

**Prequalification Team Inspection Services
WHO PUBLIC INSPECTION REPORT
of the Vaccine manufacturer**

Part 1	General information
Manufacturers details	
<i>Company information</i>	
Name of manufacturer	SK bioscience Co., Ltd.
Contact person	Ms. SookMi Hwang, Head of Global Regulatory Affairs, smihwang@sk.com Dr. Jin-yong Park, Head of Quality Unit (Qualified Person), jypark3@sk.com
Inspected site	
Address of inspected manufacturing site	Headquarters: 310, Pangyo-ro, Bundang-gu, Seongnam-si, Gyeonggi-do, Republic of Korea. Production Site (Andong site): 150, Saneopdanji-gil, Pungsan-eup, Andong-si, Gyeongsangbuk-do, Republic of Korea.
blocks	Drug substance and associated manufacturing rooms. Filling line and associated manufacturing rooms. Quality control laboratories. Warehouses.
Inspection details	
Dates of inspection	7 to 11 May 2018
Type of inspection	Initial inspection
Vaccines covered by the inspection	SKYCellflu® 0.5 mL (1-dose) vial and 5.0 mL (10-dose) vial (Trivalent Influenza Vaccine).
Representative from the National Regulatory Authority	The national regulatory authority (MFDS) of the country where the inspection took place was informed and participated to the inspection.
Introduction	

Brief summary and general information about the manufacturing activities of the company	SK bioscience has a manufacturing site located in Andong-si, Gyeongsangbuk-do, Korea, dedicated to the production of vaccine products. After being registered as a manufacturing facility in May 2013, Andong site 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). Herpes Zoster vaccine (SKYZoster inj.) was GMP approved in September 2017. Varicella Zoster vaccine was approved by MFDS in 2018. SK bioscience has several other vaccines under development and clinical trials including recombinant rotavirus vaccine. In addition, the development of new typhoid conjugate vaccine and innovative pneumococcal vaccine is ongoing in collaboration with external partners. For flexible production of diverse vaccine types, Andong site has equipped single-use and multi-modular vaccine manufacturing systems on a commercial scale. SK bioscience started the commercial production of SKYCellflu® in PFS for Korean market aimed at the 2015/2016 seasons in 2015.																									
History	This was the initial 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: <table><tr><th>Date</th><th>Inspection type</th><th>Product</th><th>Competent Authority</th></tr><tr><td>June, 2014</td><td>Pre-approval GMP inspection</td><td>SK Influenza IX Prefilled Syringe SK Influenza X Prefilled Syringe</td><td rowspan="6">MFDS</td></tr><tr><td>August, 2014</td><td>Pre-approval GMP inspection</td><td>SKYCellflu Prefilled Syringe</td></tr><tr><td>February, 2015</td><td>Pre-approval GMP inspection</td><td>SKYZoster Inj.</td></tr><tr><td>June, 2015</td><td>Pre-approval GMP inspection</td><td>SKYPneumo Prefilled Syringe</td></tr><tr><td>July, 2016</td><td>Pre-approval GMP inspection</td><td>SKYCellflu inj.(Vial)</td></tr><tr><td>August, 2016</td><td>Regular GMP inspection</td><td>Inspection for overall GMP system</td></tr></table>			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
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Brief report of inspection activities undertaken

Scope and limitations

Areas inspected	The inspection focused on the production and control of Trivalent Influenza Vaccine. 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 Trivalent Influenza Vaccine in vial were not inspected during this inspection. Filling of SKYCellflu® Trivalent Influenza Vaccine into the prefilled syringe was also outside the scope of this inspection.

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
	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
	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
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**1. Pharmaceutical quality system**

The Quality Department and the Production Department were managed and operated independently. Employees involved in GMP activities were qualified and trained. The manufacturing processes were validated and regularly reviewed. The company has premises with suitable equipment and services, appropriate materials, containers and labels. Approved procedures, instructions and batch records were implemented and followed. Suitable storage and transport condition were provided. A system for recall and complaints management was in place.

