (RA)) during adverse event/s and in case of product change. It also describes the procedures from receipt of the complaints, the responsibilities, record and handling the recall, and response timeline as per the nature of recall. The closure period of recalls should be completed within 90 days. The recall management is the responsibility of the recall office (QA manger). All the

recalled materials are quarantined and handled as returned products as per procedures. Any related documents should be archived by the QA department.
Recalled product form is included in the recall SOP to be filled by QA. The recall strategy should initially be discussed and agreed as per the product recall strategy checklist included in the SOP. Distribution section should be then issued the notification letter to the distributers/agents and the Indian NRA. Press statement may be issued in case of serious issue. The SOP contains database of any possible product recall.

The mock recall is performed once in every 2 years. The latest mock recall study was initiated in January 2016 for Tetanus Toxoid (TT) vaccine.

The company has provided the corrective and preventive actions (CAPAs) adequately addressing the raised issues regarding the recall management.

7. Contract production, analysis and other activities

This section has not been inspected in detail. The following has been reported in the provided SMF:at present no manufacturing activities are outsourced. Analytical testing, waste management and maintenance of various support systems are done through approved technical assistance centers as per procedures. Centers for the outsourced activities are identified by the concerned departments and intimated to the QA. The qualifications of these centers are done based on the activity to be contracted. Assessment of the services provided, GMP compliances and certifications held are taken into consideration before approval. Periodic assessments of the centers are done for their performance evaluation. Where required in-vivo testing services are taken from other site of BE (Gaganpahad) where same quality systems are in place.

8. Self-inspection, quality audits and suppliers' audits and approval

The procedures for the internal audit were in place. The internal audit covers yearly all GMP areas. The audit team comprises at minimum one member from QA, and members from other departments and other internal or external experts, as required.
The QA was responsible to maintain a list of 68 auditors for 2016. A two days training program was available for the auditors. The internal audit plan for the year 2016 was approved at the end of 2015 and a check list was used for each activity. 23 audits were planned and performed in due time with at least 2 days per audit and at least 3 auditors per audit team. The categorization of the raised observations and the deadline for the reporting were considered. The critical observations are to be forwarded to Head of QA/Auditee department. The QA Head will review and escalate them to the higher management through forums like the management review board.

Suppliers' audits and approval

Written specifications were available for the raw/packing materials and critical process consumables used in the production. The materials required for manufacturing were procured from qualified vendors. The vendors and contracted testing service providers were qualified as per procedures (Selection, Evaluation and Qualification of Vendors). Vendor qualification involves site visits and testing of representative samples, where ever applicable. Periodic assessment of the vendors was carried out for evaluating their performance. The accepting or rejecting of suppliers as per criteria stated in the SOP. The SOP indicates the responsibility and roles of the QC and QA managers. Once the checklist evaluated as satisfactory by BE personnel, a vendor site audit will be commenced. The procedure indicates that the frequency of audit is conducted once every 3 years for all critical and non-critical raw materials and testing service providers. It was recommended that the frequency of audits should be risk based according to the criticality of the material used.

9. Personnel The departments at the sites (Production, Quality Control, Engineering, QA and Warehouse) were having sufficient number of personnel with appropriate qualifications with respect to education, experience and

training to perform the desired functions. The organizational charts have been provided in the SMF and presented during the opening meeting for the inspection.

The organizational chart showed that the Quality Operation Unit was reporting to the Chief Operation Manager and only with a dot line to the QA Manager. It was explained that the daily reporting of the Quality Operation Unit was to the QA Manager and for administrative matters to the Chief Operation Manager. It was recommended to clearly define the level and the matters of reporting in order to demonstrate the independency from the production and the quality units.

10. Training

Provisions for training of the employees were in place including the initial induction training given at the time of joining and the GMP training. The training activities are recorded in session records. Employee training records are maintained at department training coordinator or supervisor with details of training sessions attended by the individual. Employees undergoing training are evaluated for effectiveness of the training through a questionnaire or practical demonstration and re-training are imparted, if required. Refresher courses on GMP are being conducted for all the concerned employees of the site as per approved schedule. External trainings are considered to concerned employees on various topics with relevance of their functional area. All the training activities are co coordinated by a training group of QA.

