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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	**Sinovac (Dalian) Vaccine Technology Co., Ltd.**
Inspected site	
Address of inspected manufacturing site	No. 36, 2nd Life Road, DD Port, Economic and Technical Development Zone, Dalian, China. N 39°03'31" north latitude and E121°52'11" east longitude
Inspection details	
Dates of inspection	1 to 5 November 2021
Type of inspection	Initial inspection
Introduction	
Brief summary of the manufacturing activities	The following vaccines are manufactured at the site: • Mumps Vaccine, Live (Freeze-dried Powder Injection); • Varicella Vaccine, Live (Freeze-dried Powder Injection); • MMR Vaccine, Live (Freeze-dried Powder Injection); • COVID-19 Vaccine (Vero cell), Inactivated (Small-volume Injection).
General information about the company and site	Sinovac (Dalian) Vaccine Technology Co., Ltd. (hereinafter to as Sinovac (Dalian)) is a high-tech biotechnology enterprise jointly established by Sinovac Biotech Ltd. and Dalian Jingang Group Co., Ltd. in 2010, to expand the live-attenuated vaccine market. Sinovac (Dalian) is currently owned 67.86% by Sinovac Biotech Ltd., which is listed in NASDAQ code as "SVA", and the other 32.14% is owned by Dalian Jingang Group Co., Ltd. The company, located in the Economic and Technical Development Zone, covers a floor space of 95,000 square meters with a construction area of 14,000 square meters. The main business of Sinovac (Dalian) includes research and development, production and sales of live human vaccines. The products currently on the market are Mumps Vaccine, Live and Varicella Vaccine, Live. In addition, MMR Vaccine, Live is currently in the R&D phase.

	In 2009, Sinovac (Dalian) was granted a drug manufacturing license for Mumps Vaccine, Live, and in 2012, a GMP certificate was obtained. Varicella Vaccine, Live (hereinafter as to Varicella vaccine), was approved by the National Medical Products Administration (NMPA), on December 18, 2019. The approval was updated in February 25, 2020 and is valid until December 17, 2024. On December 25, 2019, Notification of on-site GMP Inspection Results from the NMPA of Liaoning Province was also obtained. Up to the end of 2019, a total of 7 million doses of Mumps Vaccine, Live produced by Sinovac (Dalian) has been distributed in China. Up to the end of April 2020, Varicella Vaccine, Live produced by Sinovac (Dalian) obtained a batch release certificate and is being distributed in China.
History	The following inspections, related to the Varicella Vaccine, Live, have been carried out at the site: • Manufacturing site inspection Phase 1 for drug registration - NMPA (27-31 July 2019). • GMP Compliance Inspection - Liaoning MPA (27-31 Jul. 2019). • Manufacturing site inspection Phase 2 for drug registration - NMPA (13-16 Aug. 2019). • Annual monitoring inspection - Liaoning MPA (6-9 May 2020). • Stationed inspection (twice per week) - Liaoning MPA (30 Mar-31 Aug. 2020). • National vaccine inspection - NMPA (18-21 Sept. 2020). • GMP compliance follow-up inspection - Liaoning MPA (10-14 May 2021). • National vaccine inspection - NMPA (16-18 Jun. 2021).
Brief report of inspection activities undertaken	
Scope and limitations	
Areas inspected	Buildings including filling and packaging workshop, Varicella bulk workshop, Quality control laboratories, QC and Materials warehouse and Vaccines warehouse.
Restrictions	The AHUs were not physically inspected. The Microbiology laboratory was not inspected.
Out of scope	The inspection was limited to Varicella Vaccine, Live (Freeze-dried Powder Injection) and did not include any other vaccine or other activity.
Vaccines covered by the inspection	Varicella Vaccine, Live (Freeze-dried Powder Injection)

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
	MR	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

Introductory section on the inspection process

This was an onsite inspection which lasted for five days from Monday the 1st until Friday the 5th of November. Prior to the meeting the company was sent a detailed agenda for the inspection and was requested to provide documentation (site master file, product quality reviews (2019 and 2020), list of batches produced since the start of the year and their status, procedures for recall, complaints, change control, deviations, etc.) for desk review. On the last day of the inspection, the inspectors presented a detailed summary of the findings during a close-out meeting with the senior management and other officials of the company.

