### Part 1: General information

<table>
<thead>
<tr>
<th>Name of Manufacturer</th>
<th>EuBiologics Co., Ltd.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Production Block</td>
<td>Clean Utilities in the Basement. Warehouse and Packaging Room in the 1&lt;sup&gt;st&lt;/sup&gt; floor. Animal Cell Line, Pilot F/F in the 1&lt;sup&gt;st&lt;/sup&gt; floor. Microbial Production in the 2&lt;sup&gt;nd&lt;/sup&gt; floor. QC Lab in 3&lt;sup&gt;rd&lt;/sup&gt; floor.</td>
</tr>
<tr>
<td>Physical address</td>
<td>BioVenture Plaza 4, 56 Soyanggang-ro, Chuncheon-si, Gangwon-do, 200-957 South Korea</td>
</tr>
<tr>
<td>Contact address</td>
<td>As above</td>
</tr>
<tr>
<td>Date of inspection</td>
<td>24 - 28 August 2015</td>
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<tr>
<td>Type of inspection</td>
<td>Initial Routine GMP Inspection</td>
</tr>
<tr>
<td>Dosage forms(s) included in the inspection</td>
<td>Vaccines Oral</td>
</tr>
<tr>
<td>WHO product numbers covered by the inspection</td>
<td>OCV (Oral Cholera Vaccine) 10 doses of 1.5 mL suspension in 2mL glass vial with rubber stopper and flip-off plastic cap with VVM 30</td>
</tr>
<tr>
<td>Summary of the activities performed by the manufacturer</td>
<td>Production and quality control of vaccines</td>
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</table>
PART 2: SUMMARY

General information about the company and site
EuBiologics Co., Ltd is located at BioVenture Plaza 4, 56 Soyanggang-ro, Chuncheon-si, Gangwon-do, 200-957 South Korea. EuBiologics is a biopharmaceutical company established in March 2010. Its aim is to produce safe and effective vaccines for the improvement of global public health. EuBiologics supplies a range of contract R&D and manufacturing (CRMO) services to biopharmaceutical companies for the development of biologics.

EuBiologics maintains a Quality Management System (QMS) based on ISO 9001 and an Environmental Management System (EMS) based on ISO 14001. Both certificates were issued by the Korean Standards Association. EuBiologics has a notification of site inspection for high risk pathogen from Korea Centre for Disease Control and Prevention.

History of WHO and/or regulatory agency inspections
This inspection is the initial WHO GMP inspection to EuBiologics.

For Euvichol, CoPP certificate 2015-A1-047 was issued on 30 January 2015 by the MFDS and GMP certificate 2015-B1-0061 was issued on 02 February 2015 by the Seoul FDA.

Focus of the inspection
EuBiologics has submitted the application for Euvichol OCV vaccine for Prequalification purpose in January 2015. Therefore, the inspection focused on the production and control of OCV (Oral Cholera Vaccine). The inspection covered all the sections of the WHO GMP text, including Quality Assurance, Sanitization and hygiene, Qualification and Validation, Complaints, Recalls, Self-inspection, Personnel, Training, Personal hygiene, Premises, Equipment, Materials, Documentation, Production and Quality control.

EuBiologics has overall responsibility for production and quality assurance of Euvichol and is in charge of production of monovalent cell bulks (drug substance), inspection of foreign particles, packaging and QC tests of the final lot (drug product). The production of final formulated bulk Euvichol (drug substance) and filling of the bulk into vials (drug product) is contracted out to Green Cross Corporation (GCC) at their Hwasun Plant.

PART 3: INSPECTION OUTCOME

3.1 PHARMACEUTICAL QUALITY SYSTEM (PQS)
Quality Management Review Board (QMRB) was in place and periodically reviewed:
- The design, implementation, monitoring and maintenance of pharmaceutical quality system
- Review of quality system and quality issues related to product quality
- Roles, responsibilities and authorities related to pharmaceutical quality system
The GMP organization is divided into Production department and Quality department independently. Quality Assurance (QA) is responsible for reviewing and approving all the procedures from the receipt of raw materials to the release of products. All SOP’s of quality management should be controlled.

**Change Control management**
To prevent any changes that could cause unexpected result in the product quality, EuBiologics implemented the change control procedure. The list of change controls has been reviewed during the inspection.

**Deviation management**
Deviations were dealt with according to the procedure. Deviations were categorized as critical and non-critical. Critical deviations were defined as having direct or potential impact on Drug Substance or Drug Product or serious GMP violations. The company has provided the list of deviations for review during the inspection.

**CAPA (Corrective and Preventive Action)**
EuBiologics implemented the CAPA to investigate the causes of deviation, change control, OOS, audit/inspection, complaints etc..., in order to take appropriate actions, and to prevent the recurrence of problems caused by the same reason and potential deviation according to the procedure. Reports on trending and effectiveness of CAPAs were presented every 3 months during the periodic management review. The meeting minutes of the quality management review board held in August 2015 was reviewed.