In general, the current Pharmaceutical quality system and all of the elements were in place however these elements varied in their maturity and some need further attention and improvement. The company had adequately addressed the deficiencies related to the QMS and QRM through the CAPA.

Product quality review:

The procedure for the management of the annual product quality review was in place. At the time of the inspection there was no product quality review for WHO Flu in vials as only process validation batches were available. The PQRs of 2017 and 2018 for domestic flu production were reviewed. The product review period was from January to December.

In 2017, 17 lots of PFS 0.5 mL, 4 lots of 0.25 mL and 22 lots of SKYCellflu final bulk were manufactured. One lot out of the 22 lots of final bulk was rejected due to OOS of endotoxin. The root cause of endotoxin OOS was investigated and an adequate corrective action was taken. In total, 18 lots of drug substances (H1N1) were manufactured in 2017. Two lots were discarded due to contamination.

The company's PQR approach was generally in line with WHO requirements however a number of elements were not specifically called for in the SOP. The sections on statistical review were somewhat high level and made no reference to other processes and procedures for statistical tools and how they should be applied. Also, the policies on how products might be pooled in so as to maximize the usefulness of the review process and how risk assessments and regulatory commitments would be summarized were also missing.

The PQR process described in the SOP was also set up for essentially products which have no seasonality and uses a 12-monthly cycle according to the calendar year. This use of the calendar year was generally not recommended as a best practice approach as when the number of products within the company portfolio grows it could easily cause a high peak work load in the 1st quarter of each year as staff work to ensure that all PQRs were completed in the normal expected range of 60-90 days after the final batch of the review period. This high workload must be carefully managed to ensure that the quality of review is maintained at such times. WHO inspectors would encourage the smoothing of work through the year to facilitate workflow.

Furthermore, the January – December review period was not the most logical interval for a seasonal product such as seasonal flu vaccine where it is more logical to review the season as a whole and not split the season across two separate review years.

The management of the PQR was found deficient and the company adequately addressed the deficiencies raised through the CAPA plan.

The quality risk management:

The company approach to QRM was only at a basic level. Although some assessments had been performed and basic SOPs were in place, the programme was not adequately developed, robust and was not implemented in a comprehensive manner. The company had performed a number of formally documented risk assessments

but most of those reviewed during the inspection these were at a high level and not sufficiently detailed to optimally set process controls and to justify and target key quality attributes and process variables in validations. The company was aware of these short falls but did not have a fully documented short, medium and long-term plan to deal with the shortfall.

The company employed external assessors to provide a comprehensive gap analysis of its GMP weaknesses and the company stated that this had also confirmed that the company QRM implementation needed to be worked upon.

The QRM was found deficient and the company adequately addressed the deficiencies raised through the CAPA plan.

Management review:

The procedure for the management review was in place to document processes for management review meetings. This was however version 00 and only recently written, to replace an earlier SOP and so its operation could not be checked. A review of recent records of earlier systems indicated that:

- The detailed agenda for the meetings performed were not clearly defined in advance the management review meeting, e.g. deviation, OOS, CAPAs monitoring.
- The SOP was silent on how the quality metrics should be selected and developed and be tracked e.g. deviations opened and closed, meantime, number of deviations with extended closure dates etc.
- The meeting minutes did not clearly document if the purpose of the meeting was achieved and whether the format and content should be improved to meet changing circumstances and needs.

It was suggested that the company internally consider recent revised US FDA guidance regarding quality metric development.

Deviation management:

Deviation control procedure was in place. Deviations were categorized as critical, major and minor according to the quality safety and efficacy impact to the product and therefore to the patient. The procedure also covered planned deviations and incidents. An incident was defined as an event with no impact on the manufacturing of the product or the product quality, or that can be explained for the occurrence due to established procedure or specification documented and approved in advance. The OOS events were dealt with as per the control procedure. A risk assessment approach was used to classify deviations. Effectiveness of corrective actions and CAPA was discussed in the procedure. Deviation control document were required to be archived for 10 years.

A procedure for investigations was also in place.

The list of deviations from 2016 to February 2018 related to flu vaccine in vial presentations were spot checked.

