

**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	Green Cross Corporation (GCC)
Head office	107, Ihyeon-ro, 30 Beon-gil, Giheung-gu, Yongin-si, Gyeonggi-do, Korea
Contact person	Eden Jeong, Regulatory Affairs eden@greencross.com
Inspected site	
Address of inspected manufacturing site	40 Sandan-gil, Hwasun-eup, Hwasun-gun, Jeollanam-do, 519-955, Korea
Unit / block	Flu Bulk, 2F Formulation and filling of final bulk preparation, 2F Microbiology Quality Control Laboratory, 1F Immunological and Physico-chemical Quality Control Laboratory, 1F Packaging, 1F Warehouse, Utility.
Inspection details	
Dates of inspection	23-27 July 2018
Type of inspection	Routine inspection for Seasonal 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:

Green Cross Corporation (GCC), Jeollanam, Korea

23 to 27 July 2018

Introduction

Brief summary and general information about the manufacturing activities of the company

The Hwasun site of Green Cross Corporation (here after abbreviated in this report to GCC-Hwasun) at 40 Sandan-gil, Hwasun-eup, Hwasun-gun, Jeollanam-do, 519-955, Korea was inspected from 23rd to 27th July 2018.

The Hwasun site is the Green Cross Corporation's center for vaccine manufacture. The site is located within a bio-park known as the Hwasun Biopharmaceutical Industry Complex and is approximately 320 kilometers south from Seoul. The bio-park was originally built by the South Korean government to develop the domestic biopharmaceutical industry. The Jeonnam Biopharmaceutical Research Institute is also housed in the bio-park alongside Green Cross Corporation.

Buildings	Area (m ²)	Uses
Multi-purpose	8,750	1F Varicella Vaccine bulk and formulation and filling of final bulk
		1F Product packaging
		1F Raw material warehouse
		2F Japanese Encephalitis vaccine bulk, Hemorrhagic Fever with Renal Syndrome vaccine bulk
		2F Formulation and filling of final bulk preparation (Except Varicella Zoster Vaccine)
		2F Quality Control laboratory and office (Microbiology, Virus, Physico-chemical test)
Flu	10,000	Influenza vaccine bulk
Quality building	1,000	1F Quality Control laboratory and office (Immunological, Physico-chemical test)
		2F Quality Assurance
Central Utility	1,600	Provide utilities including the water for injection
WWT	1,200	Waste water treatment and waste control
Varicella Building	2,400	Varicella vaccine filling, BCG production
Administration	420	Production support, general support, meeting room
Auditorium	730	Cafeteria

In addition to Hwasun site, GCC also have two other sites located in Eumseong site (produces OTC drugs) and Ochang site (produces plasma derivatives, recombinant proteins).

The Hwasun site manufactures the following dosage forms:

Type	Product
Influenza Vaccines (8)	- GCFLU inj. - GCFLU Pre-filled Syringe inj. - GCFLU Final bulk.

