### Part 1 General information

#### Manufacturers details

**Company information**

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Corporate address of manufacturer</td>
<td>Building 1, Premises 8, Village of Institute of Poliomyelitis, Settlement 'Moskovskiy', Moscow, 108819, Russian Federation.</td>
</tr>
</tbody>
</table>
| Contact persons | - Dr. Ishmukhametov, Aydar, ishmukhametov@chumakovs.su  
- Dr. Andrew Malkin, andrew.malkin@chumakovs.su, sue.polio@gmail.com  
- Dr. Alexandra Sinyugina, sinyugina@chumakovs.su, asina.78@mail.ru |
| Unit / block | Building 1 |

#### Inspection details

<table>
<thead>
<tr>
<th>Dates of inspection</th>
<th>11 to 16 March 2018</th>
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<tr>
<td>Type of inspection</td>
<td>Routine</td>
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<tr>
<td>Representative from the National Regulatory Authority</td>
<td>The national regulatory authority of the country was informed and participated to the inspection.</td>
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#### Introduction

The Institute of Poliomyelitis and Viral Encephalitis (IPVE), Academy of Medical Sciences of the USSR was established in 1955. The campus housing scientific and manufacturing buildings is located outside the city, within the green zone of Moscow suburbs, 27th km on the Kiev highway.

FSUE of Chumakov IPVE, was established in 1957 as a pilot plant for an early scaling-up and manufacturing of vaccines developed at the above-mentioned institute starting with Oral Polio vaccine (OPV). Since 1959, the established research and production campus...
The manufacturing activities were actively involved in the eradication of paralytic poliomyelitis in the Soviet Union, Japan, Brazil, Argentina, Greece, Bulgaria, India and some African countries.

Since 2003 a renovation of the production facilities and QC laboratories has taken place in order to meet current GMP requirements.

The Company produces the following types of vaccines, diagnostic kits and other biological products:

- Bi-Vac Polio (Oral Poliomyelitis Vaccine) of 1, 3 types.
- Tick-Born Encephalitis Vaccine, inactivated freeze-dried.
- Rabies Vaccine, inactivated freeze-dried.
- Yellow Fever Vaccine, live attenuated freeze-dried.
- Diagnostic kits.
- Various nutrient media and biological solutions dedicated for cell culture.

The company is granted the License: No 00076-JIC (marketing authorization) issued by the Ministry of Industry and Trade, Russia October 2016.

### History of the regulatory inspections

Yellow Fever vaccine (YFV) from Chumakov IPVE was first prequalified on 26 March 2009. The last WHO site visits for the prequalification of Yellow Fever Vaccine took place in November, 2014 and April 2016.

