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

Part 1	**General information**
Manufacturers details	
Company information	
Name of manufacturer	SK bioscience Co., Ltd.
Contact person	Ms SookMi Hwang, Head of Global Regulatory Affairs, smihwang@sk.com
Inspected site	
Address of inspected manufacturing site	Headquarters: 310, Pangyo-ro, Bundang-gu, Seongnam-si, Gyeonggi-do, Republic of Korea. Production Site (L HOUSE): 150, Saneopdanji-gil, Pungsan-eup, Andong-si, Gyeongsangbuk-do, Republic of Korea.
blocks	Suite 8 – Varicella Bulk manufacturing area Filling line 4 Quality control laboratories. Warehouses.
Inspection details	
Dates of inspection	20 to 24 May 2019
Type of inspection	Initial inspection
Representative from the National Regulatory Authority	The national regulatory authority (MFDS) of Korea where the inspection took place was informed and the Assistant Director, Pharmacist/Biopharmaceutical Quality Management Division, participated to the closing meeting (24 May 2019).

Introduction	
Brief summary and general information about the manufacturing activities of the company	SK bioscience has the manufacturing site L HOUSE for vaccines production. L HOUSE, located in Andong-si, Gyeongsangbuk-do, Korea, is a manufacturing facility dedicated to the production of vaccine products. After being registered as a manufacturing facility in May 2013, L HOUSE initiated the production of clinical trial samples in October 2013 and received Ministry of Food and Drug Safety (MFDS) approval, which allows production of parenteral dosage forms including vaccines and other biological products in August 2014. SK bioscience has registered SKYCellflu® prefilled syringe (PFS), the first cell culture influenza vaccine in Korea (MFDS), followed by the licensure of SKYCellflu® Quadrivalent prefilled syringe (PFS) and 13-valent Pneumococcal Conjugate Vaccine (PCV). Zoster vaccine (SKYZoster inj.) was GMP approved by MFDS in September 2017. Varicella vaccine (SKY Varicella inj.) was GMP approved by MFDS in June 2018 and commercialised since September 2018. For flexible production of diverse vaccine types, L HOUSE has equipped single-use and multi-modular vaccine manufacturing systems on a commercial scale. Five commercial batches of SKYVaricella Inj. Varicella Virus Vaccine (live) [Oka/SK] were manufactured and submitted for official batch release to the national control laboratory NIFDS (V0411801, 802, 803, 804 and 901). V0411801 and V0411802 were fully released domestically. V0411803 12505 vials out of 43872 vials are still in the stock and the rest shipped domestically.
History	This was the second on-site inspection conducted by WHO PQ Inspection team. The list of Good Manufacturing Practice (GMP) inspections of the site within the last 5 years is presented below:

Date	Inspection type	Product	Competent Authority
June, 2014	Pre-approval GMP inspection	SK Influenza IX Prefilled Syringe SK Influenza X Prefilled Syringe	MFDS
August, 2014	Pre-approval GMP inspection	SKYCellflu Prefilled Syringe	
February, 2015	Pre-approval GMP inspection	SKYZoster Inj.	
June, 2015	Pre-approval GMP inspection	SKYPneumo Prefilled Syringe	
July, 2016	Pre-approval GMP inspection	SKYCellflu inj.(Vial)	
August, 2016	Regular GMP inspection	Inspection for overall GMP system	
January, 2019	Prequalification GMP inspection	SKYCellflu inj. (0.5 mL vial) and SKYCellflu Multi inj. (5.0 mL (10-dose) vial)	WHO

			(Trivalent Influenza Vaccine).	
	January, 2019	Pre-approval GMP inspection	SKYCellflu Quadrivalent Prefilled Syringe, SKYCellflu Prefilled Syringe, SKYZoster Inj., SKYVaricella Inj.	Turkey MoH

