

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

Part 1	General information
Manufacturers details	
Company information	
Name of applicant	IL-YANG Pharm. Co., Ltd. (Vaccine Plant)
Corporate address of manufacturer	ILYANG Building, 544-5, Dogok-dong, Gangnam-gu, Seoul, Korea. (06261) Tel: 02) 570-3700 82-2-570-3700
Contact person	Dr Se-won Park E-mail : swpark@ilyang.co.kr
Inspected site	
Address of inspected manufacturing site 1	IL-YANG Pharm. Co., Ltd.: 1291, Daegum-Ro, Geumwang-Eup, Eumseong-Gun, Chungcheongbuk-Do, Republic of Korea. (27632). GPS: 36° 59'06.5"N 127° 34'33.8"E
blocks	Manufacturing Area (Seed Lab) in first floor; Manufacturing Area (Monovalent Bulk) in first floor; Manufacturing Area (Formulation-Final Bulk) in first floor; QC Area (QC Lab) in second floor; Gowning Area in second floor.
Address of inspected manufacturing site 2	KOREA VACCINE CO., LTD. 128, Mongnae-ro, Danwon-Gu, Ansan-Si, Gyeonggi-Do, Republic of Korea. (15598). GPS: 37° 18'41.0"N 126° 46'34.3"E
block	KOREA VACCINE CO., LTD. <i>is the Contract Manufacturing Organization (CMO) for IL-YANG Pharm. Co., Ltd. in charge of filling, visual inspection and labelling operations.</i>
	Fill and finish building
Inspection details	
Dates of inspection	The initial inspection took place from 20 to 23 June 2016 and the follow up inspection from 4 to 5 July 2017 at IL-YANG Pharm. Co., Ltd.
	The initial inspection took place from 24 to 25 June 2016 and the follow up inspection on 3 rd July 2017 at KOREA VACCINE CO., LTD.
Type of inspection	Initial and follow up inspection.

Representative from the National Regulatory Authority	The national regulatory authority (MFDS) of the country where the inspection took place was informed and representatives participated to the inspection.
Introduction	
Brief summary of the manufacturing activities	IL-YANG's Eumseong Vaccine plant, located at Eumseong-gun, Chungcheongbuk-Do, manufactures the monovalent bulks (H1N1, H3N2, B) and the formulated bulk of the flu vaccine "IL-YANG Flu Vaccine[®] Inj." which is filled in vials, labelled and packaged at the contract manufacturing organization Korea Vaccine. KOREA VACCINE CO., LTD. produces biological products including influenza, DTaP, Polio, Typhoid vaccine and freeze-dried vial for Agkistrodon Halys Antivenom.
General information about the company and site	IL-YANG Pharmaceutical Company., LTD. is a Korean pharmaceutical company that manufactures and distributes medicines to both public and private sectors since 1946. IL-YANG's provide medicines against disease such as cancer, esophagitis, gastric ulcer, prostate related challenges and influenza flu. The IL-YANG Vaccine Plant spans 14,026m² and has a targeted production line of 60 million doses for seasonal flu vaccine. "IL-YANG FLU Vaccine[®] Prefilled Syringe Inj." has been approved by MFDS in 2013 to distribute for vaccine market in Korea. IL-YANG PHARMACEUTICAL CO., LTD. Eumseong vaccine plant, dedicated facility for Influenza vaccines (Split virion, Inactivated), has been approved as a pharmaceutical manufacturing site for bulk by MFDS since August 2013.
History	This inspection is the follow up inspection to the initial WHO GMP inspection that took place in June 2016. A follow up inspection has been conducted by MFDS in June 2017. MFDS has conducted the following inspections at IL-YANG Vaccine Plant site: • Flu Vaccine prefilled syringe INJ. from 10 to 14 June 2013; • Flu Vaccine INJ. from 05 to 07 January 2015, • PIC/S GMP compliance from 18 to 22 January 2016. KOREA VACCINE CO., LTD. received regular inspection from MFDS for verifying GMP regulation and quality system suitability of KV manufactured products and contracted services:

No.	Date	Regulatory	Audit Objective
1	2011.03.30~31	KFDA	KV Product/Contract manufacturing and laboratory service
2	2011.01.07	Pakistan FDA	Contract manufacturing Service / Customer
3	2011.08.08	KFDA	Contract storage service/Customer
4	2012.05.11	KFDA	Contract manufacturing service/ Customer
5	2012.06.28	KFDA	Contract storage service/Customer
6	2012.12.17~18	KFDA	KV Product/Contract manufacturing service for Customer
7	2013.07.10	MFDS	Contract storage, Laboratory service/ Customer
8	2013.07.22~26	INVIMA(Columbia)	Contract manufacturing service/ Customer
9	2013.08.21~22	NPCB(Malaysia)	Contract manufacturing service/ Customer
10	2013.11.05~08	MoH(Turkey)	Contract manufacturing service/ Customer
11	2014.04.07~09	MFDS	KV Product/ Pre-Qualification
12	2014.09.18	MFDS	Contract storage, Laboratory service/ Customer
13	2014.10.01~02	MOH(IRAN)	Contract manufacturing service/ Customer
14	2014.12.16~19	MFDS	KV Product(Regular)
15	2015.06.02~05	MFDS	KV Product(PIC/S GMP inspection)
16	2015.09.09~10	ANMAT(Argentina)	Contract manufacturing service/ Customer

Brief report of inspection activities undertaken

Scope and limitations	
Areas inspected	The inspection focused on the production and control of the monovalent bulks (H1N1, H3N2, B) and the formulated bulk of the flu vaccine “IL-YANG Flu Vaccine [®] Inj.” which is filled in vials, labelled and packaged at the contract manufacturing organization.
Restrictions	The inspection covered only premises and activities utilized for the manufacture and control of IL-YANG Flu Vaccine [®] Injection in vials. None of the other products was part of the scope of this inspection.
Out of scope	The inspection was limited to IL-YANG Flu Vaccine [®] Inj.
WHO vaccine covered by the inspection	IL-YANG Flu Vaccine [®] Injection in vials

Abbreviations	
AHU	air handling unit
ALCOA	attributable, legible, contemporaneous, original and accurate
API/DS	active pharmaceutical ingredient/drug substance
APQR	annual product quality review
BDL	below detection limit
BMR	batch manufacturing record
BPR	batch packaging record
CAPA	corrective actions and preventive actions
CC	change control
CFU	colony-forming unit
CoA	certificate of analysis
CpK	process capability index
DQ	design qualification

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EM	environmental monitoring
FAT	factory acceptance test
FMEA	failure modes and effects analysis
FPP	finished pharmaceutical product
FTA	fault tree analysis
GMP	good manufacturing practice
HACCP	hazard analysis and critical control points
HPLC	high-performance liquid chromatograph
HVAC	heating, ventilation and air conditioning
IR	infrared spectrophotometer
IQ	installation qualification
LAF	laminar air flow
LIMS	laboratory information management system
LoD	limit of detection
LOD	loss on drying
MB	microbiology
MBL	microbiology laboratory
MF	master formulae
MR	management review
NRA	national regulatory agency
OQ	operational qualification
PHA	process hazard analysis
PM	preventive maintenance
PpK	process performance index
PQ	performance qualification
PQR	product quality review
PQS	pharmaceutical quality system
QA	quality assurance
QC	quality control
QCL	quality control laboratory
QRM	quality risk management
RA	risk assessment
RCA	root cause analysis
SOP	standard operating procedure
URS	user requirements specifications
UV	ultraviolet-visible spectrophotometer

