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

Part 1	**General information**
Manufacturers details	
Company information	
Name of manufacturer	**Xiamen Innovax Biotech Co., Ltd.**
Corporate address of manufacturer	No. 52, Shanbianhong East Road, Haicang District, Xiamen, Fujian, China.
Inspected site	
Address of inspected manufacturing site if different from that given above	1. The headquarters as well as the manufacturing site for the Recombinant Human Papillomavirus Bivalent (Types 16, 18) Vaccine (*Escherichia. coli*), located at No. 52, Shanbianhong East Road, Haicang District, Xiamen, Fujian, China. GPS location is N24°31′49″E117°56′58″. 2. The Aluminum hydroxide adjuvant is manufactured for the Recombinant Human Papillomavirus Bivalent (Types 16, 18) vaccine at No. 130-1 Xinyuan Road, Haicang District, Xiamen, Fujian, China, 361022
Unit / block	• 1# building (Administrative building). • 2# building (facility for the commercial production of the product, Warehouse and Quality Control laboratory). • 3# building (Warehouse of hazardous materials), with two separated rooms for storage of solid and liquid hazardous materials. • 4# building (Utilities). • 5#building (Animal house).
Inspection details	
Dates of inspection	02 to 06 February 2021.
Type of inspection	Initial inspection.
Introduction	
Brief summary of the manufacturing activities	In collaboration with the National Institute of Diagnostics and Vaccine Development on Infectious Diseases (NIDVD), the company has established its *Escherichia. coli* based platform for development and manufacture of recombinant vaccines. Based on this platform, the first Hepatitis E Vaccine Hecolin® was launched in China in October 2012. In addition, Innovax is developing Human Papillomavirus vaccines; among which the Recombinant Human Papillomavirus Bivalent (Types 16, 18) vaccine is subject to prequalification by WHO.
General information about the company and site	Xiamen Innovax Biotech Co., Ltd. was established in Xiamen, in March 2005. The company is a subsidiary of Beijing Wantai Biological Pharmacy Enterprise Co., Ltd. It is the vaccine manufacturing arm of the private enterprise, Yangshengtang Co., Ltd., in China. The company has two manufacturing sites. 1. The manufacturing site for Hepatitis E Vaccine - Hecolin®, as well as the R&D center, located at No. 130-1 Xinyuan Road, Haicang District, Xiamen, Fujian, China, 361022. In the same site the Aluminum hydroxide adjuvant is manufactured for the Recombinant Human Papillomavirus Bivalent (Types 16, 18) vaccine.

2. The headquarters as well as the manufacturing site for the Recombinant Human Papillomavirus Bivalent (Types 16, 18) Vaccine (*Escherichia. coli*), located at No. 52, Shanbianhong East Road, Haicang District, Xiamen, Fujian, China. The site covers an area of more than 67,000 m^2 and the construction area is more than 35,000 m^2.

History

The history of the regulatory inspection as provided in the site mater file is presented in the table below:

Table 2.1 List of inspections conducted by authorities

Date	Body	Content	Result
Nov.29, 2017	Market Supervision Administration of Xiamen Municipality	Inspection of Manufacturing Licensure	Pass and Certified
Sept. 16-24	CFDI, NMPA	BLA(Biological License Approval)	Pass and Certified
Oct. 12-14, 2019		Inspection	
Oct. 10-14, 2019	Fujian MPA	GMP Inspection	Pass
Feb,20,2020	Fujian MPA	Critical facilities or equipment change inspection	Pass
Jun,03,2020	Fujian MPA	Critical facilities or equipment change inspection	Pass
Jul 31-Aug 03,2020	Fujian MPA	Vaccine GMP inspection	Pass
Sep 20-22,2020	Fujian MPA	GMP Inspection	Pass
Nov 12-15,2020	Fujian MPA	BLA(on pre-filled syringe packaging form)	NCL Sample testing ongoing
Nov 12-16,2020	Fujian MPA	GMP Inspection(on pre-filled syringe packaging form)	Pass

Brief report of inspection activities undertaken

Scope and limitations

Areas inspected

The following manufacturing areas and the associated activities were covered during the inspection:

- Seeds establishment and maintenance;
- Drug substance production areas;
- Drug product production (Formulation, filling, visual inspection and packaging areas);
- Warehouses and shipping areas;
- Quality control laboratories including animal house;
- Utilities;

Pharmaceutical Quality System.

