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Prequalification Unit Inspection Services
WHO PUBLIC INSPECTION REPORT
(WHOPIR)
Finished Product Manufacturer
(VACCINES)

Part 1	**General information**
Manufacturers details	
Name of manufacturer	**The Federal State Unitary Enterprise, The Saint Petersburg, Scientific Research Institute of Vaccines and Serums and the Enterprise for the Production of Bacterial Preparations of Federal Medical and Biological Agency (FSUE SPbSRIVS FMBA of Russia)**
Corporate and inspected manufacturing site address	Ulitsa Svobody 52, Krasnoe Selo, 198320, Saint Petersburg, Russian Federation
Inspection details	
Dates of inspection	22 to 26 May 2023
Type of inspection	Initial WHO inspection for: - Seasonal Trivalent Influenza Vaccine (split virion, inactivated) - FLU-M® (Seasonal Trivalent Influenza Vaccine, split virion, inactivated)
Introduction	
Brief description of the manufacturing activities	FSUE SPbSRIVS FMBA of Russia, located in Saint Petersburg, is responsible for the manufacturing of Influenza monovalent bulks and formulation of the vaccine. The formulated bulk is sent to Mechnikov Institute in Nicaragua for filling, visual inspection, labelling and packaging. The company informed that the capacity of manufacturing is 35 million doses of influenza vaccines per year and more than 120 million doses were produced since 2015.
General information about the company and site	FSUE SPbSRIVS FMBA of Russia is a government-owned pharmaceutical enterprise engaged in developing and manufacturing medical products and medical devices for domestic and foreign markets. The site located in Saint Petersburg occupies an area of 15 hectares. The immunobiological production complex "Influenza Medications" produces influenza products to obtain an intermediate product (formulated bulk). The whole process of influenza products production and control takes place in: - Manufacturing building No. 2 - Laboratory Building - Warehouse - Incubator for embryonated chicken eggs
History	The site has been regularly inspected by the Russian authorities (Ministry of Industry and Trade of The Russian Federation – MINPROMTORG and Federal Service for Surveillance in Healthcare – Roszdravnadzor, as well as by CECMED (Cuba) and Ministry of Health of the Islamic Republic of Iran. This was the first WHO Inspection of the site.

Brief report of inspection activities undertaken – Scope and limitations	
Areas inspected	- Manufacturing building No. 2 (3rd Floor) - Warehouse - Laboratory building - Utilities
Restrictions	None
Out of scope	The inspection was limited to the manufacturing of Trivalent Inactivated Split Influenza Vaccine and FLU-M® [Influenza vaccine (split virion, inactivated)] up to the formulated trivalent bulk.
WHO products covered by the inspection	- Seasonal Trivalent Influenza Vaccine (split virion, inactivated) - FLU-M® (Seasonal Trivalent Influenza Vaccine, split virion, inactivated)
Abbreviations	**Meaning**
AHU	Air handling unit
ALCOA	Attributable, legible, contemporaneous, original and accurate
API	Active pharmaceutical ingredient
APR	Annual product review
APS	Aseptic process simulation
BMR	Batch manufacturing record
BPR	Batch production record
CC	Change control
CCS	Contamination Control Strategy
CE	Chicken Embryo
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
FPP	Finished pharmaceutical product
FTA	Fault tree analysis
GMP	Good manufacturing practices
GPT	Growth promotion test
HEPA	High efficiency particulate air
HPLC	High performance liquid chromatography (or high performance liquid chromatography equipment)
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
MSL	Master Seed Lot
NC	Non conformity
NRA	National regulatory agency
OQ	Operational qualification
PHA	Process hazard analysis
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
SPF	Specific Pathogen Free
URS	User requirements specifications
UV	Ultraviolet-visible spectrophotometer
WFI	Water for injection
WSL	Working Seed Lot

Part 2	**Summary of the findings and comments**

1. Pharmaceutical quality system

The Pharmaceutical Quality System (PQS) was defined and documented in the Quality Manual, which described the quality management system, including management responsibilities.

Organization, organogram, independence of production from quality control:

The organization chart was presented and the independence of production from the quality unit was demonstrated.

Management review (MR):

A review of the pharmaceutical quality system was performed once every year. The most recent meeting minutes were presented. A copy of the presentation was part of the meeting minutes. The review included several areas such as pharmaceutical development, transfer, material and technical supply, production, storage, shipment and transportation, stability study, complaints, recalls, resources,

and several other areas. The head of QA and process owner organized the meeting, which was attended by the General Director and other department heads. The main purpose of the meeting was to set quality goals for next year. The action items were highlighted with the respective timelines, and it was noted that some actions were already planned to be put into effect.