		- GCFLU Multi inj. - GCFLU Quadrivalent Pre-filled Syringe inj. - GCFLU Quadrivalent inj. - GCFLU Quadrivalent Multi inj. - GCFLU Quadrivalent Final bulk.																																	
	Pandemic Influenza Vaccines (4)	- GREEN FLU-S Plus inj. - GREEN FLU-S inj. - GREEN FLU-S Pre-filled Syringe inj. - GCFLU H5N1 Multi inj.																																	
	Varicella Zoster Vaccine (1)	Suduvax inj.																																	
	Japanese Encephalitis Vaccines (4)	- Japanese Encephalitis Vaccine-GCC Pre-filled Syringe inj. - Japanese Encephalitis Vaccine-GCC inj. - Japanese Encephalitis Vaccine-GCC Final bulk. - Freeze-dried Cell Culture derived Japanese Encephalitis Vaccine-GCC inj.																																	
	HFRS Virus Vaccines (2)	- Hantavax inj. - Hantavax Final bulk.																																	
	Td Vaccine (1)	Td Vaccine-GCC Pre-filled Syringe inj.																																	
History	This was the third on-site inspection conducted by WHP 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>Regulatory</th><th>Audit Objective</th></tr> <tr> <td>2014.05.19-23</td><td>INVIMA (Colombia)</td><td>Periodic inspection</td></tr> <tr> <td>2014.10.20-22</td><td>MOH (Iran)</td><td>Pre-approval inspection</td></tr> <tr> <td>2014.11.17-19</td><td>MFDS (Korean NRA)</td><td>Periodic inspection</td></tr> <tr> <td>2014.12.11-12</td><td>MFDS (Korean NRA)</td><td>Pre-approval inspection</td></tr> <tr> <td>2015.06.22-26</td><td>WHO</td><td>Periodic inspection</td></tr> <tr> <td>2015.07.22-24</td><td>MFDS (Korean NRA)</td><td>Periodic inspection / Pre-approval inspection</td></tr> <tr> <td>2016.03.15-17</td><td>MFDS (Korean NRA)</td><td>Pre-approval inspection</td></tr> <tr> <td>2017.03.14-17</td><td>MFDS (Korean NRA)</td><td>Pre-approval inspection</td></tr> <tr> <td>2017.07.24-28</td><td>INVIMA (Colombia)</td><td>Periodic inspection</td></tr> <tr> <td>2018.07.23-27</td><td>WHO</td><td>Periodic inspection</td></tr> </table>		Date	Regulatory	Audit Objective	2014.05.19-23	INVIMA (Colombia)	Periodic inspection	2014.10.20-22	MOH (Iran)	Pre-approval inspection	2014.11.17-19	MFDS (Korean NRA)	Periodic inspection	2014.12.11-12	MFDS (Korean NRA)	Pre-approval inspection	2015.06.22-26	WHO	Periodic inspection	2015.07.22-24	MFDS (Korean NRA)	Periodic inspection / Pre-approval inspection	2016.03.15-17	MFDS (Korean NRA)	Pre-approval inspection	2017.03.14-17	MFDS (Korean NRA)	Pre-approval inspection	2017.07.24-28	INVIMA (Colombia)	Periodic inspection	2018.07.23-27	WHO	Periodic inspection
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Brief report of inspection activities undertaken

Scope and limitations

Areas inspected	The inspection focused on the production and control of Seasonal Influenza Vaccine. The inspection covered 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 Influenza Vaccines were not inspected during this inspection.
Vaccines covered by the inspection	Seasonal Influenza Vaccines: - Influenza, Seasonal Quadrivalent 1 and 10 dose (GCFLU Quadrivalent inj. and GCFLU Quadrivalent Multi inj.). - Influenza, seasonal 1 and 10 dose (GC FLU injection and GC FLU Multi inj.).

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
	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	Hemagglutinin Assay
	HEPA	High Efficiency Particulate Air
	HVAC	Heating, Ventilation and Air Conditioning

	IQ	Installation Qualification
	LAF	Laminar Air Flow
	LIMS	Laboratory Information Management System
	MB	Microbiology
	MBL	Microbiology Laboratory
	MF	Master Formulae
	MFT	Media Fill Test
	MR	Management Review
	NC	Non Conformity
	NCA	National Control Authority
	NCL	National Control Laboratory
	NRA	National Regulatory Agency
	OQ	Operational Qualification
	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
	SCDM	Soybean Casein Digest Medium
	SIP	Sterilization In Place
	SME	Subject Matter Expert
	SMF	Site Master File
	SOP	Standard Operating Procedure
	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 Unit encompasses Quality Assurance and Quality Control activities were functioning with appropriate independence from the production unit. The quality unit was responsible for the implementation of the written quality policy of the site and corporation. The necessary main provisions and processes expected by WHO GMP of a pharmaceutical quality management system were documented and implemented. Overall the Quality Unit had procedures and systems in place which were adequately implemented to ensure that quality products were being produced consistently.

Product quality review:

Provisions for product quality review (PQR) were in place to verify the consistency of the process and the appropriateness of current specifications to highlight the trends and identify product and process improvements. The PQR review was performed for bulk vaccine, finished products, the HVAC system and the water system. Products were reviewed for quality issues related to manufacturing and quality control activities annually according to the established 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.

The PQR was prepared for monovalent bulk, final bulk and finished product. As seasonal influenza vaccine was produced on a campaign basis, PQR was prepared taking into account the northern and southern hemisphere seasons.