The inspection covered the following systems:

- Pharmaceutical quality system
- Production system
- Facilities and equipment system
- Laboratory control system
- Materials, packaging and labelling system

The following list of documents were spot checked during the inspection:

Quality Manual of Sinovac (Dalian) Vaccine Technology Co., Ltd.
Site Master File for Varicella Vaccine, Live
Production Process Specification for Varicella Vaccine, Live
Quality Policy of Sinovac (Dalian)
Quality Objective of Sinovac (Dalian)
SMP for Quality Risk
SMP for Production, Quality and Management Organization
SMP for Post Responsibility
SMP for Personnel Training
SMP for Person Entry and Exit Control Area
SMP for Garment
SMP for Key Personnel
SMP for Biosafety
SMP for Personnel Health
SMP for Personnel Sanitation
SMP for Personnel Qualification
SMP for Use in Point of Premises, Facilities, Equipment and Utility
SMP for Pipeline Identification
SMP for Sanitation of Control Area
SMP for Premises and Facilities
SMP for HVAC System
SMP for Pest Control
SMP for Cold room (Refrigerator) and Thermostatic Room
SMP for Cleaning and Disinfection of Production Control Area

SMP for Equipment
SMP for Status and Identification of Equipment
SMP for Spares
SMP for User Requirement Specification
SMP for Process Water System
SMP for Equipment Maintenance
SMP for Equipment Maintenance & Repair
SMP for Change of Project Design of Engineering Construction
SMP for Calibration
SMP for Master List and Material Code
SMP for Materials Purchase and Storage
SMP for Raw Bioactive Materials
SMP for High Toxic Chemicals
SMP for Procurement and Storage of Hazardous Articles
SMP for Print Package Materials
SMP for Storage of Batch Release Final Product
SMP for Unqualified Product
SMP for Unqualified Intermediate Product
SMP for Product Return
SMP for Materials Classification
SMP for Use and Storage of Production Used Reagents
SMP for Handling of Unqualified Materials of Procurement Center
SMP for Dispose Supervision
SMP for Materials Transfer
SMP for Maintenance of Final Product
SMP for Materials, Expiry Date of Reagent and Retest
SMP for Filling of Large Package Materials
SMP for Bovine Serum
SMP for Qualification and Validation
SMP for Production Process Validation
SMP for Validation-Qualification of Equipment and Instrument
SMP for Validation-Validation of Analytical Method
SMP for Validation-Validation of Operating Method
SMP for Bioindicator
SMP for Validation-Validation of Computerized System
SMP for Equipment System Time
SMP for Operation of Qualification and Validation
SMP for Qualification of Premises and Facilities
SMP for Transport Validation and Other Validation
SMP for Assessment of Validation Period
SMP for Validation Archives
SMP for User and Authority of Computerized System
SMP for Validation Documents for External Supplier
SMP for GMP Document
SMP for GMP Document-Document Format

SMP for GMP Record
SMP for Batch Record
SMP for Quality Archives
SMP for Quality Specification
SMP for Data and Program
SMP for Emergency Plan of Computerized System
SMP for Process Specification
Sampling Principle for Environmental Monitoring Assessment
SMP for GMP Document-Document Code
SMP for Supporting Record
SMP for Data Integrity
SMP for Coding of Batch Number
SMP for Production used Virus Seed System
SMP for Production Plan
SMP for On-site Quality Supervision
SMP for Label (Identification)
SMP for Rework
SMP for Production Used Cell
SMP for Production and Test in GMP Workshop
SMP for Suspension and Initiation of Workshop
SMP for Production Order
SMP for Use of Liquid Nitrogen
SMP for Site Clearance
SMP for Production Identification
SMP for Product
SMP for Production Used Filter
SMP for Multi-specifies Production
SMP for Quality Supervision for Site Inspection for COVID-19 Vaccine
SMP for Laboratory
SMP for Sampling
SMP for Sample Retention
SMP for Laboratory Reagent
SMP for Test Used Medium
SMP for Test Used Cell
SMP for Standard Materials
SMP for Titrating Solution
SMP for Material Release
SMP for Release of Production Used Solution
SMP for Final Product Release
SMP for Change Control
SMP for Deviation
SMP for Laboratory OOS
SMP for Corrective Action and Preventive Action
SMP for Material Supplier
SMP for Product Annual Quality Review