Restrictions

Due to time constraints the manufacturing site of the Aluminum Hydroxide was not inspected.

Out of scope

Recombinant Hepatitis E vaccine (*E. coli*)
Prefilled syringe (PFS) formulation and filling line, and all associated activities pertaining to HPV16/18 vaccine in PFS.

Vaccines covered by the inspection

Recombinant Human Papillomavirus Bivalent (Types 16, 18) Vaccine.

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
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
MMR	Measles vaccine
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
RO	Reverse Osmosis

SIP	Sterilization In Place
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**

Part 2: Pharmaceutical quality system

The Quality Unit, which 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 sites. 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 are being produced consistently. Production and control operations were specified in written form and GMP requirements were essentially being met. Managerial responsibilities were appropriately specified in written job-descriptions. Product and processes were monitored, and the results considered during batch release; regular monitoring and reviews of the quality of Recombinant Human Papillomavirus Bivalent (Types 16, 18) Vaccine were being conducted according to documented schedules and procedures.

Management review

Quality management review procedure was in place. The quality reviews were conducted on a monthly and annual basis. The objective of the annual review was to discuss the annual target/goal, APQR, deviation, change control, CAPA, OOS/OOT, regulatory inspections, third party audit, self-inspection, continuous improvement, supplier management, recall, complaints, feedback from customers, training, new regulatory guideline, and follow-up actions from the previous annual review.

Product quality review (PQR)

The PQRs were performed in accordance with the procedure "Annual Product Quality Review Management Procedure". The procedure outlined the consistency of the existing manufacturing process and appropriateness of the specification, i.e., to confirm that the process is controlled, capable, suitable and effective. It also described the different types of reviews that will be performed and include reviews of starting materials, in-process controls, stability, deviations, OOS, complaints, OOT, review of qualification status of critical utilities and equipment, technical agreements, etc. A template for the APQR was attached.

The PQR report for HPV 16/18 Bivalent Vaccine was presented during the inspection. The report did not include activities performed for a full 12-month period as it was a new product that the company was manufacturing.

Trending

Excel was mostly used for trending analysis though a few parameters and were being trended with Minitab. No statistical trending was performed; only assessment of variability was done. Comprehension of Minitab software was very limited and most of its statistical features were not used.

Rejections
The rejected batches were identified by batch numbers and the reasons for rejection were provided in the document. Investigations were initiated to determine the root causes of the deviations that led to the rejection of the batches.
A number of rejected batches investigation documentation was reviewed.

Reprocessing and reworking
Reprocessed and reworked batches were also reported in the PQR. Reprocessing was not allowed, and reworking of batches was only permitted for visual inspection and labeling defects.

Out-of-Specifications (OOS)
A number of investigation documentation was reviewed.

Returned goods
A customer complaint was reviewed.

Outsourced activities
During the period under review the company made use of third-party laboratories to perform several quality tests. Contracts for these service providers were available. Details of the contracted service providers and tests performed were available.

Quality risk management (QRM)
The SOP "Quality Risk Management Procedure*"* described the risk management process, which included risk assessment, risk control, risk communication and risk review. Risk assessment consisted of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards. After a risk was identified and evaluated, risk control measures should be identified to reduce the risk to an acceptable level. Risk communication was the appropriate exchange or sharing of information about risk. Risk review, as a part of risk management, included outputs/results of the QRM process, the review should consider new knowledge and experience. The QRM was integrated into different quality modules and procedures in the QMS system, as well as any other risks identified in the operation. These modules include, but were not limited to, Deviation, Change control, Qualification and Validation, Self-inspection, and Recall. Risk assessments was performed using the appropriate risk assessment methodology based on the objectives, scope, life cycle phase of the product, process or system, and other relevant factors, such as Failure Mode Effects Analysis (FMEA), Fault Tree Analysis (FTA), fish bone diagram, HACCP and RRF, etc. The QRM procedure was explained by the risk administrator.