Product quality review (PQR):

Annual quality reviews were prepared in accordance with the respective SOP. The content of the review complied with the WHO GMP guideline. The objective of the review was to confirm the consistency of the process in place, compliance with external and internal regulatory documentation, to identify trends and to determine whether it is possible to improve products and processes. The reports were prepared annually. A trend analysis SOP was in place. The last available PQR for the Influenza vaccine (split virion, inactivated) covering the period of January to December 2022 was spot-checked. The APQR concluded that all batches of the product met the requirements of the regulatory documentation. There were no batches that did not meet the specification requirements.

Quality risk management:

The quality risk management SOP was discussed. The procedure stated the use of FMEA, FMECA, FTA, ETA, HACCP, and HAZOP. The list of risks extracted from the risk register was presented, and some risk analysis protocols were reviewed.

A contamination control strategy (CCS) policy was in place. The CCS covered personnel, premises, equipment, utilities, environmental monitoring, cleaning, disinfection, supplier assessment, validation, preventive maintenance, and other areas. Overall responsibility for implementing CCS rested with the QA department.

The business continuity plan was discussed. The policy outlined potential risks and threats, along with a set of actions to mitigate them.

Deviation management:

The deviation management procedure was discussed. The deviation was defined as a failure to comply with or the absence of requirements of approved procedures. The deviations were classified into critical (impact on the quality of products), significant (impact on compliance with GMP), and other. An investigation was performed using tools such as 6M, 5-Why, fault tree analysis, etc. Additionally, an impact assessment was conducted. A logbook was maintained, and some deviation records were reviewed. A trend analysis was available as part of the PQS review.

Change control (CC):

The change control SOP was available and reviewed. An effectiveness check of the change was conducted. Some change control records were spot-checked.

Complaints:

The complaint registration and investigation procedure was discussed. Complaints were recorded in a logbook, which may be received from the distributor, regulator, or person (call or visit in person). The company's webpage has a section on pharmacovigilance as well. The complaints were classified into critical (serious health risk), significant/major (may pose potential harm, packaging damage), and non-significant/minor. The QA was overall responsible for handling complaints together with the Pharmacovigilance department. The complaint was investigated using a template and several aspects were considered. Based on the initial assessment of the complaint, adequate actions are initiated. The

investigation was performed using various tools such as 6M and 5-Why. The complaint logbook was spot-checked and some records selected for review.

Product recalls:

The product recall of the finished product from the market procedure SOP was discussed. It was confirmed that since 2014, there had not been any recalls from the market. A mock recall procedure was available, and the last available mock recall record was presented. The Russian Institute signed a technical agreement with the Mechnikov Institute (Nicaragua) for mock recall arrangements.

Training:

Training of the personnel was discussed. The annual training program was in place which included external training. The training was part of the individual development plan and the institute attended world skills training, etc.

Batch Release Process:

The procedure to confirm the compliance of the bulk batch and approval for further use in the production was discussed. The head of the QA provided an overview of the release procedure. The release of a batch, along with the Certificate of Analysis, was presented. The procedure included a review of various documents, including batch manufacturing records, packaging records, changes, deviations, environmental monitoring, personnel records, intermediate analytical records of raw materials, auxiliary materials, process aids, and other relevant documents. A checklist was used as a batch compliance document for verifying the completeness of documents. It was noted that the batch was released in accordance with the quality agreement between the Russian institute and Nicaragua.

Lot Summary Product review:

Lot summary protocol was firstly prepared by SPbSRIVS for bulk production, then by Institute Mechnikov, for fill and finish and submitted to CECMED / Cuba as checked during the inspection of the respective institute.

2. Production system*Seed lots*

Master seed lot

A technical instruction was in place for the generation of the Master Seed Lot (MSL). The Reference Seed Virus) of the 3 strains (A/H1N1, A/H3N2 and B) were obtained from WHO Collaborating Centers for Reference and Research on influenza. A SOP was in place for selecting the optimal influenza virus strain/reassortant for influenza vaccine production. Specific Pathogen Free (SPF) embryonated eggs were used for the generation of the MSL. The cryovials containing the MSL were frozen and maintained at temperatures below -60 °C. The produced MSL was tested in accordance with the WHO recommendations.

The batch record of the preparation of an MSL was spot-checked.

Working seed lots

The procedure for the generation of the Working Seed Lot (WSL) was presented. The WSL production was also conducted with SPF eggs. The virus-containing allantoic fluid was collected, mixed, filled into sterile cryovials, and stored at less than -60 °C. The produced WSL was tested in accordance with the WHO recommendations.