Failure power of the filling machine during media fill test (filling 3). Corrective action was implemented. The media fill test was pass.

Contamination of the bulk during virus culture of Flu. The contamination happened during the addition of media component. Root cause was investigated, and the issue was adequately addressed through the CAPA plan.

The management of the deviations was found weak and the company adequately addressed the deficiencies raised through the CAPA plan.

Change control:

Changes were categorized as critical, major and minor according to their impact on the quality, safety and efficacy of the vaccine.

List of change control from March 2016 to March 2018 was spot checked.

Change in production process (1st chromatography) and relating document (batch record, SOP, AMV and stability test protocol) due to change in WHO northern hemisphere influenza strain (A/H1N1) for 2018-2019.

Documentation:

In general, written documentation was well designed, comprehensive, 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, however, some issues regarding the good documentation practices were noted.

Control procedures for test request, receipt and test procedure which described the procedures for samples to be tested by the QC department, was spot checked. The sample receipt process was manually handled. The procedures should be improved to include measures required for the types of containers needed to transfer (potential) infectious samples from different parts of manufacturing to the QC.

Pre-integrity test of sterilizing filters was conducted but post steam sterilization of the filters, PUPSIT was not in place. For pre-integrity tests, if the test fails twice, the filter was replaced. In case of post integrity tests, if the test fails twice, a deviation shall be initiated. No clear and predetermined requirement was in place in case of the confirmed failed integrity test requiring the rejection of all impacted products.

Batch Release Process:

Batch Release Process was spot checked. The QA officer was responsible for approval of use the intermediate/bulk, review/confirm the complete batch record, test results and packaging record and to prepare the certificate of lot release of intermediate/bulk and drug product, while the head of quality (HQ) was responsible for the approval to use of drug product. The HQ was required to review the certificate of lot release and finally determine the release of drug product. The batch release process document did not mention or include any information about the approval process for official lot release by the Korean Health Authority (MFDS).

The identified weaknesses in the batch release process document were adequately addressed by the company through the CAPA plan.

Lot summary product (LSP) review:

The company follows the WHO recommendation for the LSP according to WHO TRS 927, Annex 3, 2005 – Appendix 1 requirements. The information for inactivation method, concentration of inactivating agent, start and completion date and time of inactivation process, and total inactivation time will be considered as part of the LSP. The statement for quality assurance will be included to declare the compliance with national requirements and Part A of the Requirements for Biological Substances No. 17, revised 1990.

Further information and template of lot summary protocol for both presentations of the vaccine has been provided as part of the ongoing PSF quality evaluation process.

Complaints:

Provision for handling the complaints was in place. The complaints were classified depending on the criticality and severity of the complaints. Three complaints relating to the influenza vaccine were reviewed and were found to be closed after appropriate investigation. The records for the investigation were found to be appropriately maintained.

Product recalls:

Recall Procedure was reviewed and was found to be revised as per the requirements of the national regulatory authority. The recall in general requires intimation and permission of the national regulatory authority however in case of immediate health hazard the company can recall by intimation to the NRA. There was no incidence of the recall with any of the vaccines at Andong site. It was hold to the attention of the company that the procedure for recall should not only deals with national supply but also to include the international supply.

Pharmacovigilance:

SKYCellflu vial presentations have not yet been prequalified/marketed and thus no safety data have been collected so far. Nevertheless, safety data collected from the MFDS-approved SKYCellflu in the prefilled syringe (PFS) presentation was discussed. As per PSF submission, safety data were collected from paediatric and adult subjects. List of serious adverse events was reviewed as part of PSF application.

Risk management plan was submitted as part of PSF submission along with post-marketing pharmacovigilance.

Self-inspection:

The procedure describes the self-inspection in all departmental sections (i.e. manufacture, QC, Warehouse). Regular self-inspection was conducted once a year. The evaluation criteria for the self-inspection were defined with the categorization as critical, major and minor observations. There was a review committee for the self-audit which was described in the SOP. The procedure for the CAPA was in place. The relevant teams prepare the corrective action and preventive action plan for the observations and change control if applicable was submitted to the QA team. The SOP covered all the departments for the facility.