A number of Risk Assessment documentation was reviewed.

Deviation management
Procedure for deviation handling was in place. The procedure delineated identification, recording, immediate action, initial impact analysis, classification of deviation, root cause analysis, impact assessment and closure. The procedure stated that a separate procedure was followed for handling OOS/OOT. The procedure described the definition of various terms related to deviation and classification as critical (I), major (II) and minor (III). Risk assessment included typical RPN numbers.

A number of deviation documentation was reviewed.

Change control
A procedure for change control was in place covering process, materials, suppliers, equipment, quality control and other systems. Each department had a document controller who issued a change request form that was similar for HEV, HPV16/18, HPV9 and JADE. A checklist was used for change assessments. Changes were identified using unique codes.

A number of Change Control documentation was reviewed.

CAPA management
A procedure for CAPA management was in place. The procedure described the purpose, scope, responsibility, definition and instructions for the management of CAPA. The procedure was supported with a CAPA workflow diagram a CAPA handling form, a CAPA modification application sheet and a CAPA tracking form. A summary report of the 2020 CAPAs was presented at the management review meeting.

Complaints
A customer complaints procedure for handling of customer complaints was available. Upon receipt of a complaint, it was acknowledged and recorded. Complaints were classified into four types:

- Product quality complaints;
- Distribution/logistic complaints;
- Medical related complaints (AEFI), and
- Combined complaints.

Complaints were investigated by the QA department and should be closed within 30 calendar days otherwise an interim report should be provided. The procedure described the determination of a potential root cause by using tools i.e. *5-WHY*, fish-bone diagram.

For medical related complaints, a separate procedure was available.

A number of complaints documentation was reviewed.

Product recalls
A product recall system had been established as specified in the document "Product Recall Procedure" . The qualified person was responsible for grading a recall based on safety risks and making the decision to recall. Once a decision was made to recall the product based on existing or potential safety risks, it would be immediately reported to the regulatory authorities. The system would also be adopted whenever a regulatory authority requests a recall. To evaluate the effectiveness of the product recall process, a mock recall was conducted at least once every 2 years. The company confirmed that no recalls have been initiated to date.

Pharmacovigilance
A Management Procedure for Pharmacovigilance was available for inspection. The procedure was comprehensive and detailed the management structure of the PV unit as well as the procedures to be followed in documenting and investigating safety signals of products. In addition, a procedure for drafting of Periodic Safety Update Reports (PSURs) was available. Such reports need to be compiled once per year as from the date the approval certificate for the product was obtained.

Self-inspection
Self-inspections were performed according to SOP. The scope covered all GMP elements and was performed at least once per year as planned or in extraordinary situations. It was indicated that a self-inspection was carried out twice in 2020 and will be carried out twice in 2021. Should there be any major changes to QMS, complaints, recalls, etc., a self-inspection shall be carried out. A checklist was used to verify areas audited. In general, the procedure appeared adequate. A self-inspection schedule for 2020 and 2021 was available. A list of qualified auditors was available based on the procedure described for qualification of the auditors. It was indicated that ISO 9001 training was organized by the company for internal auditors.

Quality audits and suppliers' audits and approval
Several procedures were in place for supplier's management including:

- Material supplier management;
- Service supplier evaluation;
- Supplier Quality audit;
- Quality agreement;
- Supplier complaint management.

Four categories for materials were defined i.e. raw materials, excipients, packaging materials and consumables for production. According to the quality, compliance and safety impact, material was classified in three classes: A (Materials that have a significant impact on product quality and compliance and are a risk to patient medication safety.), B (materials that have a certain impact on product quality, but have little risk to patients' medication safety) and C (materials that have little or no impact on product quality and do not affect the medication safety of patients.).

A site audit/remote audit was required only for class A materials. The frequency of audits and quality questionnaire for class A materials and quality questionnaire for class B materials were in place.

The company had established "Material supplier assessment standard operating procedure" to assess and approve the material supplier, the requirements of the supplier's qualification, selection principles, quality assessment methods and assessment acceptance criteria. The material used for commercial production were procured from approved suppliers as listed in the "Qualified Material Supplier List.