Brief report of inspection activities undertaken

Scope and limitations

Areas inspected	The inspection focused on the production and control of SKYVaricella Inj. (Varicella Virus Vaccine (live) (Oka/SK)). The Vaccine is a lyophilized white crystalline pellet in a clear and colorless 3ml glass vial, accompanied with a clear and colorless 3 ml glass vial of diluent (water for injections) for reconstitution as a single dose. The vaccine is colorless or pale-yellow liquid when reconstituted to a suspension and the reconstituted vaccine is administered subcutaneously. The single dose of 0.5 mL is ≥ 2,400 PFU of live, attenuated varicella-zoster virus. The inspection covered all the sections of the WHO GMP text, including quality assurance, sanitization and hygiene, complaints and recalls, self-inspection, personnel, training, personal hygiene, premises and equipment, materials, documentation, qualification and validation, production, quality control and utilities.
Restrictions	None
Out of scope	Products and vaccines other than SKYVaricella Inj. vaccine were not inspected during this inspection.
Vaccines covered by the inspection	SKYVaricella Inj. Varicella Virus Vaccine (live) [Oka/SK]

Abbreviations

AHU	Air Handling Unit
ALCOA	Attributable, Legible, Contemporaneous, Original and Accurate
APR	Annual Product Review
APS	Aseptic Process Simulation
BMR	Batch Manufacturing Record
BPR	Batch Production Record
BSC	Biological Safety Cabinet
CA	Compressed Air
CAPA	Corrective Actions and Preventive Actions
CC	Change Control
CFU	Colony-Forming Unit
CIP	Cleaning In Place
CoA	Certificate of Analysis
CpK	Process capability
CQA	Critical Quality Attribute

DQ	Design Qualification
EDI	Electronic DeIonization
EM	Environmental Monitoring
FMEA	Failure Modes and Effects Analysis
FTA	Fault Tree Analysis
GMP	Good Manufacturing Practices
GPT	Growth Promotion Test
HA	Heamagglutination Assay
HEPA	High Efficiency Particulate Air
HVAC	Heating, Ventilation and Air Conditioning
IPC	In Process Control
IQ	Installation Qualification
LAF	Laminar Air Flow
LIMS	Laboratory Information Management System
LSP	Lot Summary Protocol
MB	Microbiology
MBL	Microbiology Laboratory
MF	Master Formulae
MFT	Media Fill Test
MR	Management Review
MRV	Measles Rubella vaccine
NC	Non Conformity
NCA	National Control Authority
NCL	National Control Laboratory
NRA	National Regulatory Agency
OQ	Operational Qualification
PFS	Pre-Filled Syringe
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
PUPSIT	Pre Use Post Sterilization Integrity Test
PW	Purified Water
QA	Quality Assurance
QC	Quality Control
QCL	Quality Control Laboratory
QMS	Quality Management System
QRM	Quality Risk Management
RA	Risk Assessment
RCA	Root Cause Analysis
RBC	Red Blood Cell
RO	Reverse Osmosis

SIP	Sterilization In Place
SME	Subject Matter Expert
SMF	Site Master File
SOP	Standard Operating Procedure
TNTC	Too Numerous To Count
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

Part 2: ***Brief summary of the findings and comments***

All manufacturing activities at the site, including storage and QC, were performed in one building in which several areas with independent access were created.

The bulk production area (Suite-8) was dedicated to Varicella/Zoster vaccines and was not inspected previously by WHO PQ inspection team.

The general design of the facilities for the compounding and filling of vials was having a single tunnel supplying two separate filling rooms dedicated to fill live viral vaccine and inactivated vaccines. The filling room of influenza vaccine was inspected by WHO in 2018.

1. Pharmaceutical quality system

The effectiveness of the Pharmaceutical Quality System was evaluated through the review of documentation related to: Annual Product Quality Reviews, production activities, risk assessments, management of deviations and change controls, process validations, QC testing, equipment qualifications, supplier qualifications, quality agreements, management of complaints and recalls, training activities, self-inspections and regulatory compliance.

There generally appeared to be adequate resources available for the management of the implemented QMS, which was found as well structured and operating at a good level of compliance. Quality assurance and quality control activities were functioning with independence from the production unit. Managerial responsibilities were specified in job-descriptions. Employees involved in GMP activities were qualified and trained. Production and control operations were specified in written form and GMP requirements were generally followed. Product and processes were validated and monitored, and the results considered in batch release; regular reviews of the quality of vaccines were conducted.

The company had premises with suitable equipment and services. Suitable storage and transport condition were provided. A system for recall and complaints management was present.