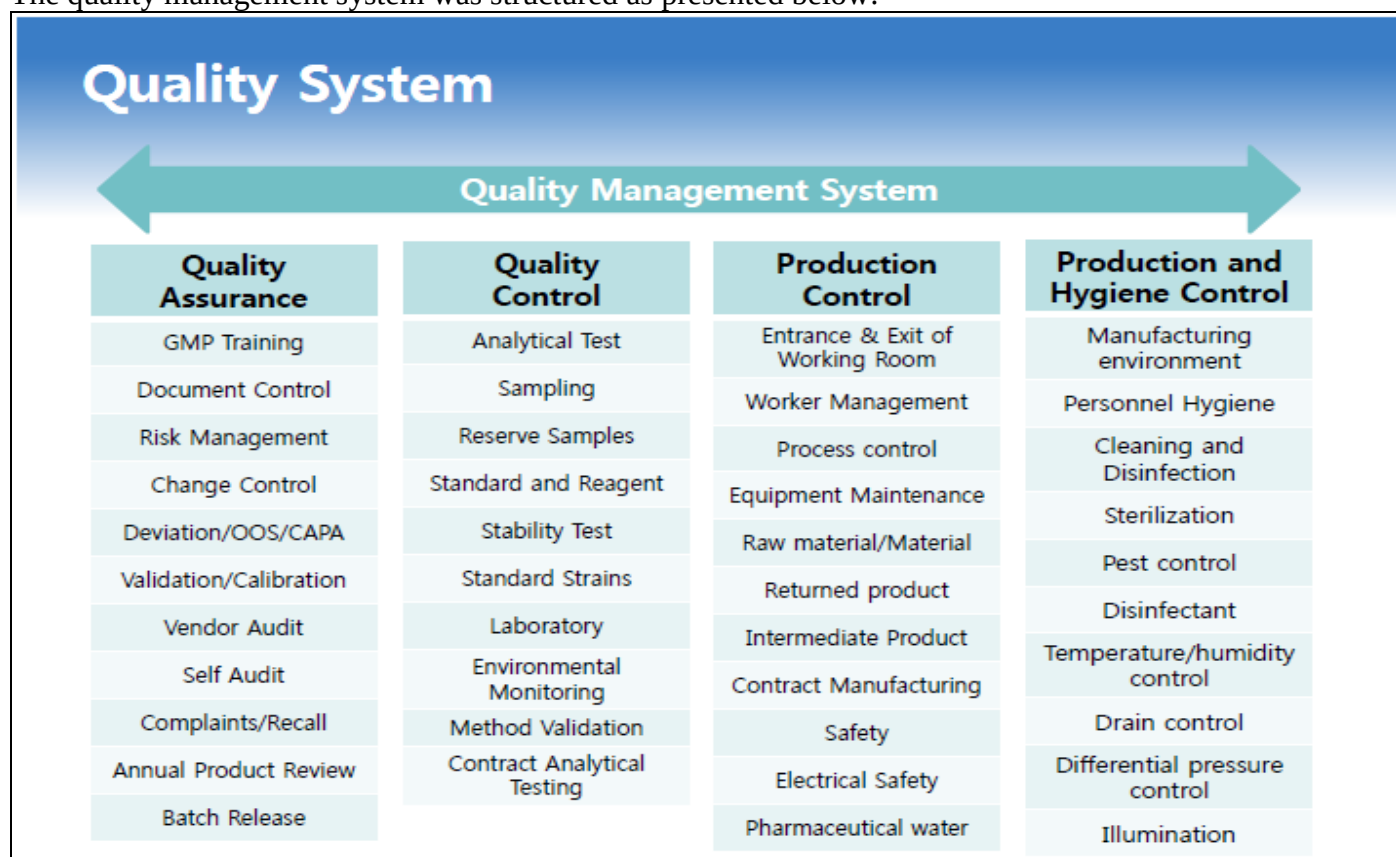
PART 2/1: Brief summary of the findings and comments regarding

IL-YANG Pharm. Co., Ltd. (Vaccine Plant):

1. Pharmaceutical quality system

In general the pharmaceutical quality system and all of the elements was in place. The production is independent from the quality control department.