SMP for Handling of Complaint
SMP for Adverse Reaction/Event and Investigation on Associated Product
SMP for Batch Release
SMP for Computerized System
SMP for Supplier of Computerized System
SMP for Medium Simulation Test
SMP for Release of Test Used Seeds
SMP for Quality Search
SMP for Technical Transfer of New Product
SMP for Stability Test
SMP for Implementation of Stability Test
SMP for Stability Test Protocol/Report
SMP for Quality Minutes of Sinovac (Dalian)
SMP for Quality Assurance Agreement
SMP for Service Supplier Audit and Approval
SMP for Multi-Collaboration Platform
SMP for Statistics Method Application
SMP for Laboratory OOS
SMP for Quality Search for Sales Client
SMP for Trend Analysis of Sinovac (Dalian)
SMP for Contract Testing
SMP for Product Shipment
SMP for Electronic Supervision
SMP for Recall
SMP for Product Sales
SMP for Storage of Logistics Distributor of Different Places
SMP for Emergency Transport for Final Product
SMP for Car Renting
SMP for Product International Shipment
SMP for Audit on Logistics
SMP for Delivery of Final Product
SMP for Self-Inspection
SMP for Personnel In and Out of Bulk Production Area of Varicella Vaccine, Live
SMP for Articles In and Out of Bulk Production Area of Varicella Vaccine, Live
Instruction for Post Responsibility of Varicella Vaccine Department
SMP for Varicella Vaccine Production Used Solution
SMP for Articles In and Out of Filling & Packaging Area for Varicella Vaccine, Live
SMP for Sterile Operation of Varicella Vaccine, Live
SMP for Center Control of Production Workshop
SMP for Personnel Control of Clean Area of Varicella Vaccine, Live
SMP for Preparation of Articles for Bulk of Varicella Vaccine, Live
SMP for Material Flow of Bulk Production Workshop of Varicella Vaccine, Live
SMP for Storage and Use of Harvest and Bulk of Varicella Vaccine, Live
SMP for Personnel Entry and Exit in the Filling Area of Varicella Vaccine, Live
SMP for Personnel Entry and Exit in the Packaging Area

SMP for Personnel and Materials Entry and Exit of Clean Area of Laboratory
SMP for Laboratory Sanitation
SMP for Cleaning and Disinfection of Garment of QC Department
SMP for Laboratory Safety Protection and Laboratory Accidents
SMP for Laboratory Operation
SMP for Analytical Electronic Data
SMP for Sample Testing
SMP for Numeric Rounding and Calculation
SMP for Handling with Laboratory Disposals
SMP for QC Stamp
SMP for Static Environmental Monitoring of Clean Area
SMP for Animal Laboratory Environment
SMP for QC Analytical Balance
SMP for QC Equipment
SMP for QC HVAC System and Clean Equipment
SMP for Aseptic Operating Standard of QC Department
Post Instruction of QC Department
SMP for Maintenance of QC Equipment
SMP for Analytical Method Transfer of QC Department
SMP for Implementation for Qualification/Validation of QC Analytical Method
SMP for QC Personnel Qualification
SMP for Comparison for QC Qualification Training
SMP for Materials Entry and Exit in Positive Pressure QC Laboratory
SMP for Materials Entry and Exit in Negative Pressure QC Laboratory
SMP for Sampling Room Where Materials In and Out
SMP for Personnel Entry and Exit in Positive Pressure QC Laboratory
SMP for Personnel Entry and Exit in Negative Pressure QC Laboratory
SMP for Personnel Entry and Exit in Material Sampling Room
SMP for Cleaning of Analytical Utensil of QC Department
SMP for Materials Preparation of QC Department
SMP for Evaluation for Key Consumable Items Supplier of QC Department
SMP for Preparation, Testing and Calibration of Titrating Reference of QC Department
SMP for Samples of QC Department
SMP for Test Report of QC Department
SMP for Test Record of QC Department
SMP for Samples of COVID-19 Vaccine
SMP for Utility System
SMP for Layout of GMP Workshop
Post Instruction of Engineering Equipment Department
SMP for Workshop, Routine Inspection, Cleaning and Maintenance
SMP for Wastewater Treatment System
SMP for Refrigerating System of Cold room
SMP for Outsourcing Construction

