



**Prequalification Team
WHO PUBLIC INSPECTION REPORT
Vaccine Manufacturer**

Part 1: General information

Name of Manufacturer	LG Life Sciences Ltd / Iksan Plant
Unit number	NA
Production Block	Production Line 3, Hepatitis B line, Hib Line, Quality Control, packaging area, warehouses.
Physical address	129 Seokam-ro, Iksan-si, Jeollabuk-do South Korea
Contact person and email address	Ms. Hyung-Shin (Helen) Kim: kimhs@lgls.com
Date of inspection	31 August – 4 September 2015
Type of inspection	Initial GMP Inspection for Eupenta Vaccine Routine GMP inspection for Euvax B and Euforvac-Hib Vaccines
Dosage forms(s) included in the inspection	Eupenta (DTP-HepB-Hib) liquid pentavalent Vaccine IM injection Euvax (HepB) Vaccine IM injection Euforvac-Hib lyophilised Vaccine IM injection
Summary of the activities performed by the manufacturer	The facility has biopharmaceutical drug substance (Hib and Hep B) manufacturing areas, finished product area (Euvax B), quality control laboratory and warehouse. It also has areas for utilities including water treatment system, clean steam generating system, air handling units and compressed air system in the basement. The facility is provided with Water for Injection (WFI), clean steam and HVAC systems for classified and unclassified environments. Other utilities include: purified water, compressed air, high and low pressure plant steam, hot and cold water, emergency power generation and waste water treatment system.



PART 2: SUMMARY

General information about the company and site

LG Life Sciences was founded in 1947 as Lak Hui Chemical, its former name LG Chemical, and is now Korea's leading company in biotechnology research.

LG Life Sciences's headquarter including Business Development, Product Development, Sales and Marketing is in Seoul, Research and Development Center is in Daejeon, Manufacturing site for chemical API and intermediates is in Onsan and Manufacturing site for Pharmaceuticals are in Iksan and Osong, Korea.

Iksan Plant of LG Life Sciences is located at 129, Seokam-ro, Iksan-si, Jeollabuk-do, Korea. This site is located within the Iksan industrial complex II. The total area of this site is approximately 80,000 m². There are three separate facilities – pharmaceutical plant, chemical API plant, and veterinary medicine plant - on this site that are used to produce pharmaceutical products.

The pharmaceutical plant was constructed in 1995 and extension building attached to the existing pharmaceutical plant for production of Erythropoietin (BEPO) was constructed in 2002. Chemical API plant for production of Gemifloxacin mesylate and Gemigliptin tartrate was constructed in 1999 and veterinary medicine plant for production of bovine somatotropin was constructed in 2001. Main office was constructed in 2008. The pharmaceutical plant for production of SR-hGH line 2 was constructed in 2009.

History of WHO and/or regulatory agency inspections

LG Life Science has undergone a series of inspections as provided in SMF and summarised below mainly for vaccines:

- ✓ 1st WHO Approval for Hepatitis B Vaccine in 1996
- ✓ 2nd WHO Approval for Hepatitis B Vaccine in 1999
- ✓ 3rd WHO Approval for Hepatitis B Vaccine in 2001
- ✓ 4th WHO Approval for Hepatitis B Vaccine in 2004
- ✓ Brazil ANVISA for Hepatitis B Vaccine and hGH in 2009
- ✓ Poland MOH for Hepatitis B Vaccine in 2010
- ✓ WHO PQ for Multivalent Vaccine in 2012
- ✓ Poland MOH for Hepatitis B Vaccine in 2013
- ✓ Brazil ANVISA for Hepatitis B Vaccine and hGH in 2015

Focus of the inspection

The scope of the inspection covered the production and control of Eupenta (DTP-HepB-Hib) Liquid form pentavalent Vaccine and Euvax (HepB) Vaccine. Furthermore, Euforvac Inj. (DTP-HepB-Hib lyophilised) vaccine was also included in the scope of this inspection.



The inspection in Iksan Plant focused on the production and control of Hepatitis B (HepB bulk) and conjugated *Haemophilus Influenza type b* (Hib bulk) active substances of Eupenta (DTP-HepB-Hib) Liquid form pentavalent Vaccine and Euvax (HepB) Vaccine.

The inspection covered all the sections of the WHO GMP text, including premises, equipment, documentation, materials, validation, sanitation and hygiene, production, quality control and utilities.