The personnel qualification for gowning for aseptic work was spot checked. 91 aseptic operators were re-qualified in July 2016 for filling activities, 37 in August 2016 for blending and 13 at different dates in 2016 for Diphtheria processes. As per the implemented procedure, the initial qualification is done 3 consecutive times and the re-qualification is performed every six months. The microbial sampling is performed at 15 locations and the target is no growth. The last re-qualification of the 13 personnel for the diphtheria aseptic process was spot checked and found satisfactory.

The routine “Manual Optical Inspection of Filled Vials/Pre-Filled Syringes” and the qualification of the operators was performed as per procedures every year. A set of 300 vials, (45 defectives + 255 good) was prepared and each inspector should perform 10 times the inspection of this set. A statistic acceptance limit of was defined for defected vials however not for conform vials.

The QC personnel involved in the swabbing performed for the validation of the changeover between the production campaign of B. pertussis and diphtheria toxoid were not qualified for this operation. In addition, only cotton swabs were used for sampling and which cannot achieve optimal recovery rate.

The company has provided the corrective and preventive actions (CAPAs) adequately addressing the raised issues regarding the training management.

11. Personal hygiene

Procedures for health requirements of personnel working in production areas were in place. Medical checks were carried out for the new hired employees and afterward on annual basis. The visual inspection operators of filled vials and containers are tested for their vision as per implemented procedure.

Based on the requirement and risk of infection, all the concerned employees are immunized and titers of personnel are checked to ensure adequate protection.

12. Premises and Equipment

The floor plans for the manufacturing and quality control areas representing the personnel, material, equipment and waste flow as well as the layouts for classification, differential pressure were provided in the SMFs and in the PSF.

The Shameerpet site is divided into the following three areas.

- The Antigen Manufacturing Blocks, the Blending and Filling Block, Warehouse, Clean Utility Block, Packaging and Finished Goods (FG) Store is located in the central area. (The clean utilities like Purified Water (PW), Water for Injection (WFI) and pure steam systems are housed in Clean Utility Block).
- The utility services including Pretreatment of water, Compressed air, Chilled water system, Standby power and the Animal Testing block.
- The Quality Control, Quality Assurance Block, the Boiler House and the Effluent Treatment Plant.

The Shameerpet site has the following vaccines manufacturing facility:

- Primary manufacturing:
  - Recombinant Vaccine Block: Hepatitis B
  - Bacterial Vaccine Block: Whole Cell Pertussis, Diphtheria, Haemophilus Influenzae type b (Hib)
  - Conjugate Block: Hib Conjugate
- Secondary manufacturing:
  - Blending, Filling and Packing
- Nine cold storage rooms of 2 to 8ºC.

➢ **Recombinant Vaccine Block for Hepatitis B bulk antigen**

- Dedicated Facility for Hepatitis B Antigen manufacturing
- Dedicated areas for Fermentation and Purification
- List of Critical Equipment:
  - Fermenters
  - Ultra centrifuge
  - Continuous centrifuge (Westfalia)
  - Ultrafiltration
  - Chromatography systems (Bioprocess)
  - Dynomill for cell lysis
- Different batch sizes at Fermentation
- MCB/WCB: *Pichia pastoris.*

➢ **Bacterial Vaccine Block for diphtheria, Hib and pertussis bulk antigens**

- A separate conjugation suite
- Fermentation for Diphtheria, Hib and pertussis runs on campaign basis with changeover in between
- Dedicated Purification areas for Diphtheria and Hib
- List of Critical Equipment:
  - Three fermenters
  - High speed centrifuge
  - Continuous centrifuge (Westfalia) for Hib only
  - Microfiltration and ultrafiltration for Diphtheria only
  - Chromatography systems for Hib only
  - HPLC for Hib only
- Different batch sizes at Fermentation
- MCB/WCB:
  - Diphtheria: *Cornybacterium diphtheria*
  - Hib: *Haemophilus Influenzae type b*

➢ **Bacterial Vaccine Block for pertussis bulk antigen**

- Dedicated process suites for Pertussis fermentation, inactivation and pooling
- List of Critical Equipment:

  - Fermenters
  - Continuous centrifuge
  - Inactivation skid
  - Different batch sizes at Fermentation
- MCB/WCB:
  - Pertussis*: Bordetella pertussis*.