Quality audits and suppliers' audits and approval:

Provisions 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 is drawn.

For the qualification of trypsin: three batches of bovine origin Trypsin was tested for adventitious virus by the company QC laboratory. The tests were for bovine polyomavirus, bovine herpes type 1. Trypsin has not been considered as a critical material. No testing was expected on trypsin and the CoA from the supplier was limited to the appearance, the protein content, the trypsin activity and the chymotrypsin impurity test results. CoA to support the viral safety tests conducted by the supplier was not provided by the company.

Purchasing of critical materials i.e. seasonal virus strains and reagents were requested online. The purchasing record was archived through the online purchasing system, but a standard operating procedure for management of purchasing/handling/requesting of critical materials was not available.

SKYCellflu is the first product of the company to be supplied with the VVM, but the VVM and the vendor had not yet been qualified. The company had stated that preparation and logistics requirements for receiving

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VVM in the future was in the process of preparation but not finalized. No document to support this claim was provided for review during the inspection.

The qualification of the supplier of critical materials was found deficient and the company adequately addressed the deficiencies raised through the CAPA plan.

Contract production, analysis and other activities And Quality agreement:

No contract production was in place.

The company uses a number of specialist contractors e.g. for HEPA testing and clean qualification. There was a quality agreement covering this activity. The company also used subcontractor for viral clearance validation studies in accordance to agreed protocols.

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.

At the time of the inspection there were a total of 170 employees with 42 people involved in the production team of SKY Cellflu inj and SKY Cellflu Multi inj.

Training:

The training SOP defines the provisions for the internal and external trainings and on job trainings. QA prepares the GMP training plan annually and arranges training were based on an annual plan. On-the-job trainings were to be provided to all the employees. A procedure existed for evaluation after the training for the employees. All personnel were required to record the trainings in their individual training records and the training coordinator of the responsible team archives the training record including individual training activity attendance sheets and evaluation sheets.

The training record for the head of influenza vaccines was found weak. The company had addressed the deficiencies raised through the CAPA plan.

Personal hygiene:

The procedure describes the monitoring and the health care and hygiene of personnel before and after joining the service. Periodical health examination was carried out once a year for all employees. Employees working in the hazardous area were required to undergo special medical examination. 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 was a record maintained for all the relevant employees on vaccination status however vaccination requirements were not defined in the health and hygiene SOP.

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 generally were well implemented. Necessary resources were generally 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. Qualification and validation were routinely performed. Manufacturing steps were recorded in batch manufacturing record and packaging records. Manufacturing processes were defined and reviewed. Deviations from procedures were recorded and investigated. Product was being released by the authorized persons of the Quality unit in accordance with written procedures.

MCB, WCB, MSB and WSB:

Seed and cell lots were stored in qualified equipment with adequate temperature monitoring and inventory system.

Drug Substance (DS) production:

The upstream manufacturing process of SKYCellflu vaccine was carried out in DS dedicated area. The DS manufacturing area was equipped with single use and multi-modular vaccine manufacturing systems in a commercial scale. The manufacturing process was reviewed.

Media and buffer solutions preparation:

The media and buffer solutions used for the fermentation, purification and sterile filtration of the single harvest were prepared in the buffer preparation room of grade D under UDLAF.

There was no microbiological testing of the solution and no bioburden testing before the sterile filtration and/or before the steam sterilization, but the company adequately addressed the deficiencies raised through the CAPA plan.

Waste management and spillage control measures:

Procedures for decontamination and disposal of used contaminated materials and waste management from production area was spot checked. Waste was collected in vinyl bags for autoclaving.

Spillages were managed through relevant procedure.

There were 2 types of waste; bio waste containing biological materials such as cells and virus, and process waste which has not been exposed to biological materials. There were receiver tanks (lift stations) for each waste. Waste water was transferred to the receiver tanks separately from the bio-waste area. In order to prevent contamination from bio-waste, vent filters were installed on the bio-waste receiver tank.