Contract production, analysis and other activities
And Quality agreement:
It was indicated by the company that no production activities are outsourced for HPV16/18.

The SOP for contract analysis management procedure and procedure on "Service Supplier Evaluation SOP" were briefly reviewed. Quality Agreements with two testing laboratories were reviewed.

Personnel
The company was adequately and sufficiently staffed. The organogram of different units was provided in the site master file and found acceptable.

Training
Training management procedure described the training procedure related to GMP and applicable to all staff including external personnel (contractors, suppliers). The procedure have stated training procedures on revised procedures. The GMP training was provided once/year as well as after changes in regulations, GMP requirements, etc.

A number of training records were reviewed.

Job descriptions of the following staff were reviewed:

- Head of manufacture.
- Head of quality.
- Head of production.
- Qualified person.

The qualification of the operators for the visual inspection was conducted as per SOP. The initial qualification was granted after performing three successful runs with the default kit. The requalification had to be performed on a six months basis. The overall training records sheet was spot checked. All the visual inspectors were stated as formally qualified. The individual training records were spot checked.

Personal hygiene
Procedures for health requirements of personnel
A procedure for "Hygiene and Behavior Management for Staff in the Production Area" was available during the inspection. The scope of the procedure entailed management of staff in production, CNC (controlled not classified) and clean areas. The document outlined the health requirements for entry into the different areas and the procedures staff should follow if they suffer from a condition that may pose a threat to the quality of the product. The SOP was found to be comprehensive and acceptable.

Documentation
Document control procedure was reviewed. A hybrid document management system (manual and electronic) was in place. The procedure was applicable for documents handled on site; however, there was no requirement established in the Document Control Procedure for handling documents of external origin (e.g., pharmacopoeias, contracts, calibration, maintenance, qualification reports and more). The documents were reviewed every 3 years (SOPs) and 5 years (specification, batch record). The document control procedure described how documents were issued, retrieved and superseded using an appropriate stamp.

Batch Release Process
The process is described in "SOP for Product Release", which was applicable to the bulk, unlabeled finished product and labelled finished product level. Final release of the finished product by the QP was performed batch release by authorities. A number of Release files for bulks were reviewed and found acceptable.

Lot Summary Product review
The template of LSP and related documents for one batch were reviewed for changes requested during assessment for prequalification and were found acceptable.

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

***Source, history and generation of the* seed lots:**

HPV16 Seed Lots
Management of the seed lot was claimed to meet the provisions of "Management Rules and Quality Control for Bacterial and Viral Strains Used for Production and Test of Biologics" specified in Volume III, *Chinese Pharmacopoeia* (2020 Edition). A three-level seed lot system was used, namely, primary, master and working seed lots, which were stored in liquid nitrogen tanks. The master seed bank (MSB) was one passage away from the primary seed lot, and likewise, the working seed bank (WSB) was one passage away from the MSB.

HPV18 Seed lots
Similarly, as for the HPV 16 seed lots, management of seed lots for HPV 18 transformed bacteria was also done in accordance with the provisions of "Management Rules and Quality Control for Bacterial and Viral Strains Used for Production and Test of Biologics" specified in Volume III, *Chinese Pharmacopoeia* (2020 Edition). A three-level seed lot system was also used, namely, primary, master and working seed lots, which were stored in liquid nitrogen tanks. The master seed lot (MSL) was the first generation of the primary seed lot and the WSL, the first generation of the MSL, i.e., it was one passage away from the MSL.

Master and working seed lots of both HPV 16 and HPV 18 strains have been extensively characterised in accordance with specifications of the National Institute for Food and Drug Control (NIFDC) and the cell banks were stored onsite in the Quality Control Department with back-up cell banks stored offsite.

***Intermediates* and drug substances**
The manufacturing process of the two drug substances (HPV 16 and HPV 18 antigen bulks), was briefly described. The procedure was divided into three parts: fermentation, initial purification and purification.