**Quality risk management**
Quality risk management (QRM) is the process for the assessment, control, communication and review of risk to the quality of the drug product. QRM is applied to development, manufacturing, distribution and inspection processes throughout the lifecycle of drug products. Especially, QRM is used to detect the potential risks during change control, validation and design process of facility and equipment. Usually, check sheets and FMEA (Failure Mode Effects Analysis) are used as the risk assessment tools.

**Product quality review**
Licensed products are reviewed for quality issues related to manufacturing and quality control activities annually according to the procedure. The reviews include the test results of raw materials and finished products, critical in-process control, deviations or out of specifications, changes of processes or analytical test methods, stability test results, returned products and complaints, recall etc...
Overall, in case of recurring deviations and out of trend identified, root cause analysis is followed and corrective and preventive actions are taken as to the standard operating procedures.
3.2 GOOD MANUFACTURING PRACTICES (GMPs) FOR PHARMACEUTICAL PRODUCTS

In general terms Good manufacturing practices were implemented. Overall necessary resources were provided, 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 steps were recorded in batch manufacturing and packaging records. Manufacturing processes were generally defined and reviewed. Instructions and procedures were generally in place. Operators were trained to carry out procedures, and records were made during manufacture.

3.3 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 are in place. Programs for cleaning of manufacturing areas and equipment are implemented. Combined cleaning agent and disinfectants are used alternatively.

3.4 QUALIFICATION AND VALIDATION

In general terms provisions for qualification and validation are in place and covers premises, equipment, utilities and systems, and processes and procedures at periodic intervals and when major changes have been made. Validation and qualification were performed in accordance with written protocols and adequate written report on the outcome of the validation were produced.

The Validation Master Plan, the Validation and qualification approaches and procedures were reviewed. Validation and qualification reports were reviewed.

Provisions for preventive and corrective maintenance were in place.

Transportation validation of DS from EuBiologics to GCC and DP from GCC to EuBiologics (summer and winter seasons) have been reviewed. Studies conducted on vials transported from GCC to EuBiologics found to be acceptable.

3.5 COMPLAINTS

Provisions for complaints handling were in place according to the procedure. No complaint was registered.

3.6 PRODUCT RECALLS

Provisions for product recall were in place according to the procedure. No recall was registered.

3.7 CONTRACT PRODUCTION AND ANALYSIS

EuBiologics has documented procedures to assess the qualifications of external companies. Companies should have a valid production license for pharmaceuticals and undergo periodic GMP inspections by MFDS. A site audit is part of the qualification process and accordingly a CAPA system is in place. At the completion
3.8 SELF INSPECTION AND QUALITY AUDIT

**Self-Inspection**
All the departments were internally inspected at least once a year to check the GMP compliance according to the procedure. The directors (or responsible person) of each department having recognised GMP experience were appointed as inspection member. There was no internal training for internal auditor, however an external training organised by MFDS was adopted. Annual internal audit plan AIAP 2014 and AIAP 2015 were presented. Triggered GMP non-compliance was treated in accordance with CAPA procedure in order to prevent the recurrence of the problem.

**Audits and Approval of Suppliers**
Supplier qualification is conducted for the suppliers who provide raw materials/packaging materials and services (including contract manufacturer). Potential supplier were in general terms assessed and selected based on their history in addition to the management structure, quality management system, quality of supplying product, delivery time and price. Site audit was performed for suppliers in regards to the major raw materials/packaging materials and contracted manufacturing company in addition to the assessment of documents.
The QA department was in charge of issuing the annual plan for the periodical supplier qualification. The periodic qualification for the major suppliers was planned every two years. This could be adjusted according to history and track records of suppliers.
The list of approved supplier was provided.

3.9 PERSONNEL
The GMP organization is divided into Production department and Quality department independently. The Production department is composed of Culture team, Purification team, Engineering team and Fill/Finish team. The Quality department is composed of QA team and QC team. The Warehouse team belongs to the Planning unit.
Qualification, experience and responsibilities of Key Personnel are provided in the Site Master File (SMF).
Personnel training was covered by procedures. Training records and analyst names have been provided. Analyst Certifications and qualification procedures are in place.
Personal Hygiene was covered as per the procedure.

3.10 Premises and Equipment
EuBiologics is located at Bio-venture Plaza 4, 56 Soyanggang-ro, Chuncheon-si, Gangwon-do, Republic of Korea. The manufacturing facility is an apartment-style factory with 4 floors above the ground and having 1 floor as basement. 5 other companies are dwelled in the same buildings.
EuBiologics occupies the whole basement floor, whole 1st floor, a part of 2nd floor and a part of 3rd floor. The use of each floor for the manufacturing of Euvichol was detailed in the Site Master File.