### Brief report of inspection activities undertaken

#### Scope and limitations

<table>
<thead>
<tr>
<th>Areas inspected</th>
<th>The inspection focused on the production and control of Yellow Fever Vaccine: 2, 5 and 10 doses and water for injection as diluent in ampoules.</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>The inspection covered all the sections of the WHO GMP text, including quality assurance, sanitization and hygiene, qualification and validation, complaints and recalls, self-inspection, personnel, training, personal hygiene, premises and equipment, materials, documentation, materials, production and quality control and utilities.</td>
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<tr>
<td>Restrictions</td>
<td>None.</td>
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<tr>
<td>Out of scope</td>
<td>The inspection was limited to the prequalified Yellow Fever vaccine</td>
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<tr>
<td>Vaccines covered by the inspection</td>
<td>Yellow Fever Vaccine: 2, 5 and 10 doses in ampoules, lyophilised active component to be reconstituted with diluent before use intramuscularly or subcutaneously.</td>
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<tr>
<td></td>
<td>Water for injection as diluent in ampoules.</td>
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<tr>
<td>Abbreviations</td>
<td>Description</td>
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<tr>
<td>AHU</td>
<td>Air Handling Unit</td>
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<tr>
<td>APR</td>
<td>Annual Product Review</td>
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<tr>
<td>APS</td>
<td>Aseptic Process Simulation</td>
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<tr>
<td>BMR</td>
<td>Batch Manufacturing Record</td>
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<tr>
<td>BPR</td>
<td>Batch Production Record</td>
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<tr>
<td>CA</td>
<td>Compressed Air</td>
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<tr>
<td>CAPA</td>
<td>Corrective Actions and Preventive Actions</td>
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<tr>
<td>CC</td>
<td>Change Control</td>
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<tr>
<td>CFU</td>
<td>Colony-Forming Unit</td>
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<tr>
<td>CIP</td>
<td>Cleaning In Place</td>
</tr>
<tr>
<td>CoA</td>
<td>Certificate of Analysis</td>
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<td>CpK</td>
<td>Process capability</td>
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<tr>
<td>DQ</td>
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<td>EDI</td>
<td>Electronic DeIonization</td>
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<td>EM</td>
<td>Environmental Monitoring</td>
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<tr>
<td>FMEA</td>
<td>Failure Modes and Effects Analysis</td>
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<td>FTA</td>
<td>Fault Tree Analysis</td>
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<tr>
<td>GMP</td>
<td>Good Manufacturing Practices</td>
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<td>GPT</td>
<td>Growth Promotion Test</td>
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<td>HEPA</td>
<td>High Efficiency Particulate Air</td>
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<tr>
<td>HVAC</td>
<td>Heating, Ventilation and Air Conditioning</td>
</tr>
<tr>
<td>IQ</td>
<td>Installation Qualification</td>
</tr>
<tr>
<td>LAF</td>
<td>Laminar Air Flow</td>
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<td>LIMS</td>
<td>Laboratory Information Management System</td>
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<td>MB</td>
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<td>MBL</td>
<td>Microbiology Laboratory</td>
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<td>MF</td>
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<td>National Control Laboratory</td>
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<td>Operational Qualification</td>
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<td>PAHO</td>
<td>Pan American Health Organization</td>
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<td>PHA</td>
<td>Process Hazard Analysis</td>
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<tr>
<td>pH</td>
<td>(-ve) logarithm of H⁺ concentration</td>
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<td>PLC</td>
<td>Programmable Logic Controller</td>
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<td>PM</td>
<td>Preventive Maintenance</td>
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<td>Performance Qualification</td>
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<td>PQR</td>
<td>Product Quality Review</td>
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<td>PQS</td>
<td>Pharmaceutical Quality System</td>
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<td>PW</td>
<td>Purified Water</td>
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<td>QA</td>
<td>Quality Assurance</td>
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<tr>
<td>Abbr.</td>
<td>Term</td>
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<tr>
<td>QC</td>
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<td>QCL</td>
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<td>Quality Management System</td>
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<td>Reverse Osmosis</td>
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<td>SIP</td>
<td>Sterilization In Place</td>
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<td>SMF</td>
<td>Site Master File</td>
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<td>SOP</td>
<td>Standard Operating Procedure</td>
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<td>SWFI</td>
<td>Sterile Water for Injection</td>
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<td>UN</td>
<td>United Nations</td>
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<td>UNICEF</td>
<td>United Nations Children's Fund</td>
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<td>URS</td>
<td>User Requirements Specifications</td>
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<td>UV</td>
<td>Ultraviolet-Visible Spectrophotometer</td>
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<td>VVM</td>
<td>Vaccine Vial Monitor</td>
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<tr>
<td>WFI</td>
<td>Water for Injection</td>
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<td>WHO</td>
<td>World Health Organization</td>
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Part 2: Brief summary of the findings and comments

1. Pharmaceutical quality system

In general the Pharmaceutical quality system and all of the elements were in place. However, these elements vary in their maturity and some need further attention and improvement.

The company had adequately addressed the deficiencies related to the QMS, PQR and QRM through the CAPA.

Product quality review:

The product quality review was performed according to the relevant procedure.

The review of the following elements were considered in the PQR: product information, manufacturing capacity, raw materials and packaging materials, manufacturing process control results, finished product control results, stability monitoring program results, quality control results, non-compliant batches, deviations, product’s reclamations, claims, complaints and recalls, changes, reference samples testing results, critical equipment qualification data, utilities systems data and process validation data, corrective and preventive actions performance and the technical agreements.

The Yellow Fever Vaccine PQR presented to the inspectors covered the period of production ranging from January to December 2017. Two YFV lots of 10D presentation were rejected due to non-compliance of weight loss on drying testing with normative documentation requirements. This was due to lyophilizer malfunction caused by electricity interruption.

No rejection of diluent was recorded in the 2017.