The batch record of the preparation of a WSL was spot-checked.

Drug Substance

Each strain of virus was grown in the allantoic cavity of the embryonated hen's eggs derived from healthy flocks. Ovoscopy and quality control of the chicken embryos (CEs) were carried out.

Preparation of Working Virus Dilution (WVD) was performed using the WSL. The WVD was inoculated in the eggs by an automated inoculator. After incubation at a controlled temperature, the allantoic fluid was harvested.

The monovalent virus pools were inactivated with β-propiolactone. Upon completion of mixing, the monovalent virus pools were transferred to a second vessel and kept for at least the required time validated for each specific strain at the specified temperature. After the inactivation was completed, the fluid was transferred to the inactive area by a fixed pipeline, sterilized by SIP.

The inactivated virus pool was purified by several steps of microfiltration, ultrafiltration, sucrose gradient, and centrifugation. The inactivated, purified and concentrated virus pool was split with detergent. Then the inactivated and split virus pools were purified by microfiltration, ultrafiltration, centrifugation and chromatographic steps.

Sterilizing filtration of monovalent bulk was conducted and the DS was collected into single-use bags from which samples were taken to quality control tests according to DS specification.

The inactivated and split monovalent virus pool can be stored at a temperature of (2 – 8) °C for a maximum of 1 year.

Formulation:

Released monovalent bulks from three different influenza virus strains: A (H1N1), A (H3N2) and B types were mixed in a reactor with the excipients and the preservative. Samples were collected for the required quality control (QC) tests before the product was sterilized by filtration. Then, sterilizing filtration is carried out in a sterile single-use bag. Samples were taken to quality control of the final trivalent bulk. The formulated bulk was stored 2-8 °C and transferred to the filling site (Mechnikov, Nicaragua) under a cold chain environment.

Batch numbering:

A procedure for batch numbering was in place and was reviewed during the inspection.

Process Validation

The validation policy and process validation SOP were reviewed. At least three batches should be used for process validation. An SOP was in place for updating the strain, which should be managed in accordance with the change control SOP. Inactivation and splitting validation were performed for each new strain.

Protocols and Reports for Inactivation and Splitting Validation were spot-checked.

Batch manufacturing record review (BMR):

Some selected batch records were reviewed during the inspection.

3. Facilities and equipment system:

The production of influenza vaccine drug substance (DS) and trivalent bulk was performed on the Manufacturing Building No. 2. The area was called Immunobiological Production Complex "Influenza Medications" (IBPC IM). Separate entrances were in place for active and inactive areas. The final bulk was stored in a cold chamber (2 - 8 °C) located in the warehouse building. Quality control facilities were located in the Laboratory building.

Waste management:

The processed CEs and eggshells were decontaminated as well as all the materials used in the active area are either sterilized in an autoclave or chemically disinfected.

Water systems:

Details of the water system were provided in the Site Master File and spot-checked on-site.

The sampling procedure for purified water (PW) and water for injection/WFI was discussed. The water systems have been qualified.

HVAC

Separate AHUs were in place for air supply of the active and inactive areas. No recirculation was performed for the infectious zone. After inactivation, the purification steps and splitting were conducted in the inactive area.

Differential pressures were monitored by displays in the production area and by the BMS.

HVAC qualification records were spot-checked.

Qualification and validation:

The company qualification and validation policy and programme were defined and documented in the Validation Master Plan.

Line clearance

The SOP for preparation of the workshop area to produce the influenza vaccine was discussed. In case of change of a strain, a full cleaning was performed. If the same strain is continued to be used, daily cleaning was performed, besides the full weekly cleaning.

Disinfection:

The SOP on the usage of disinfectant procedure was discussed. Disinfectants were rotated at least once a week for Grades A, B, C, and D, and at least once a month for non-classified areas.

Cleaning validation:

The cleaning validation procedure was discussed. The procedure delineated the scope, criteria, responsibility, and procedure for cleaning validation. Three batches were required to demonstrate cleaning effectiveness.

Computerized systems validation:

A list of computerized systems was presented.

The SOP on the usage of computerized systems was discussed to understand how computer systems were handled and controlled.

Storage equipment

Qualification of the cold chamber used for storage of monovalent bulks was spot-checked.

4. Laboratory control system

Quality control laboratories were divided into Physicochemical and Immuno-microbiological Sectors. Adequate storage areas were provided for the storage of samples and laboratory reagents. The temperature and humidity conditions were controlled and monitored. The facilities provided for carrying out the analysis were generally adequate.

At the microbiology laboratory, the growth promotion test, the validation protocol for the 4h exposition time of settle plates and the SOP for microorganism identification were spot-checked.