Inspected Areas

- Quality Assurance
- Sanitization and hygiene
- Qualification and validation
- Complaints
- Recalls
- Self-inspection
- Personnel
- Training
- Personal hygiene
- Premises
- Equipment
- Materials
- Documentation
- Production
- Quality control

PART 3: INSPECTION OUTCOME

2.1 PHARMACEUTICAL QUALITY SYSTEM

Quality Assurance is responsible for controlling the quality management system of Iksan Plant from the receipt of starting materials to the release of final product. These activities include review and approval of all quality-related documentation, process and system. The organizational Structure and Responsibilities of QA Team were provided in the SMF and the presentations during the opening meeting.

QA responsibilities stated by the company include review and approval of material and product release, review and approval of procedures and specifications, product release by qualified persons (QP), annual product review, documentation control of master batch records, SOPs, logbooks etc., change control, external and internal Audit, trainings including GMP SOP, deviation and failure investigation, approval of validation protocol and reports, customer complaints and Recall, quality risk management (QRM) and CMO control.



Corrective Actions and Preventive Actions (CAPA) management:

Provisions for CAPA handling were in place. In general terms, the procedure covers the description of issues, investigation into root cause, investigation on the impact to the quality of the product, CAPA implementation, CAPA effectiveness and CAPA monitoring processes. During the last WHO site inspection in Iksan Plant 69 observations including 4 major deficiencies were raised. All deficiencies were addressed by an acceptable CAPA and considered as implemented.

Change Control management:

Provisions for change control (CC) handling were in place according to the implemented procedure. Any changes on starting material, process, equipment, facilities, and specifications and test methods were implemented according to the written change control procedure. Changes are classified as major, moderate and minor according to the impact to the product, process, test method and/or required notification and submission to the regulatory authority. The effectiveness evaluation of implemented changes was considered for change control. The list of change controls as from January 2014 was provided to the inspector. Minor changes were defined as not affecting the product, process or test method and require no validation. The addition to the licence of Osong Plant as manufacturing site for Euvax Hep-B vaccine was considered as minor change control. Conducting the cleaning validation of Hib bulk (300g) was considered as minor.

Deviation management:

Deviations were dealt with according to the implemented deviation control procedure. Deviations are categorized as major, moderate and minor according to the criticality to the product. The list of deviations was provided. Deviations were spot checked. The investigation management of the deviation regarding defective dimension of vials gave rise to a concern that was addressed through satisfactory corrective and preventive action plan by the company.

Annual Quality Review (AQR):

AQR is performed according to the implemented procedure. All products are reviewed on an annual or periodic basis. All manufactured batches are reviewed. Change history, process deviation and investigation, in process test results and quality of final product are reviewed and quality trend is analysed on each test item. The production manager, the QC manager, and the QA manager review the annual product report. The report is documented and recorded.

AQR report of PRR-T Conjugate Bulk Product covering batches manufactured in 2013 and 2014 was authorized in August 2015, however the first version of the AQR was established in 30 June 2015.

Review of technical agreement was considered in the procedure however was not documented in the AQR. The quality of raw material is stated as not applicable in the PQR. TT specification for endotoxin is of nmt 480 EU/mg however the average results from the AQR 2013 and 2014 is around 2 EU/mg.



AQR report of Euvax B Inj covering batches manufactured in 2014 was approved 27th March 2015. 73 lot of Euvax B Inj. 100 ppm 0.5 mL all released. 21 batches of Euvax B Inj. 100 ppm 1 mL all released. 5 batches of Euvax B Inj. 100 ppm 5.0 mL all released. 10 batches of Euvax B Inj. 100 ppm 10.0 mL, 1 batch rejected. 20 batches of Euvax B Inj. 0 ppm 0.5 mL all released. 4 batches of Euvax B Inj. 0 ppm 1 mL all released. The addition of Osong Plant site for manufacturing final bulk solution and finished product was notified to MFDS. This was reported to WHO in January 2015.

The AQR was considered acceptable in general terms and the areas of concern were addressed by adequate corrective and preventive action plan by the company.

2.2 GOOD MANUFACTURING PRACTICES FOR PHARMACEUTICAL PRODUCTS

Good manufacturing practices generally were implemented. Overall, necessary resources were provided, including qualified and trained personnel, premises, equipment and services, appropriate materials, containers and labels, approved procedures and instructions, laboratories and equipment for in-process and other controls. Manufacturing steps were recorded in batch manufacturing and packaging records. Manufacturing processes were generally defined and reviewed. Instructions and procedures were generally available. Qualification and validation were performed. Operators were trained to carry out procedures, and records were made during manufacture.