The quality management system was structured as presented below:



✓ **Quality risk management (QRM)**

The procedure for the quality risk management was in place. Failure mode and effect analysis (FMEA), Failure tree analysis (FTA) and Failure mode, effects, and criticality analysis (FMECA) are considered by the company for the risk assessment.

The QRM aspect of the QMS was fairly basic and this element of the QMS requires further development to assist the company in making optimal use of resources and/or to consider required additional resources. The company has provided an acceptable CAPA adequately addressing the quality risk management.

✓ **Product quality review (PQR)**

The product quality reviews was in place. Separate PQRs for monovalent, formulated bulk and finished product. In general the PQR include review of quality control test results of critical in-process control and product, OOS batch investigation record, change control record on process or test method, results of stability test evaluation, record on return, complaint and recall, record on corrective action, record on validation. The PQR scheduled approval is up to three months following the report period.

The following PQRs were spot checked:

- Il-Yang Flu vaccine vial Inj covering the manufacturing period from January to December 2015 and approved in June 2016.
- Il-Yang Flu vaccine Final Bulk covering the manufacturing period from January to December 2015 and approved in March 2016.
- Il-Yang Flu vaccine monovalent bulk H1N1 covering the manufacturing period from January to December 2015 and approved in March 2016 was spot checked.
- Il-Yang Flu vaccine monovalent bulk H3N2 covering the manufacturing period from January to December 2015 and approved in March 2016.

The PQR were available, however were not conducted with the objective of verifying the consistency of the existing process and the appropriateness of current specifications for both starting materials, intermediates and finished product, to highlight any trends and to identify product and process improvements.

The company has provided an acceptable CAPA adequately addressing the product quality review management.

✓ **Change Control**

Provisions for change control were in place. Changes are categorised from level 1, level 2 A and B and level 3 A, B and C.

Level 1: change considered without need of qualification, validation, or stability test, which does not definitely influence the product.

Level 2 A: change considered unlikely to influence the quality of the product.

Level 2 B: change considered likely to influence the quality of the product. For these changes the regulatory impact is not considered. In the procedure, the company mentioned example of change of the supplier of an ingredient used in drug manufacturing, change of the process requiring validation or confirmation, or the specification of analytical procedure and change of release limits.

Level 3 A: critical change of supplier, contractor process, analytical criteria, and machinery & equipment, which requires notification to regulatory authorities but does not require immediate notification. The impact to the quality of the product is taken into account for each change. It is recommended to take into consideration the cumulative changes effect in the change control management.

Level 3 B: critical change of supplier, contractor process, analytical criteria, and machinery & equipment, which does not require notification to regulatory authorities

Level 3 C: critical change of suppliers, contract manufacturing organisations, analytical criteria, and machinery & equipment, which particularly requires approval of regulatory authorities.

The list of change control initiated since 2014 was spot checked. A renovation of the manufacturing area, changes to the process and equipment were implemented for the monovalent and final bulk to address the deficiencies raised during the initial WHO inspection that took place from 20 to 23 June 2016.

✓ Deviation

The deviation management was in place. Deviations are categorised as minor or critical according to the impact to the quality of the product. Minor deviations are addressed by corrective actions and critical deviations may lead to CAPAs. The target of 40 days for closing a deviation report was in place. The monitoring and trending of the deviation was not considered appropriately implemented. There was no monitoring in place of the recurrences of deviation.

The list of deviation as from 2014 was spot checked. The handling of the deviation was found weak however the company has provided an acceptable CAPA adequately addressing the deviation management system.

✓ CAPA

Provisions for Corrective Action & Preventive Action were in place. The list of CAPAs since 2014 was spot checked. The corrective and preventive actions plan to the WHO initial inspection that took place from 20 to 23 June 2016 was reviewed and found in general acceptable.