Both process and bio-waste in the receiver tanks were transferred to the utility building via welded hard pipes. The joint parts of the pipes were visually inspected on every day to monitor leaks.

Treatment of wastes (chemically and sterilization by heat) before transferred to public waste water disposal plant were well defined.

Batch manufacturing record review (BMR):

The BMR for cell expansion and Virus Harvest step process for strain H1N1 2018 was spot checked. IPC and QC performed tests during the DS production were spot checked.

Final bulk:

The final bulk was prepared, filtered through 0.5/0.22 µm into disposable plastic bag which was then transferred into a maximum two disposable plastic bags. The dispensed sterile filtered final bulk was stored at 2 to 8°C before the filling.

Final lot

The filling line was equipped with RABS. The design of the facilities for the compounding and filling of vials was appropriate however the approach of having a single tunnel supplying two separate filling rooms was somewhat unusual and creates a number of issues and risks that must be appropriately controlled. In addition, there was a big pillar in the aseptic room in front of the filling machine leading to a very restricted space for manual interventions during the setup and/or interventions during aseptic filling. The company had adequately addressed the deficiencies raised through the CAPA plan.

The labelling and packaging suite and visual inspection room:

The labelling and packaging suite was visited. The vaccine was proposed for supply in 2 vial presentations 3 mL and 5 mL vials and every 10 vials were packaged in a carton. The labelling machine, automatic visual inspection machine and package machine were inspected. The visual machine was installed and undergoes operational qualification. However, a VVM dot applicator machine and freezer for storage of VVM dots were not available. The company had adequately addressed the deficiencies raised to install a deep freezer for storage of VVM and a VVM dot applicator machine in packaging room through the CAPA.

Cold room in the labelling/packaging area was available and connected to central monitoring system. Visual inspection room was also visited which was equipped with inspection booths for future routine visual inspection of filled vials before labelling.

EM Viable and non-viable PM monitoring:

EM procedure was reviewed and the trend results from the last 6 months for the class C and B areas reviewed on filling line. Alert and action limits based upon trending were recorded.

It was noted that swab monitoring did not form part of routine monitoring with all surface monitoring being performed with contact plates.

Water systems test results:

Water production system was provided in the PSF and SMF and discussed with the company at the site. The WFI was produced from PW through distillation. Bulk WFI was maintained at over 80°C and there was also a separate ambient temperature loop with WFI supplied and maintained at lower than 20°C. The WFI system was designed to circulate continuously at the flow rate of 0.8 m/s or higher. WFI was stored in stainless steel storage tank(s). WFI was used for media and buffer preparation, final rinse of main equipment and etc. The production capacity was appropriate to the manufacturing activities. Ambient temperature loop was drained and sanitized daily after use of WFI by circulating hot water.

WFI was IQ/OQ and PQ validated in three phases as per WHO recommendations. Conductivity, TOC temperature and velocity were controlled on line.

Trend analysis report-2018 for water for injection was spot checked with no significant issues noted.

3. Facilities and equipment system

There was a manufacturing facility dedicated to the production of vaccine products. It was composed of a main building, an animal laboratory and exterior waste storages. The main building was a two-story building, containing eight vaccine bulk production suites, filling area, packaging area, warehouse, QC laboratory, utility, offices and welfare facility. The animal laboratory and the exterior waste storages were separated from the main building.

The construction of core clean area and the operations 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. 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. In general, premises and equipment were well maintained and observed to be of a satisfactory level of cleanliness. The company had standard operating procedures controlling its approach to personal hygiene and sanitation in its production facility. Production premises had generally been laid out to allow the production processes to take place in areas in a logical flow corresponding to the sequence of the operations and under the requisite cleanliness levels to minimize the risk of errors and permit effective cleaning and maintenance to avoid cross-contamination.

For flexible production of diverse vaccine types, the building had been equipped to handle single-use and multi-modular vaccine manufacturing systems at a commercial scale. Access to production premises was restricted to authorized personnel. Seed and cell lots were stored in qualified equipment with adequate temperature monitoring and inventory system.