Formulation
The human papillomavirus vaccine is a bivalent vaccine that is composed of two antigens or bulk drug substances, namely, HPV 16 and HPV 18 antigen bulks. In addition, it contains the adjuvant aluminium hexahydrate, phosphate buffered saline as well as the surfactant, polysorbate 80 to prevent adsorption of antigens to glass and tubing surfaces. All inactive ingredients were of pharmaceutical grade (*Eur. Ph.*). The manufacturer had performed pharmaceutical development studies to optimise the formulation.

***Final* Product Manufacture**
The manufacturer had performed process development studies and determined that for commercial production.
During the preparation of the monovalent antigen bulk intermediate products, each of the three working solutions was filtered in sequence through two sterilizing filters in series.

***Visual* inspection**
An SOP "Standard Operating Procedures for Visual Inspection of Bivalent Human Papillomavirus Vaccine *(E. coli)",* was in place. According to the procedure a 100% visual inspection was conducted after filling, sealing and crimping of vials and prior to labelling.

Labelling
A SOP for labelling was in place and available for inspection. The text was supplemented with graphics that showed the operation of the labelling equipment as well as facsimiles of the immediate and secondary container labels.

Packaging
SOP for Packaging of Bivalent Human Papillomavirus Vaccine (E. coli) Finished Product (Vial), was available for inspection. The procedure was detailed and not only state the purpose and scope of the activity but also the assigned responsibilities, working procedures, labeling procedures, cartoning, wrapping and line clearance. The packaging operation was inspected during the site visit and no comment was raised.

Storage
According to the outer container label the product should be stored at 2 – 8 °C protected from light and should not be frozen. These instructions were based on the *Chinese Pharmacopeia* requirements.

***Distribution* and shipping**
SOP for Packing of Finished Products for Export was available. A validation report for international shipping was not available as the company has not exported any product to date.

***Batch* manufacturing record review (BMR):**
A number of batch manufacturing records were provided for review during the inspection. The reports were noted to be detailed.

3. Facilities and equipment system
The vaccine production plant was composed of six main areas. The manufacturing buildings were access restricted and controlled. Pest control was in place. The temperature and relative humidity were controlled in classified areas, storage and warehouses as relevant. The manufacturing of the HPV16 and HPV18 antigen bulks took place in fully dedicated and separate lines. The formulation and filling line for vials were used for HPV.
Floor plans including layouts, manufacturing rooms' classification, AHU zoning, material flow, product flow, personnel flow, waste flow and air flow were presented.

Waste management:
Each line of live manufacturing area for HPV16 and HPV 18 was equipped with a decontamination autoclave. The decontamination autoclaves were used to decontaminate the waste of the live area and product contact equipment and material. Procedures for decontamination and disposal of used contaminated materials and waste management were in place.

Water system production description:
The water system in the company consisted of the purified water (PW) system, and the water for injection (WFI) system. PW was mainly used as original water for WFI generation and pure steam generation, for the initial rinse for vessels and articles, and in the preparation for sanitation solution used in grade C/D areas. WFI was mainly used for the final rinse of vessels and articles, and in the preparation of sanitation solution used in grade A/B areas.

HVAC systems:
The HVAC system was designed, installed, and qualified to meet the requirements according to different air classifications. The air supply to the HVAC system was filtered by several sets of filters. The Environmental Monitoring System (EMS) was used for monitoring/recording of differential pressure, temperature, humidity and was equipped with an alarm system. The following tests were performed as part of the requalification of AHUs:

- Non-viable particle, settle plate, viable particle, air volume and air change per hour;
- Differential pressure;
- Air velocity, light, noise, clean up time and HEPA integrity.

The smoke study (air flow pattern visualization study) was performed during initial qualification.

Qualification and validation:
Procedures for qualification and validation were in place and covered premises, equipment, utilities and systems, processes, and procedures at periodic intervals and when changes have been made. The annual validation master plan was in place. A preventive maintenance programme and calibration plan were in place.

The procedure "Calibration management procedure" detailed the company's calibration management system for all measuring instruments for consistency and data accuracy. Instruments were classified according to 4 categories based on criticality of measurement on the product for which a specific cycle of calibration is assigned. A calibration plan was then drafted at the end of each year for the coming year. Implementation and management of calibration deadlines were detailed and were applicable to all categories. A summary flowchart was attached to the document.