Product quality review:
APQRs were prepared according to the procedure in place.
No annual product quality review was available for SKYVaricella, since the production started less than 1 year ago (September 2018).
Nonetheless, the Drug Substance of Varicella vaccine followed the same production process as Zoster vaccine and some bulks were in common therefore, the Annual Product Quality Review related to SKY Zoster, manufactured in the period October 2017 - October 2018, was reviewed. The only difference between the two manufacturing processes was related to the amount of virus which was added at the level of formulation.

Several bulks and finished product lots of SKY Zoster were produced in the analyzed period; several lots of diluent (sterile WFI) were also manufactured. No rejections were identified nor OOS to be investigated. The document included all raw data and a graphical analysis of the different quantitative parameters and quality attributes, where upper and lower confidence limits were identified. When the number of produced lots will increase a more accurate statistical analysis will be needed to identify possible trends.
No comparison to previous years was possible, due to the recent approval of SKY Zoster vaccine.

Upon the evaluation of the upstream process, which was in fact in common with SKY Varicella, it was noted that IPCs were not properly set in the routine practice, leading to a weak control strategy of the manufacturing process performance and consistency. In addition, not all quality control tests foreseen by WHO TRS 848 Annex 1 were included at single harvest and drug substance stages, with no justification. Safety tests (sterility and mycoplasma) were only conducted at bulk stage, even if: i) the manufacturing process was fully aseptic, ii) a conspicuous number of sub-culturing steps were performed, iii) cells were kept in culture for several days, iv) a cytostatic antibiotic (neomycin) was present in culture media that could prevent the detectability of an eventual contamination at a microscopic evaluation, v) endotoxins were never evaluated. The company had adequately addressed all the issues raised through the CAPA plan.

The quality risk management:
Procedure for QRM was in place.
The company approach to QRM was improved since the last inspection, even if additional efforts were needed to reach the requested compliance: some of the planned assessments were not yet completed or not properly performed. The company had adequately addressed all the issues raised through the CAPA plan.

Management review:
The procedure for management review, recently reviewed as corrective action to the previous WHO inspection, was in place to document processes for management review meetings.
Meetings were planned at least quarterly and a predefined panel of managers covering different aspects of the production was requested at the meetings.
The last four meetings were indeed performed at higher frequency than expected, due to the presence of specific needs identified during production, and issues were evaluated by a multidisciplinary team.

Deviation management:
The deviation control procedure was in place. A system for managing deficiencies, categorizing severity and investigating issues to identify root causes, as well as implement corrective and preventive actions was present. To assess the system, several deviations, selected from the list related to the manufacturing of Varicella/Zoster from the initial approval (less than two years), were reviewed. Minor issues were raised and the company had adequately addressed all the issues raised through the CAPA plan.

Change control:
Changes were managed through the procedure in place and categorized as critical, major and minor according to their impact on the quality, safety and efficacy of the vaccine.

List of change controls since the approval of Zoster vaccine was reviewed, and some changes were selected for spot check. No issues were raised.

Documentation:
In general, written documentation was well designed, comprehensive, readily available and prepared, reviewed and distributed with appropriate care and control. SOPs were in place for document approval, issue and control. Documents reviewed during the inspection had generally been approved, signed and dated by the appropriate responsible persons.

The GMP related documents are kept for 10 years in a fire proof room under QA control.
There was a company policy on IT information and security. There was a data integrity control procedure mentioning the principles of ALCOA, audit trail and that the data should be complete, consistent, enduring, available and reliable.
However, the company systems to assure the reliability and integrity of data in various areas such as production and quality control were deficient. The company had adequately addressed all the issues raised through the CAPA plan.

Batch Release Process:
Batch Release Process was spot checked. The preparation of certificate of lot release included that the person in charge of release at QA shall fill the information of the drug product in the review check sheet for approval of lot release and confirm the following requirement:

- review of batch record was completed in accordance with the Manufacturing Record Review Procedure,
- testing was completed, and all testing results were complying with the Test Record Review Procedure,
- deviations were recorded and completed,
- confirm the changes and these changes were completed and applied,
- if the drug product was for national release approval, confirm it was completed.