Quality risk management:

Procedures for QRM were in place. Fault Tree Analysis, HAZOP, HACCP, FMEA and PHA were considered for the risk assessment. A summary table of FMEA was reviewed and this included scoring of process steps for risk severity, probability and detectability.

The risk management and the risk assessment approach were not inspected in details during this inspection however the use of the QRM is not considered to be satisfactorily implemented as evidenced by the deficiencies raised which relates mainly to the aseptic gowning, the aseptic practices, the environmental monitoring program and the transfer and loading of lyophilized ampoules to the sealing station.

Deviation management:

Procedures for deviations management were in place. The deviations were categorized as critical and non-critical according to the product impact on quality, safety and efficacy.

The timelines for handling of deviation were in place.

There was no trending system for the management of the deviations including the timelines for investigations and closure, the review of recurrences and the effectiveness of the implementation of corrective and preventive actions resulting from deviation investigations.

The definition of a deviation was limited to “direct product impact” and deviations that lead to rejection of the vaccine. None of other category of deviations was raised since 2015. The deviation system in place was not efficiently implemented.

The company reported only one deviation raised since 2015. This deviation was was related to the interruption of the electricity to the lyophilizer during the lyophilisation process. The impacted batches of YFV were rejected. This was the only deviation reported in the PQR 2017.

Chumakov FSC R&D IBP, Moscow, Russia-Vx
11 to 16 March 2018
This inspection report is the property of the WHO
Contact: prequalinspection@who.int
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The company had adequately addressed the deficiencies related to the management of deviations through the CAPA.

Management review:
Procedure for quality management review was in place. Management review meetings were held twice a year with the head of all departments and the director.

The last report held on March 2018 was presented. It was reported that all the systems reviewed were considered acceptable except the quality management system that needs improvement mainly in terms of CAPAs resulting from self-inspection.

Change control:
Procedure for change control management was in place. This was not inspected during this on-site inspection.

CAPA management:
Provision for CAPAs handling were in place.

Overall, the CAPAs result from self-inspection, external audits, deviations, complaints, PQR, in field QA observations, annual management reports and risk assessments. CAPAs of type A result from non-compliance that were classified as critical or major. CAPAs of type B result from non-compliances that were classified as minor or other. A monitoring and effectiveness check of the CAPA was considered at defined frequencies.

The CAPA from the last WHO inspection carried out in April 2016 was spot checked on the following:

- **The validation of the sterile filtration of the stabilizer was not considered:**
  The validation report of the sterilization by filtration of the stabilizer of Yellow Fever Vaccine was spot checked.
  This validation was not considered complete and acceptable.

- **The nitrogen filter of the freeze driers was integrity checked off line on a monthly basis and not after each lyophilisation cycle.**

  This issue was mainly related to the use of lyophilizers in which there were no built-in inert gas filters and on-line integrity check was technically impossible. Through the CAPA the company has committed:
  a. To bring the procedure of testing integrity of inert gas filters mounted in the lyophilizers into compliance with the requirements of WHO/TRS 961.
  b. To arrange and conduct a peculiar training for the staff of Freeze-Drying Department regarding the changes made in the above SOPs and new procedure of integrity check as well – with subsequent confirmation of the training efficacy.

  The external gas filter that was previously tested monthly for integrity was no more tested. This filter was replaced every six months.

  The internal mounted nitrogen filter “built-in inert gas filters” cannot be checked on-line for integrity. As a risk mitigation, the company introduced a vacuum leak test of the chamber of the lyophilizer. However, the company failed to demonstrate the correlation of the vacuum leak test with regards to the integrity of the “built-in inert gas filters”. The management of the integrity test of the nitrogen filters was not considered acceptable. The risk mitigation in place was not considered acceptable.

- **The freeze driers were not CIP/SIP after each lyophilisation cycle.**

  The cleaning and the sterilisation in place of the lyophilizers were implemented after each use of the lyophilizers.
The company had adequately addressed the deficiencies related to the implementation of effective corrective and preventive action through the CAPA.

**Documentation:**
Manufacturing activities are supported by product specific standard operating procedures and master formula. SOPs are reviewed regularly. These documents are authorized by Quality Assurance. During the inspection, the assessment of the documentation system was performed by checking procedures, instructions, trend analysis, protocols and reports. The company has provided through the site master file, details on the implemented documentation management system. The procedures, reports and batch records spot-checked during this inspection did not give rise to concerns.