✓ Management review:

Procedure for quality management was in place. Regular meeting were in place. Monthly reports for April, May 2017 were presented to the inspectors.

2. Good manufacturing practices for pharmaceutical products

Overall, resources were available, including personnel, premises, equipment and services, materials, containers and labels, approved procedures and instructions, laboratories and equipment for in-process and other controls. Manufacturing processes were generally defined. Instructions and procedures were generally available. Qualification and validation of equipment, manufacturing processes and quality control testing methods were performed. Operators were trained to carry out procedures, and records were made during manufacture.

3. Sanitation and hygiene

Most of the premises were generally maintained at an acceptable level of cleanliness. The company had provisions for personal hygiene and sanitation in its production facility. Smoking, eating, drinking, chewing, and keeping plants, food, drinks, smoking material were not permitted in production and laboratory areas. Wrist-watches, cosmetics and jewelry were not observed being worn in clean areas. Manufacturing areas were provided with airlocks for personnel and materials entries and exits. Gowning procedures for access to the classified and contained manufacturing areas were in place. The level of hygiene observed and the measures taken to maintain this were considered acceptable.

4. Qualification and validation

In general, provisions for qualification and validation were in place and covered premises, equipment, utilities and systems, and processes and procedures. Qualification and validation were considered initially, at periodic intervals and when major changes have been made. Validation and qualification reports were spot checked as presented below.

- Inactivation validation of the monovalent bulks
- Validation of the sterile filtration
- Media simulation
- Aseptic disconnection
- Autoclave
- HVAC

Deficiencies related to the validation and qualifications were raised and the company provided an acceptable CAPA to address the raised deficiencies.

5. Complaints

Procedures exist for dealing with complaints, which describes the receipt of complaints through sales department, forwarding of complaints to QA for initiating investigation, the classification of complaints and the committee structure for decision making and response. The complaints procedure includes adverse event following immunization (AEFIs). There was no medical department at Il-Yang. The procedure indicates that experts can be contracted to participate in complaint investigation but there was no proactive arrangements made. The company indicated that they have not received any complaints and so the functioning of the procedure has not yet been tested.

6. Product recalls

There was a recall procedure in place. There was an indicated recall in 2014, according to summary documentation prepared by Il-Yang for this inspection. In this case, two batches of product in PFS failed testing by MFDS and were not released for sale and had not moved from storage in the contract filling site (Korea Vaccines). Documentation reviewed included the direction for these batches to be destroyed, reconciliation of stock, evidence of destruction by a third party contractor and communication with government authorities about this destruction. These were considered satisfactory.

7. Contract production, analysis and other activities

The company has provided in the site master file and during the opening meeting presentations the list of subcontracted manufacturing and testing activities.

The filling and packaging operations of the IL-YANG Flu Vaccine® Inj. as well as one quality release test were subcontracted to the contract manufacturing operations Korea Vaccine Co., LTD. Testing of formaldehyde, potassium dihydrogen phosphate, sodium chloride, sodium hydrogen phosphate dodecahydrate, sucrose and octoxinol-10 were subcontracted.

The quality agreements were in place.

8. Self-inspection, quality audits and suppliers' audits and approval

The company has provided in the site master file and during the opening meeting presentations the procedures in place for self-audit and suppliers audit and approval.

QA department manager is lead auditor of self-audit. Audit team consists of manager of each department at Il-Yang. Therefore, the manager of a department to be audited is a member of the audit team. It was stated that their role in the team was to explain issues to the team and not to audit (but this was not described in SOP). For routine self-audit there is a common check list used for audit of any department. Some items are general, applying across departments. Some are specific to particular departments. In addition to routine audits, the system allows for special (including unannounced) audits. In that case, use of a free-form report rather than a check list is possible. The plan for routine self-audit in 2017 was reviewed. A review was also made of the last report from the special audit performed in March 2016.