The PQR of the monovalent bulks produced between 29/2/2016 and 31/1/2017 was reviewed. No rejection was recorded for the total of batches produced. The PQR provided a list of deviations and incidents raised during this period. No out of specification occurred during this period. A section on validation (process, cleaning, computerized and analytical validation), equipment qualification, facility qualification (biosafety cabinets, clean booths) and HVAC was part of the review. Trend analysis was performed using Minitab and process capability criteria were established from 0.67 to 1.67 and more. Minimum 5 batches were required for trend analysis. Ongoing stability studies were part of the review. There were no complaints, returns, recalls reported for the period. There was no conclusion and recommendation made whereas no comparison was done from previous PQR to demonstrate consistency in process.

PQR of multi final bulk 2016-2017 (1 April 2016 to 31 March 2017) was reviewed. The results from monovalent bulk were referred.

Final results of monovalent flu vaccine were summarized and results were within the established specification limits. No deviation and OOS was reported during the period. Equipment and facility qualification was part of the PQR. Minitab was used for trend analysis of the results. No complaint, recall and return were reported. Total of 4 change controls were raised.

PQR of GCC multi flu vaccine (2016-2017) for the batches manufactured between 1/4/2016 and 31/3/2017, 5ml (10 dose) was reviewed. The finish product was tested for visual inspection, pH, extractable volume, visible particles, sub-visible particles, endotoxin, Hemagglutinin content ($\geq 80\%$), identification of Hemagglutinin, thimerosal (80-120%), sterility and animal testing. There was no process, analytical, cleaning

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and computerized system validation performed during this period. Equipment and facility qualification was part of the review. Trend analysis of the in-process test results was performed using Minitab. Water, environmental monitoring and stability study evaluation was part of the PQR. No complaint, deviation, out of specifications, returns and recall were reported during this period. Evaluation of previous product quality review was not performed in detail as no confirmation was available. Typographical errors were found which cast a doubt that PQR was not adequately reviewed. Thimerosal test results of 2015-2016 were copied as 2016-2017.

The PQR covering the manufacturing period ranging from 2017.03.01 to 2018.03.05 of Seasonal Influenza vaccines for both Northern and Southern hemispheres was spot checked.

The PQR of Trivalent flu 1 dose presentation 2017-2018 was spot checked and found acceptable however the visual inspection trend on defects and types of defects were not presented. Water and compressed air results and trends were not considered in the PQR.

The quality risk management:

The SOP for risk management described the procedure for risk analysis, risk assessment, risk review and risk mitigation. The purpose of the procedure was not clear as to if QRM applies across the product lifecycle or not. The procedure applied to “certain” quality system elements such as complaints, deviations, CAPA, changes. It should have been useful to include other quality system elements such as recalls, out of specifications and incidents and introduction of new products. The procedure did not require use of cross functional team for the risk assessment. Also, procedure was found inadequate as follows:

No details provided for tools required for various risk assessment;

FMEA was briefly described without any details pertaining to RPN criteria;

FMEA was calculated taking into account severity and likelihood. There was no consideration of detectability and this was not documented and discussed.

The QRM was managed through e-QMS which has been in use since 2011. e-QMS was used for managing change controls, deviations, incidents, complaints, out of specification, CAPA, internal audits, calibration and maintenance. Recalls were handled manually.

Management review:

A procedure on the GMP committee was in place. The procedure described the agenda, frequency, attendees etc. The committee meetings were held once every month with presence of the senior quality management (head of quality management). It was however noted from April 2018 minutes of the meeting that quality system elements such as change controls, deviations, complaints, recalls, audits and CAPA were not discussed during their recent committee meeting.

Deviation management:

Provision for deviations handling were in place according to the implemented procedures. The list of deviations was spot checked. Out of specifications were handled through a separate procedure “OOS”. The procedure was found ambiguous as definition of quality incident was defined “all events which were generated based on unexpected cause such as deviation, OOS to require an investigation or root cause analysis”. Deviations and incidents were not supported with examples for systematic implementation. The procedure stated that “reporting of the event is performed within 2 days to QA”. The deviations were classified as planned and unplanned. It was noted that planned deviations were handled through change controls.