**Complaints:**
The procedure for complaints management was in place. The document described how complaints were handled. Chief of QA Operative Control Department receives and sends the complaints to the Quality Committee which determines if it is appropriate for investigation. There is a protocol document for dealing with complaints.

Members of the quality committee are Quality Director, Production Director, Chief of Quality Department, Chief of QC, Chief of QA, Chief of QA Operative Control Department and Chief of Administrative Director.

According to the procedure, complaints associated with safety and quality are reported to “Roszdravnadzor or Rospotrebnazor”, the competent Russian agencies responsible for surveillance. During the investigation of complaints, considerations were given to check whether other batches are affected hence the batch before and the batch after are checked. No complaint has been recorded for YFV since the last audit in 2016. Records from November 2016 to September 2017 of other vaccines were spot checked and showed one complaint on Oral Polio vaccine. The complaint was about five missing vials from a pack of Oral Polio vaccine.

**Product recalls:**
Recall is dealt with as relevant procedures. Recalls classification and recall transmission time were specified. Major recalls (24 hours), Ordinary recalls (1 to 5 days) while minor recall is to be reported from 10 to 30 days.

There has been no recall in the past three years for all company’s products. Simulation of recall was done in February 2018.

According to the procedure, recall stimulation should be performed at least once in two years initiated by head of operations QA. All recalls are reported to “Roszdravnadzor or Rospotrebnazor”, competent Russian agencies for surveillance. The SOP describes the batches which recall may affect depending on the outcome of the investigation of the Quality Committee, while all affected countries should be informed and product recalled.

The Quality Committee amongst other functions are the recall committee and comprise of Quality Director, Production Director, Chief of Quality Department, Chief of QC, Chief of QA, Chief of QA Operative Department and Chief of Administrative Director.

**AEFI/Pharmacovigilance:**
Pharmacovigilance was not mandatory in Russia prior to 2015 hence full activities were commenced by the company in 2015.

Pharmacovigilance system master file statement was in place.
Document was developed by Chief Pharmacovigilance Specialist and approved by Head of Quality Assurance Department. According to the statement summary document, two persons (Chief Pharmacovigilance specialist and a backup person) are nominated to carry out all pharmacovigilance responsibilities and have been trained.

As stated in the document, Pharmacovigilance system is organized in cooperation with Russian national regulatory authorities in accordance with the requirements of the Federal laws of the Russian Federation and recommendations from Ministry of Health, WHO and EMA. Specific requirements for countries which issued marketing authorisation are also considered. Any changes in the Pharmacovigilance system are made based on legal requirements and directives from the national regulatory authorities.

Periodic safety Update is a requirement to be submitted to the Russian NRA. It was initially 5 years interval but has been changed to 3 years effective from 2017 for immune-biological products.

No Adverse reaction following immunization has been reported for the yellow fever vaccine since the establishment of the Pharmacovigilance system. Forms have been distributed to various countries together with the shipment of vaccines yet no feedback.

**Self-inspection:**
Self-inspection is carried out based on relevant procedure. The procedure provides for both planned and unplanned self-inspection. The procedure describes the conduct of a yearly self-inspection.

Approved list of auditors and self-inspection schedule for 2017 and 2018 were spot checked. The lead auditor was from the QA department and confirmed utilization of schedule.

There were individual personal files of the auditors, containing their basic education, job position, table of performed self-inspections and training certificates.

The methodology for planned self-inspection involves sending out a 7 days’ notice planning by inspection team and development of checklist. Each inspection is usually carried out by three inspectors. After self-inspection, reports are developed within 10 business days, listing observations classified as critical, major and minor.

Corrective actions and preventive actions (CAPAs) are developed by the audit department after the report in 10 days and forwarded to inspected department. Date of implementation of CAPA is agreed by the auditors and concerned department. The last self-inspection audit report and CAPA for Yellow Fever Department was reviewed at the time of this inspection.

**Quality audits and suppliers’ audits and approval:**
According to a Federal Law about the purchase of raw material and services it should be through a tender system.