The following list of buildings, manufacturing and testing rooms were visited during the inspection:

Varicella Bulk Production Workshop
Formulation, Filling & Packaging Workshop
QC lab (Physical-chemical lab)
QC lab (Bio-negative lab)
QC lab (Bio-positive lab)
QC lab (Animal lab)
Materials Warehouse and sampling room
Cold room for Finished Product

1 Pharmaceutical quality system

The company has established its quality management system. The heads of departments including production, quality assurance, quality control, procurement, research and development, sales and clinical research, were all members of quality management system. Quality control activities were independent of the production unit. Managerial responsibilities were specified in written job descriptions.

In general terms, the production and control operations were specified in written form (SOPs) and GMP requirements were generally followed. Product processes were monitored, and the results considered in batch release. Regular reviews of the quality of the Varicella Vaccine, Live (Freeze-dried Powder for Injection) were being conducted according to documented schedules and procedures.

Management review:

Regular quality meetings were held in accordance with the Management Procedure for Production and Quality Regular Meetings. The meetings were organized to ensure the periodic exchange, communication and transfer of quality information among senior managers, head of quality management and all the GMP related departments. The quality meetings were divided into monthly, quarterly and special meetings. The agenda of regular meetings included the following: current periodic changes, deviations, OOS, complaints, validation, documents, suppliers and materials. Attendees included the Head of quality management, Head of production management, Managers of related departments of the production quality system, recorders, etc. Meeting minutes were taken by the meeting recorder of the Quality Assurance Department and the Document Management Group of this department was responsible for archiving.

Product quality review (PQR):

A procedure for annual product quality review, Management Procedure for Product Annual Quality Review was in place. The quality head was responsible for supervising the implementation of the annual product quality review and the Quality Assurance (QA) Department was responsible for initiating the review work according to the workflow. All the related departments had to complete the work according to the undertaken tasks and submit it to the QA department. The quality supervisor of each product of the Quality Assurance Department or designated personnel summarized the information and data, developed the annual quality review analysis report of the product and submitted it to the quality head for review and approval.

The PQR of Varicella Vaccine was reviewed. The product dossier was under assessment at the time of inspection. No Commercial batches have been supplied to foreign markets, but the company has started to supply the domestic market since.

Quality risk management:
Quality risk management was controlled according to the Management Procedure for Quality Risks and the SMP for Common Risk Management Tool Applications. The scope of quality risk management covered all the life cycle of the vaccine including the organization, personnel, premises, facilities, equipment, materials, product, qualification and validation, document management, production management, quality control, quality assurance, product transportation, recall and self-inspection, etc. The risks that could affect the vaccine quality were evaluated using common risk assessment tools, such as FMECA, FMEA and HACCP. The risk assessment report for Sterile Filter of Varicella Vaccine, Live, was reviewed.

Change control:
Change control procedures were described in SMP for Change Control. Change controls were spot-checked.

Deviation management:
Deviations were recorded and investigated as per the procedure, SMP for Deviations. Deviation logs were maintained. Some deviation reports were spot-checked.

CAPA management:
The SMP for Corrective Action and Preventive Action was discussed. The CAPAs can results from self-inspections, OOS, OOT, deviations, product defects, complaints, external inspections, etc. A CAPA register was kept, which was spot-checked. In general, the CAPAs had been implemented in accordance with the written procedure and according to the planned timelines.