The approval of certificate of lot release required that the qualified person reviewed the certificate of lot release and finally determined whether the drug product could be released, if the quality was failed, the vaccine lot release was not released.

The procedures for national release of vaccines was spot checked. The procedures were initiated with that:

- a request to KFDA to national release was established, the Lot Summary Protocol was prepared and confirming the information of the batch record and QC test record,
- vaccine samples to be collected by KFDA's officer directly from SK bioscience to conduct testing,
- once vaccine samples tested as pass, the KFDA approved for national lot release issued and the national lot certificate was addressed to the person in charge of QA team.

An example of lot release of SKY Varicella inj. vaccine was spot checked and found appropriately managed and documented.

Lot summary product review:

The procedure describing the process required for lot release was spot checked. Two templates for LSP (Domestic and International) were considered for use in the release of varicella vaccine.

Since September 2018, five lots have been released by MFDS and three lots were released for domestic market for national immunization program (NIP).

Complaints:

The procedure for handling complaints was in place. Complaints were classified depending on the criticality and severity.

The list of complaints related to both Zoster and Varicella vaccines since the initial approval (October 2017 and June 2018 respectively) was reviewed: only two complaints were received, both related to the presence of black particles in the reconstituted vaccine.

A proper investigation was conducted, and the root cause identified as depending on small fragments released by rubber stoppers when punched by the needle.

Product recalls:

The procedure for recall management was in place.

There was no incidence of recall with any of the vaccines at SK bioscience since the initial approval of the facility. According to an internal policy, after five years with no recall, a mock procedure should be foreseen. The first mock recall was planned for the second half of 2019.

Pharmacovigilance:

The pharmacovigilance was regulated through a set of procedures to ensure the best practices to identify incidence rates of adverse event (AE) and adverse drug reaction (ADR) post vaccination sessions.

According to regulation on post marketing safety management of medicinal product, any AE relevant to the product received from patients and healthcare professionals was collected and reported to Korea Institute of Drug Safety & Risk Management (KIDS). In case of serious adverse drug reaction (SADR), the individual case safety report was reported in an expedited manner to KIDS within 15 days from the date of awareness and the other cases which were not expedited should be reported within 1 month after the end of each quarter. SKY Varicella inj. was subject to Post marketing surveillance (PMS) for 4 years from the date of approval in Korea, during which period, safety information from 600 subjects should be collected and reported.

Since September 2018, five lots (V041801, V041802, V041803, V041804 and V041901) of SKY Varicella Inj. vaccine were produced, three lots were released by MFDS for domestic market as per NIP, hence safety data were collected. In total, 37 cases of AE/ADR were reported until May 2019. 11 out of 37 cases were with unexpected AE/ADR. One out of 11 unexpected AE/ADR cases was with a serious condition (Shock). Seven out of 11 AE/ADR cases were with vaccination site blisters.

Quality audits and suppliers' audits and approval:

Procedures for the qualification of the supplier of materials were in place. A categorization of the material based on the contact with the product was considered and accordingly a site audit of the supplier and the material testing are drawn. The audit can be based on onsite audit and/or questionnaire. Provision for disqualifying a supplier was considered.

The categorisation of the material was as follows:

Category 1: Materials in direct contact with product and materials affecting product quality. Suppliers of category 1 were expected to be audited at least once every two years by means of audit and testing sample (if necessary).

Category 2: Materials used for manufacturing but removed during intermediate process or without direct effect on product quality. Suppliers of category 2 were expected to be audited at least once every three years by means of questionnaire, audit or testing (if necessary).

Category 3: Materials not used for manufacturing. Suppliers of category 3 were expected to be audited at least once every three years through questionnaire.

The list of qualified suppliers with the approval date and the next planned audit was spot checked.
The qualification of the supplier of animal origin materials was spot checked.

The company has stated that preparation and planning requirements for receiving VVM in the future was in the process of preparation but not yet finalized. No document to support this claim was provided for review during the inspection. This was raised in the last WHO inspection. The company had adequately achieved the calibration of the VVM scanner, established SOPs for heat marker and heat marker test, and implemented the preparation and maintenance protocol of the spectrodensitometer, and then completed the qualification according to the established VVM verification protocol.