Blending, Filling and Packaging Block

- Separate Block for Blending and Filling and Packing
- 3 Blending Suites I, II and III for commercial Production
- 1 Blending Suite IV for clinical products
- 3 Vial Filling Lines -1,3 and Line-4 for commercial manufacturing
- Filling Line 4 is equipped with Lyophilizer
- 1 PFS line for commercial manufacturing
- 2 Labeling machines and Packing areas
- Cold Storage Facilities: 9 for storing of filled vials at various stages including quarantine, release etc.

The Gaganpahad site has the following vaccine manufacturing facility

This site is also used for snake antivenom production. The company acknowledged that the tetanus building Gaganpahad site is an old facility with limited space and scope for renovation. They indicated an intention to consolidate vaccine production of the Shameerpet site by establishing a tetanus production facility on the site. There are currently two tetanus products produced, BPTT (for inclusion as tetanus moiety of vaccines) and CPTT (used as a carrier for conjugated Hib vaccine). The company indicated that the production process for these bulks is the same.

➢ **Tetanus Antigen Block**

- Dedicated facility for Tetanus Antigen manufacturing
- Dedicated areas for fermentation and purification
- Two product variants get manufactured:
  - BPTT – Bulk Purified Tetanus Toxoid
  - CPTT- Carrier Protein Tetanus Toxoid (for Hib conjugation)
- List of critical equipment
  - Fermenters
  - Microfiltration and Ultrafiltration
  - High speed centrifuge
- Different batch sizes at fermentation
- MCB/WCB: *Clostridium tetani*

HVAC

The minimum air changes per hour maintained was 25 for grade D, 40 for grade C and 60 for grade B.
Clean corridors in the block are maintained at 5 (±3) Pa higher than the atmospheric pressure. A pressure differential of 15 (±5) Pa is maintained between the rooms of different Classification. A positive pressure is maintained between the rooms of same Classification.
One airlock is provided for each grade change to enter into the classified areas. Air supply to Grade D, C and B area is through terminal HEPA filters. All live area air returns are through HEPA filters.

Water Systems

The source water for the site is taken from municipal water supply and bore well water.

Feed water for purified water is generated from source water through several stages of pretreatment and finally through RO (Reverse Osmosis) system. Feed water from pretreatment is stored in feed water tank before the second RO system to get the purified water. Purified water is the feed for multiple effect distillation still (MEDS). WFI from MEDS is stored in main WFI storage tank. This tank feeds WFI to each of the three WFI tanks meant for three manufacturing blocks through a distribution loop (mother loop) which is maintained at not less than 80° C. Each of the 3 WFI storage tanks has dedicated loops (sub-loop) running through the blocks. These distribution loops from each of these tanks are also maintained at not less than 80°C. Procedures for sanitation of water systems were in place.

Pure Steam
The purified water is fed to the Pure Steam generator to generate pure, pyrogen free steam

Compressed Air
Compressed Air is passed through a receiver tank and filter bank having 4.0µ, 1µ and 0.2µ filters to downstream points.

Although the manufacturing facility visited and the equipment seen in the Bioprocess Suite I, Bioprocess Suite II, Tetanus Toxoid manufacturing blocks and filling line-3 were considered in general terms adequate for manufacturing of pertussis, diphtheria, tetanus toxoid and Hib bulks and the finished vaccines, deficiencies were raised and the company has provided the corrective and preventive actions (CAPAs) adequately addressing the raised issues regarding the premises and equipment management.

14. Materials
Arrangements for the handling of starting materials, packing materials, bulk products and finished products including sampling, quarantine, release and storage were in place. Procedures for the handling of rejected materials and products and for their destruction were implemented.

Raw materials for production was received by the warehouse department, inspected and quarantined. Sampling procedures for received raw material were in place. Raw material was release for use by QC department based on the test results. Approved materials were stored in Approved Material Storage Area in Warehouse.

Packaging materials undergo the same procedures as starting materials. The packing materials like printed cartons and labels were stored under lock and key.

The company has provided the corrective and preventive actions (CAPAs) adequately addressing the raised issues regarding the materials management.

15. Documentation
Procedures were in place for material and product specifications, equipment operations, process activities, batch production records and testing procedures. The procedures were prepared, reviewed by supervisor and approved by QA. The procedures were reviewed at least once in three years as per procedure. The production activities were recorded in BPRs, equipment log books and General Control Records (GCR). The testing data were recorded in Laboratory Control Records (LCR). The supporting data, i.e. equipment usage and standards preparation were recorded in Equipment log books and GCRs. Provisions for records reviews, controls and archival were in place.