A number of Qualification protocols and reports were spot checked.

Validation of aseptic process through media simulations:
The MFT was performed twice a year. TSB media were used. Growth promotion tests were conducted at the end of the MFT incubation periods at 20-25 °C followed by 30-35 °C. The media simulation included the formulation steps and the aseptic filling. There was no record of any positive vial of the media fill test during the last two years.

Qualification of major production vessels:
Tanks used for the adsorption of the aluminum hydroxide and the active substances as well as the pooling tank of HPV vaccine were dedicated. The mobile tank KK was used for the adsorption of the active substance and the aluminum hydroxide. The IQ/OQ-Report and the PQ-Report were available. The tanks were manually cleaned. Cleaning validation was conducted every two years.
The sterilization of the tanks by autoclave was conducted on an annual basis. The cleaning validation of the 80L tank used for formulation was spot checked. Samples were taken for rinse water and swabs.

Autoclaves:
Overall, the autoclaves were qualified on an annual basis. All loads were re-qualified annually. The leak test was performed only once during the qualification. The Bowie Dick test was performed on a weekly basis. The vent filters were integrity tested offline once a month.
The qualification report of the decontamination autoclave in the live area of HPV 18 monovalent was spot checked.

Depyrogenation Tunnel:
The depyrogenation tunnel was qualified on an annual basis. The PQ-Report was spot checked. Overall, the qualification included an integrity test of HEPA filters, non-viable particles (NVP), heat distribution, heat penetration and endotoxin challenge.

Vial washing machine:
The last qualification report was spot checked. Cleaning coverage studies were checked.

Filling and stoppering machine:
The qualification of the filling and stoppering machine was performed every two years. The last requalification report was spot checked.
The stoppering station had a sensor to control the position of the stoppers.

Capping machine:
The requalification of the capping machine was conducted every two years. The qualification report was spot checked.

Fumigation of manufacturing facility:
Not inspected due to time constraints.

Warehouse:
A separate software package was used for monitoring the temperature and relative humidity in the warehouse area.

4 Laboratory control system

The quality control (QC) part of building X had personal/material/sample flows and waste flows segregated by design. The production part and warehouse part were housed in the same building and connected to the QC part, directly or via an elevator, respectively. Entrance of personnel for the quality control laboratory was separated from the other parts of building.

Test management:
The SOP "Test management procedure" described the establishment of the test management and the management of analysis work in QC. A test plan was drafted during production and covered sampling for QC or IPCs. Operators from QC requested the samples for testing, which were released by a sample administrator. Once control was performed, results were generated and double checked for equipment, reagents and calculation by a second operator. The testing report was drafted by a sample administrator and double checked by another sample administrator. The report was finally approved and signed by the QC manager.

Management of OOS test results:
The SOP "OOS/OOT/OOE handling" covered detection, root cause analysis, correction and handling through investigation of out-of-specifications, out-of-trends and out-of-expectation (outliers). If a case of OOS/OOT/OOE results, a phased investigation system was triggered, each phase being covered by a specific investigation document and set off by non-assignment of root cause during a previous phase.
The report on out-of-specification results was reviewed.

Qualification and use of reference standards:
According to information in Module 3.2.S.5 in the dossier, reference standards used for purity, identity, antigen concentration and peptide mapping (identification) of drug substance and vaccine final product were all prepared in-house from the individual HPV bulk drug substance batches (HPV 16 and HPV 18).
The approach of the manufacturer with respect to the selection of reference standards was to:

- Procure from the National Institutes for Food and Drug Control
- If not available, purchase an International reference standard (WHO, EDQM, etc.)
- If an international RS is not available, then either purchase from a company or develop one in-house.

A two-tier reference system (primary and secondary reference standard) was used only in the case of in-house developed reference materials. In such an instance the purpose of the primary reference standard was to calibrate all subsequent secondary standards that were developed. Secondary reference standards were developed from normal commercial batches without additional purification.

Analytical methods and their validation:
In vivo relative potency
The activity assessment of the vaccine in mice was reviewed.