Complaints:
Complaints were managed according to the SMP for Handling of Complaints. One complaint listed in the above APQR regarding diluent quantities in ampoules was checked and discussed.

Product recalls:
Product recalls were managed according to the SMP for recalls. The company stated that there were no product recalls in the past three years.

Self-inspection:
Self-inspections were divided into regular self-inspection related to drug production and quality management completed within a year, and targeted self-inspection conducted under the following circumstances:

- When a complaint is received, if necessary;
- Major deviations of the Quality Management System resulting from accidents or events related to quality management;
- Major changes in the regulatory environment;
- Major changes to production and quality conditions;
- Before Chinese and foreign GMP.

Quality audits and suppliers' audits and approval:

Material supplier qualification was managed according to the SMP for material suppliers. Suppliers of raw materials were managed according to the Management procedure for audit of material suppliers. The audit of material suppliers was divided into two types: a qualification audit and an on-site audit. If the materials were supplied directly by manufacturers, only the manufacturers will be audited; if supplied by distributors, both the manufacturer and distributor will be audited.

The materials grading is carried out according to the requirements in Requirements for Quality Control of Raw Materials and Excipients of Biological Products in the Chinese Pharmacopoeia. In general, materials were graded according to risks into Grades 1 to 4 for raw materials and excipients, Grades 1 to 2 for packaging materials and Grades 1 to 3 for auxiliary materials. The audit requirements for suppliers differ in stringency according to the material grades.

A qualification audit entailed establishing that the supplier was a legal enterprise, has the required documentation (business license, etc.), which are valid (or current) and met specific requirements according to the type or grade of material. Onsite audits occurred under specific conditions. They were based, firstly, on an annual audit plan drawn up by the QA department at the beginning of every year according to the supply quantity of the previous year, the quality of the supplied products, as well as their use in the following year in combination with risk assessment results. Secondly, if there was a deviation due to a noncompliant test result for the material or an OOS during production of the vaccine. Thirdly, if there was a change in the production conditions, process, specifications and analytical procedures that may affect the quality of the product. Finally, an onsite audit may be required for new suppliers. It must be noted that under all circumstances QA decides whether an onsite audit was necessary.

Requirements for onsite audits for suppliers of different Grades of materials was reviewed.

The audit report of the supplier of the diluent, WFI, was reviewed.

Contract production, analysis and other activities and quality agreement:

The company does not engage in contract manufacturing, nor does it contract out any part of the manufacturing process of varicella vaccine. Suppliers of contract services were managed according to SMP for Service Supplier Audit and Approval. Contract services included contract validations (e.g., sterilizing filters and final bulk bags), contract calibrations (laser airborne particle counters, spectrophotometers, etc), contract disposal of wastes and contract pest management. Contract testing was restricted to tests that could not be performed in-house, such as identification tests on cell banks, seed lots, full testing of drinking water, and tests on components of the primary container-closure system (e.g., hydrolytic resistance of glass, penetration force for rubber stoppers, opening force of aluminium-plastic caps, etc).

Personnel:

The manufacturer appeared to have an adequate number of personnel to carry out the tasks in production, quality assurance, quality control, and engineering services. Specific duties were recorded in written job descriptions for responsible staff. Personnel met during the inspection were aware of the principles of GMP and it was obvious that they had all received initial and continuing training, including hygiene instructions, relevant to their needs.

An organizational chart showing the relationships between different areas, including quality assurance, production and quality control, was provided to the inspectors during the company presentation on the first day of the inspection. It showed that the heads of production and quality control were independent of each other.

Training:

Training management procedures were available for review. The documents described the training related to GMP as well as qualification training for QC personnel. Training management personnel were in place and their responsibilities were detailed. Training methods and assessments were described and procedures to determine training requirements were provided. The following procedures were spot-checked:

- SMP for Personnel Training;
- SMP for QC Personnel Qualification;
- SMP for Comparison for QC Qualification Training;

Overall, the training procedures were found to be acceptable.