The company has provided the corrective and preventive actions (CAPAs) adequately addressing the raised issues regarding the documentation management.

16. Good practices in production Dedicated facilities and equipment were in place for manufacturing in order to control the risk of cross contamination. One manufacturing suite was used for multiple products on campaign basis with procedures for change over, cleaning and/or line clearance to prevent cross contamination.

Bacterial Vaccine Block
Bioprocess Suite I was dedicated for manufacturing of Pertussis bulk antigen.
Bioprocess Suite II was used for manufacture of Diphtheria, Pertussis and Hib bulk antigens on campaign basis with procedures for changeover. The changeover includes fumigation of the area followed by cleaning.
Bio Process Suite - I and Bio Process Suite - II shared a common area for washing and media preparation with separate entry for personnel and material. Transfer of material was carried out through pass boxes/sterilizers from this washing/preparation area to respective bio process suites.
A Separate Suite named as Purification Suite was dedicated for purification and sterile filtration of Diphtheria Toxoid. Another Separate Suite named as Conjugation Suite - I was used for purification and conjugation of *Haemophilus influenza type b* (Hib) polysaccharide (PRP).
A separate suite Conjugation Suite - III in second floor of Blending and Filling block was used for purification and conjugation of Haemophilus influenza type b (Hib) polysaccharide (PRP).

Recombinant Vaccine Block
Hepatitis B Purified Bulk (bulk antigen) was manufactured in the recombinant vaccine.

Blending and Filling Block
There were three Blending Suites, which caters to all the filling lines. The Filling area has four lines. Three were vial filling lines (line-1, line-3 and line -4) and one was Pre-Filled Syringe (PFS) line. The Filling line-4 was equipped with freeze drier. These suites are used for multiple products on campaign basis with procedures for cleaning/segregation to prevent cross contamination.

Packing Area and Finished Goods Storage Block
Packaging activities of the final lots were carried out in the packaging area. There were dedicated cold rooms for storage of final lot for pre- and post-visual inspection and for the finished product which is ready for dispatch.

Visual Inspection of VVM mounted labels:
Visual inspection on VVM mounted labels for LPV vaccine was observed during the visit. VVMs mounted on labels were the subject of inspection for misplacement and for incomplete adhesion as per written procedures. The VVM mounted labels were complete printed with the required information including the lot number and expiry date. A few rejected samples were observed due to misplaced VVMs on the labels. The VVM dot applicator machine used in the process of mounting was duly qualified and maintained.

Gaganpahad site for Tetanus Toxoid
There were three separate blocks, housing the various departments. The first block was the tetanus block dedicated for the manufacturing of the Tetanus Toxoid. An adjoining section houses the supporting utilities for generation of purified water, water for injection and pure steam. The second block has areas for quality control department and the warehouse. The third block houses the experimental animal house. There are separate areas for the security office, canteen and engineering utilities such as water treatment plant, boiler house, power house and effluent treatment plant in the premises.

Master and working cell:
MCB and WCB were stored at different locations including quality control laboratories and manufacturing facilities. The deep freezers used for the storage of MCB and WCB were access controlled and the logbooks for recording entries and pull out of WCB for manufacturing or other activities were appropriately maintained. The company reported that an inventory was performed every six months and occasionally during the maintenance of the deep freezers a physical inventory of cell banks was considered.

The company has provided the corrective and preventive actions (CAPAs) adequately addressing the raised issues regarding the good manufacturing practices.

17. Good practices in quality control Quality Control departments were sufficiently staffed and independent from the production. QC was in charge of testing the incoming raw materials, packing materials, intermediate products and final products. Quality control was in charge of testing purified water, water for injection, pure steam, compressed air and the environmental monitoring program. The intermediates and finished products were tested according to the specifications as per approved testing procedures.

The samples were received at the sample reception area and recorded in the LIMS before being transferred through a pass box to the QC Laboratories central corridor. The QC personnel in charge of reception were in charge of dispatching the samples to the chemical, microbiological and sterility test laboratories. The raw data of chromatographic equipment connected to the LIMS were saved independently.