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Trend analysis on deviations and incidents were done on quarterly basis.

It appeared that sufficient manpower was not in place to effectively review PQR, change controls, deviations, risk management and effectiveness check of CAPA.

Change control:

Change control procedure was in place. The procedure applies to six systems namely, quality system (deviation, OOS, non-conformance), production system (formula, manufacturing process, process management), facilities & equipment (facilities, utility, information system), packaging & labelling system (packaging process, secondary packaging materials), laboratory controls (testing method, testing equipment) and materials system (drug substance, primary packaging materials). E-quality management system was being used to manage changes. The process flow chart provided step by step process and responsibility of various departments. The procedure was unclear pertaining to the introduction of new product, new equipment and new facility.

Changes were categorized into major, moderate and minor classification. In addition, emergency change was raised to prevent the loss of resources or decrease in product quality. This was handled through planned deviation. The procedure was cross referenced to deviation management procedure and other procedures (document change and training procedure). It was claimed that temporary changes were handled through deviations. Changes raised between 1 July 2016 and 30 June 2018 were provided for review.

It appeared that there was some misunderstanding regarding initiation of change control.

Change control pertaining to change of strain for southern hemisphere 2016 was classified as major. H3N2 and B strains were changed in accordance with WHO recommendations. An impact assessment was performed. The process validation, training, regulatory authority and stability study were impacted and applicable to monovalent bulk, final bulk and finished product. The batch record of monovalent bulk was not revised instead updated strain was recorded by hand in batch record.

Documentation:

In general, documents were designed, prepared, reviewed and distributed with care. Documents were approved, signed and dated by the appropriate responsible persons. Documents were regularly reviewed and kept up to date. Records were made or completed when any action was taken. A documentation management system was in place to guide production and control of products. These included validation master plans (VMP); standard operating procedures (SOPs); batch manufacturing and packaging instructions and records (MIs, BMRs, BPRs); specifications of starting materials, packaging materials, packaging components and finished products; standard testing procedures, analytical records and certificates of analysis; qualification and validation protocols, schedules and reports; training schedules and records. There were corresponding records in form of reports, forms, checklists, logbooks, registers maintained as evidence of compliance with the procedures and specifications.

The procedures were revised after every 3 years.

Raw material management procedure described that reduced testing was acceptable if same batch number was receipt from the supplier. Justification for reduced testing was not available.

CAPA Management

Provision for management and development of CAPAs handling were in place according to the implemented procedures.

Complaints:

Complaint handling procedure was discussed. The procedure described the handling of complaints including responsibility, type, grading and timelines. The complaints were categorized as product defect, customer service and adverse drug reaction. The grading was done based on the risk assessment. It was however noted that risk assessment of the complaint was based on severity and likelihood but detectability was not taken into account and not documented and discussed. The complaints used to be trended on quarterly basis and changed to yearly from 2018.

It was noted that there was no agreement or contractual arrangement available between GCC and airline agent on the shipping route.

As there were not many complaints received, trend analysis was not comprehensively analyzed.

Pharmacovigilance System:

Two procedures were used to describe the Pharmacovigilance system in place. The procedures described the collection, categorization, and upload of the relevant safety reports onto the company PV database. There was no specific provision for investigation specific to possible quality defect of products (including influenza vaccine)

Product recalls:

No product recalls have been done by the manufacturer to date. The procedure for Recall specified that a mock recall should be done every two years, one for domestic market and one for export market.

The exception to the mock recall was inventory quantities supplied to UNICEF and PAHO. The countries these products were distributed to were therefore excluded from the inventory of mock recalls. UNICEF and PAHO have informed GC Pharma that the countries which were recipients of the vaccines were confidential so no simulation recall information can be shared with GC Pharma.

Self-inspection:

This section was inspected during the last inspection however not reviewed during this inspection due to time constraint.

Quality audits and suppliers' audits and approval:

This section was inspected during the last inspection however not reviewed during this inspection due to time constraint.

Contract production, analysis and other activities And Quality agreement:

This section was inspected during the last inspection however not reviewed during this inspection due to time constraint.

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 available. The Quality Unit (QU) was separately managed from the production unit.