There is one month timeframe for completion of the audit report. Observations are categorised. The standard CAPA form used across all processes is used. There is a defined timetable for receipt of the CAPA plan from the relevant department(s) and a review of its implementation by QA. At subsequent audits, past findings are also reviewed.

Vendor Qualification was described in relevant procedure. The periodicity and type of vendor audit is classified according to the type of material/service provided by the vendor. [A: performed once per year by on site audit: egg supplier, sub-contractor for filling and QC testing; B: performed once per year by document review. These are for materials with potential impact on product quality but with CoA provided as part of basis for review; C: once per two years by document review for materials with “no impact” on quality- cartons, labels]. There was documented plan for vendor review. There was scoring sheet for vendor considering: reputation, prior experience, audit findings. Based on this vendors are accepted for use; require further review or are not accepted as a vendor.

9. Personnel, training and hygiene

46 employees were working in Eumseong site at the time of the inspection. The break-down of employees was as follows.

- Vaccine production division manager: 1
- Production Department: 18
- Quality Assurance (QA) Department: 7
- Quality Control (QC) Department: 7
- Management & Maintenance Department: 7

Additionally seasonal employees were used during the production period. Qualification and training program requirements of the seasonal employees were similar to the Il-Yang permanent staff.

Job descriptions were in place for the staff of Il-Yang however not for seasonal employees.

The training was governed by the procedure “Management of Training”.

Training records of the aseptic operators and one operator for purification were spot checked.

Gowning, access to the manufacturing areas and Hygiene training were considered for employees. Gowning qualification program for aseptic operators including operators performing sterility tests were in place.

10. Premises and equipment

Simple floor plans show room layout classification including air flow, flows of materials, product, personnel, waste, and Air Handling Unit (AHU). Identification by room of manufacturing and quality control areas in IL-YANG Vaccine Plant were provided in the Site Master File.

IL-YANG Vaccine Plant was divided into Vaccine Manufacturing (VM), Quality Control (QC), Utility Building (UB) in Eumseong site.

Quality control areas

The quality control comprises the following:

Mycoplasma laboratory,
Virology laboratory,
Chemical laboratory,
Sterility laboratory,
And microbiology laboratory

11. Materials

Arrangements for the handling of starting materials, packaging materials, bulk and finished products, including sampling, quarantine, release and storage were in place through standard operating procedures.

Arrangements for the handling of rejected materials and products, and procedures for their destruction were in

place through standard operating procedures.

Incoming raw materials are tested according to pharmacopoeial requirements. Testing of raw materials takes place at Il-Yang based on pharmacopoeial requirements. The company does not base its decision on use solely on supplied certificate of analysis results from the supplier.

The major supplier of eggs for routine production is from the country. The renewed quality agreement with the supplier was reviewed. There is two monthly health check of the flock with sera from 50 chickens (from 30K) to test by ELISA for Avian Influenza Virus, E.coli, infectious bronchitis inhibition, Newcastle disease virus inhibition, mycoplasma, salmonella.

12. Documentation

Document Management procedure was in place. SOPs have appropriate clearance. Also record of effective date and change history. Default review of SOPs occurs at three year intervals.

13. Good practices in production

In general production operations followed defined procedures. Deviations from procedures were recorded and investigated. Access to production premises was restricted to authorized personnel.

Environmental monitoring of clean area was discussed. EM was performed by settle plates, contact plates and airborne particle counts. Action and alert levels were specified. EM monitoring results for 2017 were discussed.

Bio-waste management: liquid bio-waste were sent to the Bio-kill tank in the basement and decontaminated.

Solid waste: after harvest, eggs waste was grinded and dehydrated in the basement station. The other type wastes were decontaminated by autoclave.

14. Good practices in quality control

Provisions for handling out of specification (OOS) test results were in place as per the procedure. A report is raised by responsible QC staff in the case of OOS. The initial investigation examines if there was an assignable lab error leading to the result and if so, allows for invalidation of the assay and retest. If there is not there is a broader investigation to production processes to investigate a possible root cause for the OOS. The list of OOS since 2014 was spot checked.