Contract production, analysis and other activities And Quality agreement:

Contract production was in place for manufacturing of MCB and WCB cell bank. Agreement with subcontractor was in place and new GMP license was valid.

Personnel:

Organizational charts showing the relationships between different departments, including QA, Production, QC, Warehouse and Engineering with identification of the key personnel were available. Curricula vitae and the job responsibilities for key personnel, with qualification, experience and responsibility were provided. The teams of the quality unit and their operational responsibility were defined.

Training:

Training was managed through several procedures. For new employees, for existing employees, for aseptic training of people working in the fill/finish facility. QA prepared the GMP training plan annually and arranged training both from internal and external sources.

Each new employee is firstly subjected to theoretical training on general manufacturing and GMP aspects and then assigned duties outlined in the relevant job description. Extensive on-the-job trainings were provided to all the employee, based on the duties assigned.

For aseptic operations, each employee must undergo 3 successful runs of gowning and should participate to 3 Media Fill/Media Simulation tests for initial qualification, then repeated at least annually to be confirmed as qualified.

Lists of staff units qualified to perform manufacturing operations were in place, as well as a list of QC personnel qualified to perform Environmental Monitoring.

The operators in charge of the visual inspection were qualified on annual basis and had eye check once per two years.

The qualification record of one visual inspector was spot checked, as well as the procedure for establishing the default kit.

The procedure for "Education and Training Regulation" for assigning and qualifying of QC analysts was spot checked. The education and training in relation to basics, team training, on-the-Job training, new employee training, and external training were carried out. Trainings included sample receipt, sampling and sample control, evaluation and qualification of test results. Evaluation test was carried out for all trainees. Competency test should be carried out for at least three validated tests. Delivery training and re-training was carried out for not new trainees and for not passed analysts.

Training record for an analyst in training area of deviation was spot checked.

Personal hygiene:

The procedure for monitoring the health care and hygiene of personnel before and after joining the service were in place. Periodical health examination is carried out once a year for all employees. Employees working in the hazardous area were required to undergo special medical examination. Vaccines are administered to personnel who have been at possible risk of infection by virus.

Personnel having health problems such as respiratory disease, external wound, supportive disease, cold and diarrhea were required to write a report to the supervisor. The supervisor of each team was required to record and check the health status of each employee.

There existed a well-defined gowning requirement for each manufacturing area based on cleanliness classification and type of operation to prevent contamination and safety of personnel.

2. Production system

Good manufacturing practices were generally implemented. Necessary resources were provided, including qualified and trained personnel, adequate premises, suitable equipment and services, appropriate materials, containers, approved procedures and instructions, laboratories and equipment for in-process and other controls. Manufacturing steps were and recorded in batch manufacturing record (BMR) and packaging records. Deviations from procedures were recorded and investigated. Product was being released by the authorized persons of the Quality unit in accordance with written procedures.

The following processes and procedures were spot checked:

- Cell Bank and Seed Bank
- Characterization of MCB and WCB
- Characterization of MSB and WSB
- Drug Substance (DS)
- Media and buffer solutions preparation
- Validation of aseptic process through media simulations
- Drug Product (DP)
  - Final bulk
  - Final lot
- Process Validation
- Lyophilisation
- Leachability & Extractability (L&E) studies of Container Closure System EVA Bag
- Validation of aseptic processes through media fills
- Validation of the sterile filtration of EDTA buffer, MgSO4 buffer, phosphate buffer, sonication buffer and gelatin buffer used in drug substance manufacturing and formulation
- Filter integrity test
- Waste management and spillage control measures
- Batch manufacturing record review (BMR)
- The labelling and packaging suite and visual inspection room
- Water systems test results

3. Facilities and equipment system

The facility was dedicated to the manufacturing of vaccines and it was composed of a main building, an animal laboratory and exterior waste storages. The main building was a two-storey building, containing eight vaccine bulk production suites, filling area, packaging area, warehouse, QC laboratory, utilities.
The animal laboratory and the exterior waste storages were separated from the main building.

Finishing of manufacturing areas were of adequate standard. Exposed surfaces were smooth, impervious and unbroken so as to minimize the shedding or accumulation of particles or microorganisms and were of materials suited to the repeated application of permitted cleaning agents and disinfectants, where used.