Personal hygiene:

Procedures were in place for managing the health of personnel engaged in production. In particular, they specified requirements for immune status for production personnel as well as outside contract service personnel entering the manufacturing areas. Appropriate vaccination was mandatory for production staff and included vaccination against mumps and varicella. External personnel who enter controlled areas must first complete an application form, which must be reviewed and approved by the head of the relevant department before they will be granted permission for entry. Confirmation that external personnel had received the required vaccinations must also be confirmed first, as unvaccinated personnel will not be allowed to enter controlled areas. The following procedures were reviewed:

- SMP for Personnel Health;
- Management Procedure for Personnel Hygiene.

Overall, the procedures on health management were found satisfactory.

Documentation:

A procedure for managing company documents, Management Procedure for GMP Documents, was in place. The document system included: Regular updates, destruction of non-current valid documents and preparation of new documents, change control of the documents and archiving and retention of the documents. The related documents of the site were usually kept in a filing cabinet of the corresponding department at the site. The current GMP related documents and the original old version documents were preserved by the Quality Assurance Department for the long-term. No document was kept offsite.

However, the good documentation practices at the site were found deficient from several standpoints as outlined under Part 3 “List of deficiencies” of this report.**Batch Release Process:**

Batch release was handled in accordance with the Management Procedure for Release of the Final Products. The qualified person (QP) was responsible for batch release. Before batch release of the vaccine, the heads of quality control and production, as well as the qualified person, would review the production and testing processes and batch records to decide whether a batch release application should be made to the National Control Laboratory (NCL). Once the application had been submitted and a Batch Release Certificate for Biological Products obtained from the NCL, the batch would be officially released by the QP. Thus far, several batches have been released by the company to domestic market and none have been rejected.

Lot Summary Product review:

The procedure for LSP review with relevant information to be provided to NCL was implemented as agreed between the NCL and the company. The SOP for National Batch release managing procedure, was available.

2 Production system

Resources were available, including qualified and trained personnel, premises, equipment and services, materials, containers and labels, procedures and instructions, laboratories and equipment for in-process and other controls.

Procedures for qualification and validation of equipment, manufacturing processes and quality control testing methods were in place.

In general production operations followed defined procedures and master formulas. Deviations from procedures were recorded and investigated. Qualifications and validations were performed. Systems were in place for handling complaints and recalling batches of product from sale or supply.

The following systems and areas and associated document were spot checked during this inspection:

- Seed lots;
- Cell banks;
- Manufacture of the bulk and final product;
- Formulation;
- Filling, sealing & capping;
- Visual inspection;
- Labeling & Packaging;
- Batch manufacturing record review (BMR).

3. Facilities and equipment system

Access to production premises was restricted to authorized personnel. Overall, dedicated facilities were in place for manufacturing the drug substance and final product. Seed lots were stored in qualified equipment with adequate temperature monitoring and inventory system. 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.

The following list of buildings, manufacturing and testing rooms were visited during the inspection:

- Varicella Bulk Production Workshop;
- Formulation, Filling & Packaging Workshop;
- QC lab (Physical-chemical lab);
- QC lab (Bio-negative lab);
- QC lab (Bio-positive lab);
- QC lab (Animal lab);
- Materials, Warehouse and sampling room;
- Cold room for Finished Product.

Waste management:

The SOP, Management procedure for materials in and out of the production area of Varicella Vaccine Bulk was spot-checked. The SOP also applied to the transfer of waste.

The SOP, Management procedure for the hazardous waste was spot checked. The EHS department, after receiving the waste, sends it to a 3rd party for destruction. Waste was sent or collected at least once per month. The frequency was determined by the quantity of waste – not the type. The waste was stored in a securely locked facility (no alarm). Two service providers were used – one for chemical waste and the other for bio-hazardous waste. Flammable waste (alcohol) was not separated from other waste.