The company places one batch per season on stability study at real time temperature conditions (2-8°C). These studies extend beyond the 12 month assigned shelf life for the vaccine.

Accelerated stability studies (25°C) have not been performed.

The three batches that have been produced in vials were stress tested (37°C). Samples were tested at 1, 3, 7 and 14 days. For two of the three batches, the HA test for at least one strain failed at 7 days. This data does not support the use of a VVM7 with this product. Staff suggested testing of additional batches. However, if formulation is unchanged, and production process is consistent, different results would not be expected.

Environmental monitoring:

The trending of the environmental results was performed annually. The environmental monitoring was performed according to the procedure “management of manufacturing environment”.

Water systems:

Sampling, testing, specifications of city water, purified water, water for injection and pure steam were in place

according to the management of pharmaceutical water procedures. Alert and action limits were established. WFI user points were sampled weekly including the return sampling point. WFI was continuously circulating at over 80 °C, temperature and flow rate are monitored. The same loop of water was supplying the upstream and downstream processes. A risk assessment was performed regarding the risk of cross-contamination by using the same water loops in the infectious (upstream process facility) and non-infectious (upstream process facility) and a mitigation risk plan was accordingly implemented. PW loop is sanitized every 6 months by heating up to 80°C over two hours.

Water monitoring trend analysis of WFI report for 2015 was spot checked. Water monitoring trend analysis of PW report for 2015 was spot checked. Trend analysis was performed annually.

PART 2/2: Brief summary of the findings and comments
KOREA VACCINE CO., LTD.
1. Pharmaceutical Quality System

In general the pharmaceutical quality system and all of the elements were in place. The quality department was independent of production and was in charge of quality assurance and quality control responsibilities. The organization chart is presented below:

Production	Production Support	Quality Assurance	Quality Control
Production	Production equipment maintenance	Document	Laboratory control
In-process control	Utility maintenance	Validation	QC test
Packaging & Labeling	Raw material control	Deviation & OOS & CAPA	- Chemical & Physical
Cleaning & Sanitation	Finished product receiving & Distribution	GMP Training	- Microbiological test
Hygiene	Waste control	Calibration	- Sterility test
Manufacturing contract	Pest control	Change control	- Animal test
Intermediate/Finished product control	Safety control	Self-audit	Laboratory investigation
	Key control	Supplier Audit	Stability test
	Rejected product control	Complaint & Recall & Return	Reference & Reagent
		Annual product review	Sampling control
		Lot release	Environmental monitoring
			Method validation
			QC contract

Subcontracted activities:

An up to date quality agreement between both parties covered all subcontracted activities and responsibilities. The manufacturing and quality control activities subcontracted to KV by IL-Yang are as summarized below:

	Final Bulk	Transportation	Final Bulk Weighing	Fill & Finish	Holding	Distribution
KOREAVACCINE		- Final bulk Transportation (IV -> KV) - Temp. Control	- FB Receipt & Receiving Check - Final Bulk Weighing	- Primary Material Test (Vial, Stopper, Cap) - Filling & Packaging - IPC (Fill Volume, Packaging Identification)	- Holding at cold storage room - Temp. Control (2~8°C)	- Dispatch - Final Product Transportation (KV -> IV) - Temp. Control
IL-Yang	- Manufacturing - FB Release test - Stability test			- Release Test - Sampling - Printed material test - Retention Sample control - Stability test		- Batch Release approval - Distribution & Sales

Self-audit:

Provisions for the internal audit were in place. The internal audits were performed annually as per the established check list. The reports were generated and the raised observations addressed within acceptable time limits.

Although the internal audit system was in place, it was considered weak to meet the principle of the self-audit evaluate the manufacturer's compliance with GMP in all aspects of production and QC and to detect any shortcomings in the implementation of GMP and to recommend the necessary corrective actions. In addition, there was no qualification of the internal auditor. The company has provided adequate corrective action plan to address the raised deficiencies regarding the self-audit system.