The production of monovalent cell bulks (drug substance) for Euvichol is performed in the Microbial Production area. The inspection for foreign particles in filled vials and packaging after the filling process are conducted in the packaging room. Production processes related to contract manufacturing take place in the multi-purpose building of the Hwasun plant (GCC).

Layouts and drawings of manufacturing areas and differential pressure diagram as well as the material, product and personnel flows including warehouse and packaging areas were reviewed. Layouts and drawings of QC laboratory and differential pressure diagram were reviewed.

The major equipment used in OCV production were reviewed.

Heating, Ventilation and Air-Conditioning (HVAC) systems, temperature and relative humidity, differential pressure are detailed in the provided SMF. The production area of OCV is kept with real-time monitoring and records the differential pressure, temperature, and RH by built-in control system.

Packaging room was inspected including, weight area, vial labeller machine and VVM sticker machine, visual inspection room and cold storage room. VVM 30 label sample was observed. Procedures for introducing vials from the warehouse until labelling for final marketing were illustrated.

3.11 MATERIALS

Received raw materials and packaging materials are checked for their names, quantity, specifications and manufacturers written in the order sheet and attached the respective COAs of materials at the buffer room in warehouse. The warehousing inspection is conducted to identify whether there is any defect on the quality of materials during transfer to the warehouse.

Accepted materials are transferred to the quarantine area of the storage place and assigned with a warehousing No, and QC test is requested by attaching the label “quarantining for test” on the materials. Rejected material is returned back to the supplier. Sampling of materials is performed in accordance with the approved procedures and requests for the QC test. Sampling is taken randomly from the materials kept in the quarantine area, and materials are attached with the label “under testing”. Approved materials are affixed with a green labels and transferred to the defined area of the warehouse. Rejected materials are affixed with red labels and are discarded or returned to supplier.

The procedures for test request, sampling, judgement of pass/fail and labelling methods of the drug substance or drug product are similar to those of raw materials and packaging materials. Drug substances are released after completion of QC testing and QA approval, the drug products is released after receiving the approval of National Lot Release Certificate from MFDS, KOREA.
Rejected materials are stored in a separated and dedicated area for rejected materials and locked to restrict the access. The rejected material is discarded (destroyed) by a contracted company.

The storage, control and discard procedures for the recalled products are same as to the rejected material.

3.12 DOCUMENTATION

The Document Structure has four levels, the first level consists of the Quality Manual, the overview policy document that describes the program and presents the key requirements. The second level consists of system level standard operating procedures that set forth the system requirements and processes. The third level of documents includes detailed work instructions, plans, protocols and specifications, and the fourth level is the supporting documentation or records that provide evidence that procedures have been followed appropriately.

Overall Provisions for archival and classification of controlled document was in place. Retention period for batch record (including COA) is 3 years after the expiration date of the corresponding product. Environmental monitoring, water monitoring, validation report, etc. will be preserved over 5 years.

3.13 GOOD PRACTICES IN PRODUCTION

Euvichol is composed of four strains of *V. cholerae*. Among them, one strain is formalin inactivated and heat inactivated. Thus, Euvichol contains 5 monovalent cell bulks.

Vaccine composition:

<table>
<thead>
<tr>
<th>Vaccine Component</th>
<th>Number of Doses</th>
<th>Pharmaceutica form</th>
<th>Container: type and capacity</th>
<th>VVM type</th>
<th>2nd Packaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>Euvichol</td>
<td>10</td>
<td>1.5 mL suspension</td>
<td>2mL glass vial with rubber stopper and flip-off plastic cap</td>
<td>30</td>
<td>Carton containing 10 Vials</td>
</tr>
</tbody>
</table>

Processing and packaging operations of drug substance were considered adequately implemented. The production process of the Euvichol final lot (drug product) was subcontracted to Green Cross Corporation (GCC).

Prevention of cross-contamination and bacterial contamination during production after production of one product, the cleaning of production area is performed in accordance with Product Change-over Procedures in order to prevent the cross-contamination or mix-up between products. The fumigation is performed for the production area in accordance with the “Fumigation Procedure”.

3.14 GOOD PRACTICES IN QUALITY CONTROL

The Quality Control (QC) Department is separated from the Quality Assurance Department (QA). QC laboratory is divided into three labs including chemical lab,
microbiology lab and sterility test room and is completely separated from the production area.

QC is in charge of setting up the test methods and performing the tests for raw material, intermediate product and finished product as well as the stability tests. QC is in charge of analytical method validation, qualification of test instrument, calibration and storage of reagents and standards.

Out of Specification (OOS) test results are dealt with as per the procedure.

Stability studies: Standard procedures for DS of Euvichol proposed 36 months and the stability results have been provided and are within the acceptance criteria. The stability studies protocol and results were reviewed and revealed to be satisfactory.

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, EuBiologics 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.