In view of the fact that procedure(s) and documents (both paper & electronics) were not timely and adequately (e.g. PQR with typographical errors) reviewed, consideration should be given by the management to provide sufficient manpower resources.

Training:

The training of the personnel regarding the aseptic filling operations through the review of the validation of the aseptic simulation reports and video was found adequate. The qualification of the operators to the gowning to access aseptic rooms was spot checked and found adequate except for the specification of the microbial limits.

Personal hygiene:

The premises were generally maintained at an acceptable level of cleanliness. The company had provisions for personal hygiene and sanitation in its production facility. Manufacturing areas were provided with airlocks for personnel and materials entries and exits. Gowning procedures for access to the classified manufacturing areas were in place. Cleaning, disinfecting and decontaminating procedures along with the environmental monitoring program were in place to control the non-viable and viable contamination levels in the production areas.

The company had adequately addressed the deficiencies related to the QMS, PQR and QRM through the CAPA. The satisfactory implementation of the CAPA will be verified during future inspections.

2. Production system

Resources were available, including qualified and trained personnel. Premises, equipment, laboratories, materials, containers and labels, procedures and instructions were in place. Qualification and validation of equipment, manufacturing processes and quality control testing methods were in place. Manufacturing processes were defined and reviewed. Records were made for the production operations. Deviations were recorded and investigated, root causes were determined and corrective and preventive action were implemented. Systems were in place for handling complaints and recalling any batch of product from sale or supply.

SPF Eggs were provided from qualified supplier through a domestic agency. GCC did not have a direct arrangement for the supply of SPF eggs. The domestic agency had a supply contract with the supplier of SPF eggs. It was reported by GCC staff that the transportation of the SPF eggs from the supplier of SPF eggs to domestic agency was the responsibility of the supplier. GCC was responsible for the collection of eggs from the domestic agency. There was an audit report conducted on February 2016 by GCC to the supplier of SPF eggs. The transportation of SPF eggs was not validated. The transportation conditions for the eggs and the viability were defined and checked at reception by GCC. The total time from the collection

and disinfection of eggs by Charles River to the arrival at GCC was unknown. There was no back up supplier for SPF eggs.

At reception, GCC inspected CoA and performed visual inspection of SPF eggs. Candling was conducted before use.

Analytical method validation of the infectivity by Reed-Muench test method was spot checked. There was no validation of the test sensitivity. As testing of residual virus infectivity after inactivation may be problematic due to aggregation, validation of test sensitivity should be performed.

Bulk vaccine was manufactured in the Flu building and stored there.

The aseptic and clean processes being operated in production were examined in detail.

The control of environmental monitoring was performed as per the relevant procedure. Alert and action limits were established. The microbial limit for the sampling location for the gowning of the aseptic operator in grade A for forehead, mask and head were ≥ 4 cfu.

The environmental monitoring with regards to the sampling locations was not based upon formal risk assessment. This was raised during the last WHO onsite inspection (The Environmental monitoring was not based upon documented risk assessment). The company had improved the EM mainly in terms of frequency. Regarding the sampling locations, only a draft procedure “Locating environmental monitoring sample sites” was undertaken at the time of the present inspection.

Trend analysis report for manufacturing areas including used gases was spot checked. All the results were within the established limits.

The compressed air used on batch basis was controlled quarterly and this was not upon risk based.

UT: Utility building. Major utilities come from this building including water, steam, compressed air and electricity. Emergency generator and UPS were also located. PW: sanitization by temperature over 80 °C every two months and chemical sanitization every two years. WFI: chemical sanitization every two years.

The testing of water systems was performed. Return user points were sampled and tested on daily basis. The annual report for trend analysis for water systems was spot checked. Water was tested as per EP. TOC was continuously monitored online for main loop and fill and finish loop and conductivity was monitored online for all water loops.

The microorganism identification from pharmaceutical water from 2016 to June 2018 was presented. There were recurrent contaminations of the PW system with *Sphingomonas (melonis, echinoides, aqualitis)*, *Ralstonia pickettii*, and for WFI with *Bacillus (cereus, licheniformis)*. The nature, type and recurrence of these contaminations were not documented, discussed and justified. The corrective and preventive actions and the effectiveness of the implemented corrective and prevented actions were silent, not documented nor justified. The trend analysis of the test results was barely limited to gather data in tabulated forms and graphs without critical review and analysis in order to undertake the appropriate measures to control the quality of water which was extensively used through the manufacturing process of the Influenza vaccines.