The Quality control operations were organized as presented below:

The Out of Specification (OOS) handling
The procedures for OOS describes the process of OOS handling and results observed in labs of chemical, immunological and microbiological testing of raw materials, packaging and in process /intermediate/ finished product samples including stability/process /cleaning validation samples. As part of OOS investigation, the OOS report form should be filled by the analyst and signed by the QC and QA managers. The OOS including nonconformity investigation has to be reported and finalized within 30 days except for sterility and animal testing. The lists of OOS from January to December 2014 and 2015 were spot checked..

The sterility test procedure indicates only 4 possibilities to invalidate the test as per the International Pharmacopoeia however in case of “Microbial growth is observed in negative controls” this SOP added also syringe controls or negative product controls in contrast to Pharmacopoeia (Eur Ph. 2.6.1). No invalidation of sterility tests was observed.

Procedures for sampling of raw material and finished products were in place. Sample registry was operated using LIMS system. Test results hard copy for a vaccine was spot reviewed. The document was controlled with the date, name of analyst and number of pages.

Procedures for calibration and maintenance were in place. 37°C Incubators, equipment and pipettes were regularly calibrated. Chemicals in Schott bottles were labelled correctly with names, date of preparation and expiry dates. Pipettes were being calibrated every 6 months and verified monthly.

The waste disposal containers were available with instruction for sharps, infectious and biologicals and all color coded. A First Aids kit was available in the main corridor of the main QC lab. Autoclave was qualified yearly. Calibration of gauges performed every two years.

Culture laboratory room used for growth promoting test (GPT) and genotyping by sequencing equipped with a biological cabinet class II also used for manipulation of EMP samples obtained from the manufacture.

Incubator rooms for 20 – 25 °C and for 30 – 35 °C were connected to temperature central monitoring system. Temperature was checked twice a day during working hours.

Stability chamber room includes 2-8°C cold room for real time stability study, 25±2°C room for accelerated stability studies and -20°C freezer used for intermediate bulks sheflife studies. The cold room was equipped with five temperature probes and one probe for humidity. Segregation of products was clearly observed and found satisfactory.

The sterility test suite was equipped with an access control reserved only to the authorized personnel, all other parts including Microbiological Laboratories were not access controlled.

There were no separate flows for sample of products before inactivation and after inactivation, and thus there was a risk of cross contamination giving false positive results for samples of products after inactivation.

Water monitoring at Gaganpahad manufacturing site

Procedures for water systems monitoring were in place.

The trends for WFI from January 2015 to June 2016 were spot checked. The trends for purified water from January to June 2016 were spot checked. The trends for pure steam condensate (monthly) from January to March 2016 (dryness value, non-condensable gasses and superheat were tested annually) were spot checked. Monthly sanitization program of water systems was in place by using a temperature of over 90 °C for PW and over 121 °C for WFI systems.

Environmental monitoring (EM) at Gaganpahad manufacturing site

Procedures for environmental monitoring were in place. Grade D rooms were sampled monthly however contact plates sampling were not considered. EM for contact surfaces was performed by cotton swabs for grade C, grade B and grade A manufacturing areas, there was no recovery studies for swab sampling method. Surface contact was introduced for personnel in grade A and grade B gowning since April 2016.

Environmental monitoring trends were done quarterly. No review of more than 3 months was in place.

EM results (for aseptic rooms and the laminar air flow of grade A) from January to March 2016 were spot checked. The list of OOS results for microbial environmental monitoring for rooms of grade C where the centrifugation takes place and the aseptic rooms of grade B showed a high rate of contamination on settle plate and air sampling including fungal contamination. The identified strains were mainly *Staphylococcus haemolyticus*, *staphylococcus arlettae* and *Koccuria varians*. Although the company has history and data showing recurrence of contamination including fungal, this was not considered for investigation into root cause of such type of contamination. The non-viable particle monitoring was implemented since July 2016.

PART 4: CONCLUSION

Based on the areas inspected, the personnel met and the documents reviewed, and considering the findings of the inspection, including the deficiencies listed in the Inspection Report, as well as the Corrective Actions taken and planned, Biological E. Limited. was considered to be operating at an acceptable level for compliance with WHO GMP guidelines.

All the non-conformances observed during the inspection that were listed in the full inspection report as well as those reflected in the WHO Public Inspection Report (WHOPIR), were addressed by the manufacturer, to a satisfactory level, prior to the publication of the WHOPIR.

This WHOPIR will remain valid for 3 years, provided that the outcome of any inspection conducted during this period is positive.