Residual DNA Derived from the Expression System
rDNA was evaluated with "Quant-iT PicoGreen dsDNA Reagent and kit" (InVitrogen).

Stability of drug substances, bulks and finished products:
The stability chamber was in the finished product warehouse. There was no DS on stability at the time of the inspection whereas DP and adjuvant were found stored in this cold room. Continuous temperature monitoring was performed using EMS, which was in the Engineering Department.

Equipment
The equipment were stability samples were stored was within their maintenance and calibration period. Temperature was monitored through a centralized automated system.

Stability data:
Stability data were available for HPV 16 monovalent bulk and HPV 18 monovalent bulk. No OOS results have been observed at the 2~8 ℃ storage condition at any of the time points.

VVM
Related stability data was reviewed and *in vitro* relative potency results for each serotype were found compliant with VVM14 requirements. VVM dots were stored in the warehouse at NMT -24°C in a specific key locked deep freezer.

Environmental monitoring results:
The environmental monitoring data was available for inspection. The environmental monitoring was in place for all classified areas in static and dynamic conditions. The environmental monitoring results from June 2019 to December 2020 was spot checked.

Water(s) monitoring results:
The procedure for pharmaceutical water sampling, purified water testing and WFI testing were in place. The WFI was massively used in the production of HPV vaccine throughout the upstream and downstream manufacturing processes, during the critical manufacturing steps for adsorption and formulation as well as for the cleaning of product contact equipment.
The results for the year 2020 were presented. The conclusion was conclusive.

Visit of Quality control laboratories:

Physico-chemical:
A quality control laboratory (Physico-chemical & biological) was inspected briefly. The laboratory was equipped with 83 staff members (operators, technicians and supervisors), equipment and instruments for the performance of various tests such as purity and peptide mapping tests.

Microbiology:
Microbiology laboratories were visited and found acceptable. The media for sterility, bioburden and environmental monitoring are purchased from approved suppliers, adequately tested for growth promotion test and stored. The incubators were well maintained, and the plates incubated at the required temperatures. The reading of the plate was not performed with magnifiers.

5 Materials, packaging and labelling system

The storage, sampling testing, 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. Packaging/Labelling store was visited. Labels were well segregated and locked. Labeling and packaging line were visited. The area was of adequate space and appropriate flow of material and product during the labeling process.

6 International shipping

Information regarding shipping have been updated since submission for prequalification but not communicated to WHO. Procedure "SOP for finished product packaging" covered packaging procedures of finished products and was included in the submission for prequalification. Following a change in shipment procedure, a special SOP for packing of finished products for export was written to cover specifically packing of vaccines shipped outside China. Procedure "SOP for distribution of export orders" covered the workflow of transportation of finished products and intermediates and other materials such as reagents. Current procedures for shipping

Part 3	**Inspection outcome**

Based on the areas inspected, the people met and the documents checked, and considering the findings of the inspection, including the observations listed in the Inspection Report ***Xiamen Innovax Biotech Co., Ltd.*** located at ***No. 52, Shanbianhong East Road, Haicang District, Xiamen, Fujian, China,*** was considered to be operating at an acceptable level of compliance with WHO good manufacturing practices for pharmaceutical products guidelines.

All the non-compliances observed during the inspection that were listed in the full report as well as those reflected in the WHOPIR, were addressed by the manufacturer, to a satisfactory level, prior to the publication of the WHOPIR

This WHOPIR will remain valid for 3 years, provided that the outcome of any inspection conducted during this period is positive.

DEFINITIONS

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

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

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

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

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

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
   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
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17. WHO good manufacturing practices for biological products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fiftieth 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. WHO Recommendations, Guidelines and other documents related to the manufacture, quality control and evaluation of biological products. WHO Expert Committee on Biological Standardization. Seventy-first Report. Geneva, World Health Organization, 2021 (WHO Technical Report Series, No. 1028), Annex 1. Short name: WHO TRS 1028, Annex 1
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21 WHO good manufacturing practices: water for pharmaceutical use. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fifth Report. Geneva, World Health Organization, 2021 (WHO Technical Report Series, No. 1033), Annex 3.
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