3. Facilities and equipment system

Floor plans including layouts, manufacturing rooms Classification, AHU zoning, material flow, product flow, personnel flow, waste Flow and air flow were presented for floors 1 and 2 of Flu bulk building and Multi-purpose building.

Exterior construction materials were ALC (Autoclaved Lightweight Concrete) Panels and PIR (Polyisocyanurate) Panels. ALC Panels were used on the 1st and 2nd floor production facilities and PIR Panels used on the exterior walls of the AHU area on the 3rd floor. PIR Panels were also used on the walls and ceiling of the GMP area inside the production facility. Two-ply panels were used on both sides, and the corners of the ceiling and the floor were covered using aluminium mouldings to facilitate cleaning. Polyurethane panels were used on the cold storage areas. Interstitial spaces between floors were provided to access the lighting and mechanical services. Cat-walks were used for maintenance and repair. Entrances to the interstitial spaces were separated from clean areas. Fixed equipment such as autoclaves had their own technical service area on the floor. Access for maintenance was generally seen to be from the less clean area.

The HVAC system treats air through a pre-filter, medium filter, and HEPA filter to provide filtered air to the manufacturing area. Environmental monitoring programme was in place.

During the inspection, various buildings and locations were visited where upstream and downstream production of monovalent bulk were produced, where trivalent seasonal bulk was formulated and aseptically filled into vials and packed, as well as those for associated QC activity was carried out.

All vaccine bulks were produced in dedicated facility, and the finished products were manufactured with dedicated equipment.

➤ **Qualification and validation:**

Overall, provisions for qualification and validation were in place and covers premises, equipment, utilities and systems, processes and procedures at periodic intervals and when changes have been made. Validation and qualification protocols and reports were spot checked as presented below.

- Aseptic media simulation and media fill tests:
- The validation of the sterile filtration:
- HVAC qualification and requalification:
- Depyrogenation tunnel:
- Computerized system:

4 Laboratory control system

The quality control carried out activities such as the analytical method validation, test of the physical, chemical, microbiological and biological test in manufacturing site. The animal testing was performed in O-Chang site. The Quality Control unit was in-charge of sample tracking and sampling, testing for raw materials, intermediates and products, stability study and testing for utility samples.

Procedures:**Out of specification (OOS)**

OOS procedure was available in Korean and OOS handling flowchart was part of the procedure. From the flowchart, it was noted that manufacturing and laboratory investigations were conducted in parallel whereas flow chart depicted that laboratory investigation was performed after manufacturing investigation. The analyst notified to the supervisor when OOS was discovered. An initial investigation was jointly performed by the analyst and supervisor to find out obvious laboratory errors. OOS were handled through E-QMS. The procedure did not require hypothesis or investigative testing before retesting was performed. If initial investigation confirmed laboratory error, repeat testing will be done on the same sample once. If laboratory error was not found, retesting will be performed five times for chemical and twice for microbiological test.

List of OOS (2016-2018) was reviewed. It was noted that total of 14 OOS were reported during this period.

Data security and Integrity:

This section was found inadequate as equipment and procedures were not adequately controlled to ensure good data and record management practices. In particular, quality control in-charge was responsible as the administrator. Most of the equipment and instruments were not connected to the server and privileges were not adequately controlled.

5 Materials system

The reception, sampling, testing, storage and releasing or rejecting of starting materials, packaging materials, bulk and finished products was performed according to implemented specifications and SOPs. Controls were in place at receipt, checking, sampling, storage, release, storage of approved materials in segregated areas (quarantine, approved and rejected) with adequate labeling. Appropriate storage conditions were provided. Procedures and dedicated storage were in place for rejected and returned material.

6 Packaging and labelling system

The labelling and packaging system areas were spot checked however not inspected in detail during this inspection due to time constraint.

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, ***Green Cross Corporation (GCC), 40 Sandan-gil, Hwasun-eup, Hwasun-gun, Jeollanam-do, 519-955, 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-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
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