Out-of-specification (OOS) management:

The procedures for handling OOS were discussed. The procedure was supported with a flow diagram and an investigation was performed in two phases/levels. The OOS logbook was presented.

Environmental monitoring results:

The SOP for Environmental Monitoring was reviewed. Sampling locations were based on a risk analysis. Trends were evaluated periodically. A trend analysis report was spot-checked.

5. Materials management:

In general, adequate space and conditions were provided for storing raw materials, in-process materials, and finished products. Monovalent and formulated bulks were kept in cold rooms (2-8°C) and monitored continuously for temperature by the BMS system.

Starting materials were purchased from approved suppliers. The supplier qualification and approval were managed according to a SOP. Approval of new suppliers was managed by change control. Audits were performed according to a risk assessment considering the type of raw material, requirement of transportation, contact with the product, experience with the supplier and use of the product.

6. Packaging and labeling system:

Bulk monovalent bulks (DS) and trivalent bulk vaccine (bulk DP) were filled in single-use bags. The vaccine formulated in bulk was shipped from St Petersburg to Managua. The transportation was contracted with a third-party company. The transport validation report was reviewed.

Part 3	**Conclusion – 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, the **FSUE SPbSRIVS FMBA of Russia**, located at **Ulitsa Svobody 52, Krasnoe Selo, 198320, Saint Petersburg, Russian Federation** was considered to be operating at an acceptable level of compliance with WHO GMP 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.

Part 4	List of WHO 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***

2. WHO good manufacturing practices for biological products. WHO Expert Committee on Biological Standardization. Sixty-sixth Report Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 999), Annex 2. ***Short name: WHO TRS No. 999, Annex 2***

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***

4. Good manufacturing practices: guidelines on validation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-third report. Geneva, World Health Organization, 2019 (WHO Technical Report Series, No. 1019), Annex 3. ***Short name: WHO TRS No. 1019, Annex 3***

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 3***

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***

7. 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 3. ***Short name: WHO TRS No. 957, Annex 3***

8. WHO good manufacturing practices for sterile pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-sixth Report Geneva, World Health Organization, 2022 (WHO Technical Report Series, No. 1044), Annex 2. ***Short name: WHO TRS No. 1044, Annex 2***

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***

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***

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***

12. 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***

13. 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***

14. 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***

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***

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***

17. WHO general guidance on variations to multisource pharmaceutical products. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fiftieth Report* Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 10. ***Short name: WHO Multisource guidance*** or ***WHO TRS No. 996, Annex 10***

18. Stability testing of active pharmaceutical ingredients and finished pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-second Report Geneva, World Health Organization, 2018 (WHO Technical Report Series, No. 1010), Annex 10. ***Short name: WHO TRS No. 1010, Annex 10***

19. Production of water for injection by means other than distillation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fourth Report. Geneva, World Health Organization, 2020 (WHO Technical Report Series, No. 1025), Annex 3. ***Short name: WHO TRS No. 1025, Annex 3***

20. Good chromatography practice. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fourth Report. Geneva, World Health Organization, 2020 (WHO Technical Report Series, No. 1025), Annex 4. ***Short name: WHO TRS No. 1025, Annex 4***

21. Points to consider for manufacturers and inspectors: environmental aspects of manufacturing for the prevention of antimicrobial resistance. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fourth Report. Geneva, World Health Organization, 2020 (WHO Technical Report Series, No. 1025), Annex 6. ***Short name: WHO TRS No. 1025, Annex 6***

22. 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***

23. New and replacement WHO international reference standards for biological products. WHO Expert Committee on Biological Standardization. Seventy-first Report. Geneva, World Health Organization, 2021 (WHO Technical Report Series, No. 1028), Annex 4. ***Short name: WHO TRS 1028, Annex 4***

24. Points to consider when including Health-Based Exposure Limits (HBELs) in cleaning validation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fifth Report. Geneva, World Health Organization, 2021 (WHO Technical Report Series, No. 1033), Annex 2. ***Short name: WHO TRS 1033, Annex 2***

25. 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. ***Short name: WHO TRS 1033, Annex 3***

26. Guideline on data integrity. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fifth Report. Geneva, World Health Organization, 2021 (WHO Technical Report Series, No. 1033), Annex 4. ***Short name: WHO TRS 1033, Annex 4***

27. Recommendations for the production and control of influenza vaccine (inactivated). WHO Expert Committee on Biological Standardization. Twenty-ninth Report. Geneva, World Health Organization, 2005 (WHO Technical Report Series, No. 927), Annex 3. ***Short name: WHO TRS 927, Annex 3.***