Warehouses:

Starting materials and packaging materials for vaccine products were stored in different warehouses located on the site. Finished vaccine products were stored at a facility about 2 - 3 km away from the manufacturing site and rented from an external organization. The warehouses were managed by the SAP system and a manual system. Incoming materials and finished products were quarantined after receipt until released for use or distribution. Materials and products were stored under specified conditions. Areas for rejected, returned, and recalled products were available. Temperature monitoring and alarm systems for the different warehouses were checked.

Water system production description:

The water system was located in the Bulk Production Workshop for varicella vaccine. The source water was municipal city water, which had to pass through the multi-media filter treatment, softening apparatus treatment and filtration process by the active carbon filter and security filter. After this pre-treatment, the water was stored in an intermediate tank as source water for PW. PW was produced via double ROs and served as source water for WFI, as well as for pure steam. Details of the water system production, capacity and sanitization were provided in the site master file. The following documents were reviewed during the inspection.

- Annual water system review, as well as chemical and microbiological monitoring results of PW, WFI and steam;
- P & ID of Purified Water Preparation System;
- Retrospective Qualification for Process Water System of Varicella Vaccine Workshop;
- SMP for process water system management..

HVAC systems:

A procedure, SMP for HVAC system for the operation of the HVAC system was in place. The company's HVAC system consisted of primary, medium, sub-high and high efficiency air filters and an air conditioning automatic control system. The air in the clean room was returned to the air conditioning air supply unit through the air return duct or was discharged outdoors after air treatment based on different production requirements. The fresh air ratio of overall air supply in the workshop was designed to be in specific range. When the fresh air or returned air passed through the air conditioning unit, heating, refrigeration and humidification treatment of the air using the hot water coil pipe, cooling water coil pipe and humidifier, etc., were carried out to ensure that the temperature of the clean room was controlled within specific ranges. The overall humidity of the Varicella Vaccine, Live workshop was controlled within specific range. The overall design requirements of the temperature in workshops complied with the specifications of General Rule, Filling, Packaging and Storage Management of Biological Products of the Chinese Pharmacopeia (Volume III, 2020 version).

The formaldehyde fumigation method was adopted for disinfection of the air conditioning system. It was performed according to the cleaning and disinfection plan.

The qualification of the HVAC system was conducted on a yearly basis. The last qualification report was spot-checked.

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 general policy and strategy for the validation and qualification was defined in the company's VMP.

Equipment and process validation identified the qualification and validation activities that were required. Revalidation was required when changes were made to the process or equipment.

Equipment were qualified according to the in-house procedure. Critical equipment was re-qualified every 12 months. The most recent annual requalification report of the autoclave used for parts sterilization and of the lyophilizer for the varicella vaccine product, were reviewed.
The following validation protocols and reports were reviewed:

- Autoclave qualification protocol and report;
- SOP for sterilization of autoclave;
- Lyophilizer performance qualification procedure;
- Lyophilized performance qualification protocol and report;
- Aseptic Process Validation for Varicella Vaccine;
- Assessment Report of Production Critical Process Parameters of Final Product of Varicella Vaccine, Live;
- SMP for Filter Used for Production;
- Compatibility Study Report, Vaccine Diluent of Varicella Vaccine, Live and Filter Element;
- etc.

Cleaning:
The SOP and validation report for Cleaning of the clarification filter for Varicella Bulk were reviewed.

4 Laboratory control system

The QC function was independent of other departments. The QC laboratories were separated from production areas. It was housed across three floors. The microbiology laboratory was segregated from the wet chemistry laboratory.

The procedure, Management procedure for maintenance of equipment in QC laboratory was available. The procedure included cleaning and protective maintenance. Cleaning maintenance was conducted for all equipment and entailed the cleaning of equipment surfaces and label checking.

Visit of Quality control laboratories:
The biological and physico-chemical laboratories were briefly visited. Laboratories were cleaned and well-maintained. Logbooks for refrigerators, incubators and other equipment were available and those spot-checked, were up to date. The sample receipt area was well-organized. Data were entered manually into sample receipt forms. All samples were stored securely in an access-controlled locked refrigerator.