Procedures for decontamination and disposal of used contaminated materials and waste management were in place. Cell culture area and purification area (contained area of live virus processing, purifications, filtration and dispensing of monovalent bulks) were provided with decontamination autoclave. A kill tank was provided for liquid waste.

The general design of the facilities for the compounding and filling of vials was appropriate however the approach of having a single tunnel supplying two separate filling rooms was somewhat unusual and creates a number of issues and risks that must be appropriately controlled.

There were a number of risks of cross contamination in that had not been completely documented and were inadequately mitigated. Furthermore, the location of the fill line within the fill room was not optimal and accesses to several parts of the machine were restricted due to the location of supporting pillars. The company had adequately addressed the deficiencies raised through the CAPA plan.

➤ **Qualification and validation:**

The company had identified what qualification and validation work was required to be performed and the key elements of the qualification and validation programmer 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. The documentation of QRM activities within the validation plan overall and in the decision as to the selection of key quality attributes and process control parameters was however limited and the company needs to build upon its activities in this area of its operations.

The following qualification and validation reports were spot checked:

Qualification and validation of compounding and filling activities:

Process media fill simulations:

HVAC qualification and requalification:

The validation of the sterile filtration of SK flu vaccines:

Ultrafiltration/diafiltration PBUF01 and PBUF02.

Chromatography (1st and 2nd):

Cleaning and disinfection studies:

Process Validation:

Qualification and temperature mapping cold room:

Leachability & Extractability (L&E) studies:

Trypsin concentration optimization for influenza virus study:

Characterization of MCB and WCB:

Characterization of MSB and WSB:

4 Laboratory control system

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

The Physicochemical Laboratory, Microbiology Laboratory and Virology Laboratory were appropriately segregated from the Animal Testing Laboratory.

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.

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

Analytical method for extractable volume (drug product), test of protein content in Influenza Vaccine (BCA method) and test for insoluble particulate matter (drug product) were reviewed and found adequate.

The physiochemical laboratory was visited. Measuring the ring sizes and scanning of the SRID gels using the auto-colony counter reader was observed to determine the HA content of final product.

Equipment and pipettes as well as reagents were appropriately labelled, qualified and calibrated.

Disposing of wastes for biological/infectious/non-infectious materials were in place.

The storage room for cells and reagent was visited. Freezers and liquid N2 tanks were well labelled with the specific strains and cell culture stock names.

The Weighing room was visited, and the balance was calibrated and labelled appropriately.

Stability room was visited and found fridges well labelled, calibrated and clean and samples storages were well organized.

The stability samples of finished Flu vaccine were stored inside walk-in cold room with up-right and inverted positions. Other vaccines were also stored in this cold room. The vaccines containers were identified and segregated in different shelves. The cold room was monitored with fixed sensors.

All fridges were connected to central monitoring system. SMS text warning system to alert on call personnel when an alarm was triggered outside working hours was available.

QC Infection laboratory was visited and TCID50 assay watched. Pipettes found calibrated and well labelled as well as reagents and medium. Waste bottles were used to collect liquid waste.

The Serial dilution infectivity TCID50 test method was observed during the visit. It was observed that there was only one operator performing the test. It was also observed that the operator was not performing mixing to RBC prior to dispensing into wells (Hemagglutination test).

The waste management procedures for QC area was spot checked. The procedures describe waste management of the infectious and non-infectious liquid and hard general waste (paper, oil etc.). Infectious material is collected in hazard bags undergo autoclaving and then collected by contracted authorized third party for external destruction.

The method validation of the *virus inactivation by formaldehyde and the infectivity method TCID50* was spot checked.

Stability:

Stability protocol for stability study of the final product was spot checked. All test results for up to 12 months were within acceptance criteria.

Data security and Integrity:

The company has basic controls over data security and integrity in place in its laboratory systems and to a lesser extent for its automated systems in production such as plcs.