Media Fill Simulation and Media Bulk Simulation:

Aseptic Processing Validation is performed according to the implemented procedures. In house isolated strains are used in addition to required ATCC strains. 3, 5 and 20mL vials were covered in the media simulation program. Results of MFT since 2012 were presented and no failure was recorded by the company.

The Environmental monitoring of the manufacturing facilities: acceptance criteria and control method for cleanliness monitoring, specifications, alert and action limits were in place. Locations of sampling points and the frequency of sampling were implemented considering a risk assessment approach. Monitoring results and trend analysis were spot checked.

2.3 SANITATION AND HYGIENE

Manufacturing areas are provided with airlocks for personnel and materials entries and exits. Gowning procedures for access to the classified and contained manufacturing areas were in place. Programs for cleaning of manufacturing areas and equipment were implemented. Control of Environment, Sanitation and Operation, Cleaning and Disinfection of Working Area and Equipment were in place.



2.4 QUALIFICATION AND VALIDATION

Provisions for validation and qualification were implemented.

Validation Master Plan in 2015 was established. Routine performance qualification plan for 2015 including the qualification status of major equipment was presented.

Depyrogenation tunnel is qualified every year.

The frequency for vial wash qualification was 5 years.

Formulation SIP is qualified every year.

The preventive maintenance of the filling machine was expected every 6 months.

Sterilisation autoclave is qualified every year. 12 pattern loads of hard goods are considered for qualification. Currently, leak test is performed once every week and Bowie Dick before each use. Vent filter Integrity are integrity tested every two week and sterilised before each sterilisation run.

Qualification of Pattern load containing assembly parts of the filling machine was reviewed.

Cleaning validation:

Cleaning policies for drug products vessels were established considering worst case scenario for most soiling products in contact material. Every 6 months, after performing MFT with TSB 3%, bioburden, TOC, conductivity, pH and endotoxin are checked on final rinse water (WFI) from the used vessels.

Water system:

Acceptance criteria, control method and sampling method for water monitoring were in place. Tests for raw water, pre-treatment water, purified water and water for injection were performed according to USP and EP monographs. Monitoring results and trend analysis for raw water, pre-treated water, PW and WFI as well as clean steam were spot checked.

Sanitization of water systems:

Periodic sanitization and appropriate measures to prevent microbial proliferation were in place. Water is circulated at over 75°C every two weeks for PW system and every 6 months circulation of Sodium Hydroxide (0.5%) during two hours.

The WFI storage tank and the recirculating distribution system are maintained at minimum 80°C and Sodium Hydroxide (0.5%) is circulated during two hours every 6 months. Control measures were in place for draining out the chemical.

Sephacryl columns were used for Hib Drug Substance purification processes. A target of maximum use was set as 30 for each column. Column life cycle validation protocol was ongoing. The qualification of the column was part of the manufacturing process validation as well as the cleaning and sanitisation of the column. TOC, pH, conductivity, Bioburden, endotoxin were considered for the cleaning validation of Hib column.

Validation process of Hib/Phenol has been reviewed.



Overall, qualification and validation provisions were implemented and considered acceptable. The raised areas of concern were addressed through adequate corrective and preventive actions by the company.

2.5 COMPLAINTS

Complaints are managed according to the implemented procedure. Complaints received in writing, verbally, or via visits are dealt with by a designated responsible in QA. All received complaints are recorded in complaints list and then investigated. QA investigates the plausible cause and makes a corrective and preventive action plan. The corrective actions are followed up by the responsible departments. The results of investigation are informed back to the customer via marketing and sales department. The above activities are all documented and recorded, and complaint documents are kept for permanent record.

The list of complaint of Euvax-B as from January 2014 was reviewed. Two Customer Complaint Reports were recorded.

2.6 PRODUCT RECALLS

Recall is managed according to the procedure “Regulation of Product Recall”. The SOP addresses retrieval of distribution data, notification of customers, receipt and segregation of returned product, investigation and reporting to authorities, and follow-up corrective and preventive actions. According to the SOP, a recall-committee is organized with QA manager, QC manager, production manager, distribution manager and the people concerned. The committee is responsible for investigation of the status, sets up of a preventive measure and orders the related department to follow up. QA manager notifies the recall to the Competent Authority as well as the customers. The managers of QA and QC deal with post recall management. As necessary, the Competent Authority may be involved in the complaints and the decision to recall. Recalls can be effected to below the wholesale level.

No recall for any of vaccines including Euvax B was recorded since last 3 years.