Clean areas for the manufacturing were classified in accordance with the required characteristics of the environment demanded by the sterile products and containment of live microorganism. Clean rooms were routinely monitored while in operation. Appropriate alert and action limits had been set for the results of particulate and microbiological monitoring.

Production premises had generally been laid out to allow the production processes to take place in a logical flow, corresponding to the sequence of the operations and under the necessary cleanliness levels to minimize the risk of cross-contaminations and permit effective cleaning.

As a general approach, or flexible production of diverse vaccine types, the facility was equipped to handle single-use and multi-modular vaccine manufacturing systems at a commercial scale, whenever possible.

Access to production premises was restricted to authorized personnel.

The BMS (Building Management System) was in place to monitor critical environmental parameters, like temperature, humidity and pressure differentials. Appropriate sensors for alarms were available in critical areas, and a system to raise and manage alarms on a daily basis was in place.

The Temperature Recording System was instead used for monitoring critical process parameters related to equipment, like temperature of deep freezers and cold rooms, temperature and CO_2 of incubators. Some incubators were also equipped with local continuous recordings.

Cleaning activities were managed through relevant procedures and a risk assessment was performed to identify product contact equipment for which cleaning validation was requested. Cleaning activities were foreseen before and after any operation, at regular intervals and in special circumstances.

Upstream manufacturing premises

In general, premises and equipment were well maintained and observed to be at a satisfactory level of cleanliness. From the general corridor it was possible to access the different suites.

In the inspected manufacturing Suite, there were 2 separate areas were distinguished, one dedicated to clean operations and the other used for manufacturing steps in the presence of virus. Gowning rooms were in common, while degowning took place in separate airlocks, to avoid any risk of virus spreading. Separate AHUs were used to support such segregation also in terms of air supply. A positive pressure and an airflow relative to surrounding areas of a lower grade was maintained: adjacent rooms of different grades had a pressure differential of approximately 10 Pascals, while adjacent rooms of the same grade maintained a difference of 5 Pa.

Procedures for decontamination and disposal of used contaminated materials and waste management were in place. A decontamination autoclave was present in the infected area for waste disposal.

Downstream manufacturing premises

The general design of the facilities for the compounding and filling of vials was appropriate and already discussed in the previous WHO inspection report (2018).

For Grade A and B zones, particle monitoring was undertaken for the full duration of critical processing steps. To control the microbiological cleanliness of Grades A–D in operation the clean areas were monitored. Appropriate alert and action limits had been set for the results of particulate and microbiological monitoring

QC laboratories

In general, finishing of QC areas were of adequate standard. The Physicochemical Laboratory, Microbiology Laboratory and Virology Laboratory were appropriately segregated from the Animal Testing Laboratory.

QC laboratories including microbiological laboratory were separated from production areas. The laboratories were of sufficient space and design to allow for proper segregation of activities and avoid mix up during testing activities. Adequate storage space was provided for samples, reference standards, solvents, reagents and records.

Equipment qualification

The company had identified what qualification and validation work was required to be performed and the key elements of the qualification and validation programme were generally well defined in the validation master plan (VMP) and specific study protocols and reports. Appropriate documentary evidence was available that relevant equipment and processes for the products under review had been designed, installed, and performed in accordance with their design specifications.

Preventive maintenance program and calibration plan were in place. Records and logbooks were available.

Qualifications and validation reports of the following equipment were spot checked:

- Incubators
- Cold rooms
- Autoclaves
- Depyrogenation tunnel of filling line
- Lyophiliser
- HVAC qualification and requalification.

4 Laboratory control system

The QC function was independent of other departments. Adequate resources were available to ensure that all the QC arrangements are effectively and reliably carried out.

QC laboratories including microbiological laboratory was separated from production areas. The laboratories were of sufficient space and design to allow for proper segregation of activities and avoid mix up during testing activities. Adequate storage space was provided for samples, reference standards, solvents, reagents and records. Gowning and shoe covering at QC area were practiced at entry.

The testing procedure and facilities were reviewed and considered generally acceptable.

5 Materials system

Overall, provisions for incoming materials, intermediates and finished products were in place for reception, quarantine and release processes. Appropriate storage conditions were provided. Rejected and returned material procedures were in place.