Personnel:

The company is adequately staffed. The organization charts, training programme and records, health and personnel hygiene requirements were provided in the Site Master File and briefly presented during the opening meeting.

Provisions were in place for the management of complaints, recall and adverse event following immunizations (AEFI).

2. Production System,

Resources were available, including personnel, premises, equipment and services, materials, containers and labels, approved procedures and instructions, laboratories and equipment for in-process and other controls. Manufacturing processes were defined. Instructions and procedures were available. Qualification and validation of equipment, manufacturing processes and quality control testing methods were in place. Operators were trained to carry out procedures, and records were made during manufacture.

Premises were generally maintained at an acceptable level of cleanliness. The company had provisions for personal hygiene and sanitation in its production facility. Smoking, eating, drinking, chewing, and keeping plants, food, drinks, smoking material were not permitted in production and laboratory areas. Wrist-watches, cosmetics and jewelry were not observed being worn in clean areas. 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. The level of hygiene observed and the measures taken to maintain this were generally considered satisfactory.

3. Facilities and Equipment System,

Simple floor plans including layout, air flow, flows of materials, product, personnel, and waste, room classification and Air Handling Unit (AHU) identification by room of manufacturing and quality control areas in KOREA VACCINE plant were provided in the Site Master File and during the opening meeting of the inspection.

The product contact equipment including filling manifold, syringes, buffer bottles are product dedicated and tracked in the batch record of each product.

Qualification and validation:

Provisions for qualification and validation were implemented and the validation master plan, the protocols and reports were in place. Validation and qualification reports were spot checked as presented below.

- Autoclave
- Tunnel sterilizer

- HVAC
- Media Fill Test Simulation
- Container Closure Integrity Test

4. Laboratory Control System,

Tests performed on Il-Yang product are sterility, endotoxin, insoluble particles and abnormal toxicity.

Environmental Monitoring

Environmental monitoring is performed according to the procedure “EM program”. A risk based approach had been considered for the environmental monitoring program.

Trend analysis for environmental monitoring results from January to December 2015 was spot checked. Alerts and action limits are in place.

Water Monitoring

Pure Steam: the test results of 2015 were spot checked. pH, conductivity, TOC, microbial monitoring and endotoxin. Dryness, super heat and non-condensable gases test were performed annually during the qualification.

WFI: conductivity and TOC and continuously monitored on line. The test results of 2015 were spot checked.

5. Materials System,

Arrangements for the handling of starting materials, packaging materials, bulk and finished products, including sampling, quarantine, release and storage were in place through standard operating procedures. Arrangements for the handling of rejected materials and products were in place through standard operating procedures.

6. Packaging and Labelling System

Packaging and labelling procedures and instructions were in place. The staff was trained to carry out the packaging and labelling operations. Instructions and measures to prevent mix ups were in place and regularly verified.

Shipping validation

For use of the vaccine in Korea, Il-Yang branded vaccine is distributed directly from KV to a distribution site (KV sales) in a refrigerated truck. Il-Yang had yet to conduct Shipping Validation studies for final product in compliance with WHO requirements. Data from this study would need to be reviewed before a decision on prequalification. If the product for supply through UN agencies is to be shipped directly from KV, an updated contract between the manufacturers would need to specify packaging requirements.

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, IL-YANG Pharm. Co., Ltd. (Vaccine Plant), Daegum-Ro, Geumwang-Eup, Eumseong-Gun, Chungcheongbuk-Do, Republic of Korea, and KOREA VACCINE CO., LTD. Mongnae-ro, Danwon-Gu, Ansan-Si, Gyeonggi-Do, Republic of Korea. were considered to be operating at an acceptable level for compliance with WHO GMP guidelines.

All the non-conformances observed during the inspection that were listed in the full 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.