2.7 CONTRACT PRODUCTION AND ANALYSIS

Provisions for contract product and analysis are in place.

2.8 SELF INSPECTION AND QUALITY AUDIT

Internal audit of the site is performed regularly. The internal audit is performed as outlined in Annual Audit Master plan at least once a year for all departments. Findings in audit are informed to the responsible department for implementation, and corrective and preventive actions are documented.

External or vendor audits are also performed in order to qualify the suppliers of important starting materials and packaging materials. The audits are conducted at the vendor site by experienced and qualified auditor. The audit is documented and recorded in a report and follow-up of corrective actions are taken as necessary.



2.9 PERSONNEL

LG Life Sciences at Iksan Plant was staffed by around 279. Quality Assurance (19), Quality Control (45), Finished Product Production (61), Drug Substance Production I (24), Drug Substance Production II (39), Boostin Production (39), Chemical API Production (10), Production Management (11), Utility/Maintenance (12), Purchasing (2), Human Resources (5), Accounting (6) and Safety/Environment/Health (6).

Organizational chart showing the relationships between different areas including quality assurance, production and quality control, with identification by name and title of key personnel (Heads of Production, QA, QC, Warehousing, and Engineering) was provided in the SMF and the presentation during the opening meeting.

LG has a backup system for QC and manufacturing officers who are trained for performing duties in the QC tests and in the manufacture. Safety regulation of QC laboratory was provided.

Training

Arrangements for basic and in-service training and how records are maintained are in place. Personnel at Iksan Plant are trained regularly by qualified individuals on the job and GMP related subjects. The GMP training program is outlined in the annual training master plan for all departments. The efficacy of the training is assessed by conducting tests. A program of periodic proficiency testing is conducted with all laboratory analysts. The individual training records of the employee are kept and managed by the QA.

Spot check review of training record for operators from QC and production were reviewed and found satisfactory.

Personnel hygiene

All employees are trained to practice good sanitation and health habits. Each of the production units is equipped with isolated washing, changing and rest areas. Different working uniforms are provided to the employees depending on the classification of working areas. Smoking, eating, drinking and storage of food are prohibited and restricted to certain designated areas. According to the individual hygiene checklist, all personnel are monitored for clothing, health status and hygiene. The microbial contamination is checked regularly on the surface of clothes and hands of employees who work in critical area.

Personnel involved in the visual inspection are checked every 12 months for eye check. Health checks for all personnel are applied once every year. Hygienic checks for all personnel are provided once a week.

2.10 PREMISES

The company has provided an acceptable Site Master File with relevant documentation regarding the manufacturing processes, buildings, utilities and maintenance plans.

The facility is constructed as a three-story building and has biopharmaceutical drug substance production area, finished product area, quality control laboratory and



warehouse. It also has areas for utilities including water treatment system, clean steam generating system, air handling units and compressed air system in the basement. The facility is provided with Water for Injection (WFI), clean steam and HVAC systems for classified and unclassified environments. Other utilities include: purified water, compressed air, high and low pressure plant steam, hot and cold water, emergency power generation and waste water treatment system.

The first floor of pharmaceutical plant is separated into the biopharmaceutical drug substance production area, the finished product production area and storage for container and packaging material.

The biopharmaceutical drug substance production area has dedicated lines; Hepatitis B vaccine, human growth hormone, interferon, hyaluronic acid, *Haemophilus influenza type B* and erythropoietin.

Finished product production area comprises several production areas depending on the characteristics of finished product.

The second floor of pharmaceutical plant consists of quality control laboratory, production area and storage. The storage for starting material is located in this floor. QC testing of materials and products is done at QC lab on the second floor.

The building is equipped with separate air handling units that serves different rooms or areas in the building including high efficiency particulate air (HEPA) filters. HEPA filters have an efficiency of 99.99 % and are tested at regular intervals for aerosol penetration, air velocity, pressure differential, etc. The temperature and humidity are controlled in major working rooms. The facility was designed to have different HVAC zones, and positive and negative pressure differentials within and between zones for the prevention of cross contamination. There are different air handling units that control the different zones. In the biological containment area, ambient atmospheric pressure is maintained negative relative to its entrance and exit.

Haemophilus influenza type B is BSL2. Before detoxification, it is handled in separated rooms. The supplied water system and air handling unit are also separated from other products line.

The Manufacturing buildings involved in the production of Euvax B and Eupenta vaccines at Iksan Plant were in general terms considered suitable to the operations to be carried out. The areas of concern raised during this inspection were addressed through satisfactory remedial corrective and preventive action plan by the company.