All incoming raw materials, including packaging materials, were examined and stocked in the warehouse and subjected to transfer into quarantine area. Raw materials recorded in a computerized system. Samples requested for QC test before release. Quarantined and Passed samples were labelled with “under testing” and “Pass material” labels, respectively. Rejected material room, cold room for storage and sampling room for QC sampling were visited. Sampling room divided into gowning/de-gowning room, clean booth is available and samples are passed through designated pass-box.

6 Packaging and labelling system

Packaging/Labelling store was visited. Labels were well segregated and locked.

Labeling and packaging line was visited. The area was of adequate space and appropriate flow of material and product during the labeling process.

The machine for application of dot of VVM on label was available. Freezer for storage for VVM temperature indicator dot was available.

Shipping container configuration

Packaging of Varicella vaccine for the international shipments using containers were validated by contracted laboratory according to *WHO/IVB/05.23, Guidelines on the international packaging and shipping of vaccines*. Two types of packaging are to be used for a period of 48 hours and the other is for 72 hours to ensuring the class C packaging. The international shipping validation protocol and report for 72 hours were spot checked. The validations were conducted at temperature conditions 43°C and -5°C. The agreement for contracting the international shipping validation study was spot checked. The agreement was valid.

PART 3

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, and committed to be implemented, ***SK bioscience Co., Ltd***. located at ***Production Site (L HOUSE): 150, Saneopdanji-gil, Pungsan-eup, Andong-si, Gyeongsangbuk-do, Republic of Korea*****,** was considered to be operating at an acceptable level of 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.

DEFINITIONS

Critical deficiency
A *critical* deficiency may be defined as an observation that has produced, or may result in a significant risk of producing, a product that is harmful to the user.

Major deficiency
A *major* deficiency may be defined as a non-critical observation that:

- has produced or may produce a product that does not comply with its marketing authorization and/or prequalification application (including variations);
- indicates a major deviation from the GMP guide;
- indicates a failure to carry out satisfactory procedures for release of batches;
- indicates a failure of the person responsible for quality assurance/quality control to fulfil his or her duties;
- consists of several other deficiencies, none of which on its own may be major, but which together may represent a major deficiency and should be explained and reported as such.

Other deficiency
A deficiency may be classified as other if it cannot be classified as either critical or major but indicates a departure from GMP. A deficiency may be other either because it is judged as minor or because there is insufficient information to classify it as major or critical.

Classification of a deficiency is based on the assessed risk level and may vary depending on the nature of the products manufactured, e.g. in some circumstances an example of another deficiency may be categorized as major.

PART 5

List of GMP guidelines referenced in the inspection report

1. WHO good manufacturing practices for pharmaceutical products: main principles. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Eighth Report Geneva, World Health Organization, 2014 (WHO Technical Report Series, No. 986), Annex 2.
   Short name: WHO TRS No. 986, Annex 2
   http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_986/en/

2. WHO Good Manufacturing Practices: water for pharmaceutical use. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fourth-Sixth Report. Geneva, World Health Organization, 2012 (WHO Technical Report Series, No. 970), Annex 2
   Short name: WHO TRS No. 970, Annex 2
   http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_970/en/

3. WHO guidelines for sampling of pharmaceutical products and related materials. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-Ninth Report. Geneva, World Health Organization, 2005 (WHO Technical Report Series, No. 929), Annex 4
   Short name: WHO TRS No. 929, Annex 4
   http://whqlibdoc.who.int/trs/WHO_TRS_929_eng.pdf?ua=1

4. Supplementary guidelines on good manufacturing practices: validation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fortieth Report. Geneva, World Health Organization, 2006 (WHO Technical Report Series, No. 937), Annex 4
   Short name: WHO TRS No. 937, Annex 4
   http://whqlibdoc.who.int/trs/WHO_TRS_937_eng.pdf?ua=1

5. WHO Good Practices for Pharmaceutical Quality Control Laboratories. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957, Annex 1
   Short name: WHO TRS No. 961, 957), Annex 1
   http://www.who.int/medicines/publications/44threport/en/

6. WHO Good Practices for Pharmaceutical Products Containing Hazardous Substances. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957), Annex 2
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