Controls had been put in place for its HPLCs which were running Empower 3 with data backed up to a local server, but other systems showed both instrumental and procedural weaknesses. Although a high-level system security SOP exists, detailed application of specific data access rights e.g. for amendment/deletion were not fully documented in associated system SOPs. Similarly, system audit trail configurations were not fully documented in the system management SOPs.

The failures to implement robust data reliability and data integrity controls and the management of the quality control activities were raised and the company had adequately addressed the deficiencies raised through the CAPA plan.

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 was available and samples were passed through designated pass-box.

6 Packaging and labelling system

No finished product has been supplied to United Nations agencies so far. The labelling machine, automatic visual inspection machine and package machine were inspected. The automated visual machine was installed and undergoes operational qualification. VVM applicator machine was not available and was not yet installed.

Packaging/Labeling store was visited. Labels were well segregated and locked. Freezer -20°C for storage for VVM temperature indicator dot was not available.

The company had adequately addressed the deficiencies raised to install a deep freezer for storage of VVM and a VVM dot applicator machine in packaging room through the CAPA

Only the staff in charge of materials management can have access to the warehouse and hazardous materials warehouse.

Shipping container configuration

The outer box and lid were made of EPS (expanded polystyrene), and 8 ice packs (2 on the top, 2 on the bottom, and 1 each in a side) were placed between outer box and inner box. Inner box and lid were made of EPS, and 8 PCM packs (2 on the top, 2 on the bottom, and 1 each in a side) were placed between inner box and product. In one shipping container, 280 cartons (3mL vial) or 110 cartons (5 mL vial) were loaded. The shipping container with refrigerant was 25.7 kg, and total packaging weight was 48.4 kg for 3mL vial and 47.0 kg for 5 mL vial. The temperature within the container maintained at 2 – 8°C during the validation at 43°C and -5°C for 48 hours.

International Shipping validation was not available and has not yet been commenced by the company. The company adequately addressed the deficiencies raised by conducting the International Shipping validation in line with ISTA 7D through the CAPA.

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., 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.

PART 4***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-eight 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-six 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

Short name: WHO TRS No. 957, Annex 2

<http://www.who.int/medicines/publications/44threport/en/>

7. WHO good manufacturing practices for sterile pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 6

Short name: WHO TRS No. 961, Annex 6

http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

8. WHO guidelines on transfer of technology in pharmaceutical manufacturing WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 7

Short name: WHO TRS No. 961, Annex 7

http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

9. Model guidance for the storage and transport of time-and temperature-sensitive pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 9

Short name: WHO TRS No. 961, Annex 9

http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

10. General guidelines for the establishment maintenance and distribution of chemical reference substances. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-First Report Geneva, World Health Organization 2007 (WHO Technical Report Series, No.943) Annex 3

Short name: WHO TRS No. 943, Annex 3

http://whqlibdoc.who.int/trs/WHO_TRS_943_eng.pdf?ua=1

11. WHO good practices for pharmaceutical microbiology laboratories. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 2

Short name: WHO TRS No. 961, Annex 2

http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

12. WHO guidelines on quality risk management. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Seventh Report Geneva, World Health Organization, 2013 (WHO Technical Report Series, No. 981), Annex 2

Short name: WHO TRS No. 981, Annex 2

http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_981/en/

13. WHO guidelines on variation to a prequalified product. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Seventh Report Geneva, World Health Organization, 2013 (WHO Technical Report Series, No. 981), Annex 3

Short name: WHO TRS No. 981, Annex 3

http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_981/en/

14. WHO guidelines for drafting a site master file. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 14

Short name: WHO TRS No. 961, Annex 14

http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

15. WHO General guidance on hold-time studies WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 4

Short name: WHO TRS No. 992, Annex 4

http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

16. WHO Technical supplements to Model Guidance for storage and transport of time – and temperature – sensitive pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 5

Short name: WHO TRS No. 992, Annex 5

http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

17. WHO good manufacturing practices for biological products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifties Report Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 3

Short name: WHO TRS No. 996, Annex 3

http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex03.pdf

18. Guidance on good data and record management practices. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifties Report Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 5

Short name: WHO TRS No. 996, Annex 5

http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex05.pdf