2.11 EQUIPMENT

Product contact equipment (pipelines and tanks) are made of 316L stainless steel. Silicone hoses are used for liquid transfer where fixed transfer lines are not used.

Equipment and utensils employed in the production of drug substance and drug product are subjected to cleaning at regular intervals and, where appropriate, immediately before and/or after use according to established procedures.



Major production equipment includes filling machines, automatic washing & sterilization machine, autoclaves, hot air sterilizer, tanks, fermenters, and various chromatographic separation and purification columns. Equipment are periodically inspected in accordance with the maintenance master plan.

Preventive maintenance (PM) activities are performed and recorded, and corrective actions are taken as necessary according to the provisions in place.

2.12 MATERIALS

Provisions for incoming materials, intermediates and finished products are in place for reception, quarantine and release processes. Appropriate storage conditions are provided.

Starting materials and packaging materials are purchased from approved suppliers. For each delivery, the containers are checked for integrity of the package and seal and for consistency between the delivery note and supplier's labels. Incoming starting materials are stored in quarantine area with quarantine labels until tests are completed. Procedures for sampling with adequate equipment in suitable sampling rooms are in place. After approval of sample testing, starting and packaging materials are properly labelled with released labels and moved to the storage area.

Starting materials are weighed by warehouse personnel and cross-checked in weighing room of warehouse before use in production. The first in/first out (FIFO) principle is adopted for starting materials dispensing.

Rejected material storage area with locking system is available.

2.13 DOCUMENTATION

In general, documents were designed, prepared, reviewed and distributed with care. Documents were approved, signed and dated by the appropriate responsible persons. Documents were regularly reviewed and kept up to date. Records were made or completed when any action was taken. A documentation system was in place to guide production and control of products. These included Validation Master Plans (VMP); standard operating procedures (SOPs); Batch Manufacturing and Packaging Instructions and records; specifications of starting materials, packaging materials, packaging components and finished products; standard testing procedures, analytical records and certificates of analysis; qualification and validation protocols, schedules and reports; training schedules and records.

2.14 GOOD PRACTICES IN PRODUCTION

The Diphtheria, Tetanus, and whole cell Pertussis bulk concentrate are manufactured by BB-NCIPD Ltd., Bulgaria. The HBsAg and the *Haemophilus influenzae* type b - tetanus toxoid are manufactured by LG Life Sciences. Formulation, filling, testing, packaging, and release of the vaccine are performed by LG Life Sciences.

Overall, Manufacturing operations were in general terms carried out according to established procedures and approved document and batch processing records. In-process control tests and release control tests were in place.



2.15 GOOD PRACTICES IN QUALITY CONTROL

The Quality Control department consisting of chemical, instrumental, biological and microbiological analysis working teams is responsible for testing of starting materials, packaging materials, drug substances, and drug products. The quality Control are in charge of validation of test methods, establishment of specifications and test methods, environmental monitoring and water monitoring, stability test, management of laboratory equipment and instruments, standards and reagents.

A written procedure exists for handling of Out of Specification (OOS). The scope is covering raw materials quality test, stability quality test and finished product quality test. Provision for handling Out Of Specification results was available. No OOS was recorded since January 2014.

2.16 DISTRIBUTION AND SHIPMENT

Drug substances released by QA are stored according to their required storage condition. The temperature of storage is monitored. Drug substances are transferred to filling area for internal use just before filling and packed just before shipping outside. The products are shipped on the basis of the first-in/first-out (FIFO)

The released products are distributed to the customers via the distribution centre.

The storage access is restricted to authorized personnel.

Materials and products are stored at orderly storage of the various categories with proper separation and segregation: starting and packaging materials, intermediates, bulk and finished products, products in quarantine, and released, rejected, returned or recalled products. Finished products are stored on the pallet and away from the wall.

All material and product lots are identified as to its status (i.e., quarantined, approved, or rejected). The finished drug products are stored according to their required storage condition (e.g., temperature, humidity). The biopharmaceutical drug products are stored at cold condition. The temperature and humidity of storage area are monitored and recorded.

The validation of Shipment Studies of Euvax vaccine from Iksan to international destination has been reviewed.



PART 4: CONCLUSION

Based on the areas inspected, the people met and the documents reviewed, and considering the findings of the inspection, including the deficiencies listed in the Inspection Report, as well as the Corrective Actions taken and planned, LG Life Sciences Ltd (Iksan Plant) 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 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.