The physico-chemical laboratory was clean and well-organized. Solutions and reagents were adequately labeled with manufacturing/prepared date, expiry date, name, etc.

The testing procedures and operations relevant to the varicella vaccine, such as the KF test for moisture content, vial leak test, etc., were spot-checked.

Reference standards:

The reference standard was developed from a finished product commercial. From the batch, Several vials were prepared to serve as internal RS. The samples were not subjected to additional purification but were characterized in greater detail through expanded testing compared to the release tests of the finished product. One of the additional assays included the test for uniformity of virus titer.

The Management procedure for preparation, testing and calibration of the reference standard for virus titration was available. The reference standard was calibrated against the National Standard. The national reference standard was obtained from the NCL.

Virus titer assay:

The following validation reports (initial and supplementary) on the virus titration assay were presented for review:

- The analytical method validation of virus titration of varicella vaccine;
- The supplemental validation for analytical method for virus titration of varicella vaccine.

Stability:

- Bulk: the company had generated long term data for 12 months on three batches.

- Final product: Long term data of 30 months (at 0, 1 M, 3 M, 6 M, 9 M, 12 M, 18 M, 24 M & 30 M) on three batches at 2 – 8 °C was generated to support the allocated shelf life. In addition, the company had performed stability under accelerated (at 25 °C for 0, 7 d, 14 d, 21 d, 28 d, 3-month, 6 month) and stress conditions (37°C: 0, 7 d, 14 d, 21 d, 28 d).

- Freeze & Thaw study:

The study report on the stability of the vaccine bulk during freezing and thawing, The study for storage conditions for Varicella Bulk, was presented during the inspection. The study was performed on samples of three bulk batches.

Environmental monitoring results:

The following two procedures dealing with environmental monitoring were reviewed:

- Sampling Principle for Environmental Monitoring Assessment;
- SMP for Static Environmental Monitoring of Clean Area.

5 Materials management

Several material handling procedures were spot-checked, which included but are not limited to, the following: SMP for Materials Purchase and Storage, SMP for Materials Classification, SMP for Handling of Unqualified Materials of Procurement Center, SMP for Standard Materials, SMP for Packing Materials of Production Workshop, SMP for Materials Preparation of QC Department.

Sampling:

Materials were sampled by QC following documented sampling procedures before release. The sampling procedure applied to release of final product was the following, Sampling procedure SOP for finished product of Varicella vaccine.

The number of samples of finished product collected for release testing was based on the quantity required to perform all tests.

6 International shipping

The product was still under assessment by the WHO PQ group at the time of the inspection. Thus far, batches produced have only been for the domestic market. Since no exports have been done, information on international shipping was not available.

Part 3	Inspection outcome

Based on the areas inspected, the people met, and the documents reviewed, and considering the findings of the inspection, including the observations listed in the Inspection Report, **Sinovac (Dalian) Vaccine Technology Co., Ltd.**, located at **No. 36, 2nd Life Road, DD Port, Economic and Technical Development Zone, Dalian, 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 other 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 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**
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   http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_986/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. 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**
   http://whqlibdoc.who.int/trs/WHO_TRS_943_eng.pdf?ua=1

6. 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. 957, Annex 1
   http://www.who.int/medicines/publications/44threport/en/

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   Short name: WHO TRS No. 957, Annex 3
   http://www.who.int/medicines/publications/44threport/en/

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Short name: WHO TRS No. 961, Annex 6
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9. 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

10. 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**
http://whqlibdoc.who.int/trs/WHO_TRS_961_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**
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http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_981/en/

15. WHO General guidance on hold-time studies WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 4. **Short name: WHO TRS No. 992, Annex 4**
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

16. WHO Technical supplements to Model Guidance for storage and transport of time – and temperature – sensitive pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 5. **Short name: WHO TRS No. 992, Annex 5**
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

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Short name: WHO Multisource guidance or **WHO TRS No. 996, Annex 10**
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Short name: WHO TRS No. 1010, Annex 10
http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex10.pdf

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