The list of approval of starting biological material includes embryonated eggs. SPF eggs are provided by the only supplier of SPF eggs in Russia. Egg suppliers are evaluated and qualified as per relevant procedure and national guidance. Focus is on eggs (quality) and flocks (wellness, environment) as well as on supplier performance (packaging, shipment, quality system). A certificate of analysis (CoA) is supplied for each batch of eggs. Analysis of last shipment CoA and comparison with TRS978 annex 5 section A.4.1 showed that information regarding screening of pathogens and flock status requirements were incomplete.

The Suppliers of glass (ampoules), Leaflet and ampoules labels and critical reagents was spot checked.

For Yellow Fever vaccines, no contract production or analysis is performed by the company.
**Personnel:**
An overall organizational chart indicating key personnel involved in manufacturing, quality control, quality assurance, warehouse, engineering and department wise organogram was available. Individual responsibilities are defined, described and accepted by personnel in job descriptions. All departments at the site have sufficient number of personnel with appropriate qualifications with respect to education, experience and training to perform their functions.

**Personnel training:**
There was in place a standard document for personnel training. Other procedures related to training include:
- Professional education for staff,
- Procedure for primary staff training,
- Procedure for organization for staff training,
- Procedure for organization of unplanned staff training,
- Evaluation of training Education.

Individual training files were maintained by departments and easily retrievable and monitored by the QA department. Training relating to GMP, ISO, quality system management, documentation and SOPs are handled by QA department.

Training effectiveness was evaluated by various means as described in the SOP.

Training schedule of 2018 for staff in working with yellow fever was presented to the inspector and reviewed. Different departments had individual training schedules.

Trainings for staff who work within Grade A & B areas for gowned and aseptic preparations were reviewed. Qualification for this class of staff is done by qualification committee which consists of Chief of HR, Head of Filling Department, Representative of Trade Union, Representative of financial Department and External experts. Qualification is carried out with a 3 months programme of primary training consisting of three parts; background introductory training, theoretical and practical training. Periodic theoretical and practical training is carried out yearly or bi-annually depending on the topic to maintain staff qualification.

**Personnel health and hygiene:**
Personnel health and hygiene are maintained as described in relevant procedure. Other SOP’s relating to health and hygiene were in place.

All staff undergoes annual medical check according to Russian law and a summary report is submitted to Human Resource Department indicating Health status of staff. Staff is vaccinated based on their responsibilities and specific vaccine required as stated in the relevant procedure.

In the case of medical emergency while at work, a trained staff is to administer first aid before an ambulance is called. The company does not have a sick bay. It is recommended that a sick bay be created as a waiting area before transferring a sick staff to hospital.
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. Manufacturing processes were generally defined. Instructions and procedures were generally available. Qualifications and validations were performed. Systems were in place for handling complaints and recalling batches of product from sale or supply. Key elements of GMP were available however additional efforts were required to be in compliance with WHO GMP guidelines.

Virus seed lots:

Working seed lots (WSL) are produced from master seed lot procured from NIBSC. MSL and WSL are stored at -70°C in dedicated room. Temperature are manually recorded once a day and continuously monitored with circular chart recorder. Storage equipment is connected to a centralized alarm system.

Upstream manufacturing process:

Prior to inoculation, appropriate amount of 17D strain working seed virus ampoules is dissolved in physiological solution and diluted at a defined rate.

The inoculation of the embryos with YF virus is carried out under aseptic conditions. Eggshell is pierced in the centre of air sac border by a puncher. The inoculum is injected directly into the embryo's body through the aperture in the eggshell. This aperture is then sealed with sterile paraffin and the inoculated eggs are transferred, through an airlock for incubation.

After incubation, inoculated embryos are examined using ovoscope to select viable ones for vaccine production. The eggs are treated with disinfectant and transferred through airlock for next sanitary processing in laminar shelter and subsequently transferred for dissection. Eggshells are cut with scissors; embryos are taken out using tweezers and placed in Petri dishes. Beak, eyes, paws and inward parts of the body are removed. The dissected embryos are placed in a measuring flask and added with stabilizer to obtain embryonic tissue is homogenized. The resulting pulp is subsequently frozen at minimum -60°C in a low-temperature refrigerator until results of sterility and potency tests are obtained.

Upon termination of sterility test, stabilizer is added to frozen homogenate (single harvest) until reaching a defined concentration in suspension and the whole is transferred under aseptic conditions for centrifugation. Supernatant is collected and sampled for sterility; biological activity and absence of mycoplasmas tests.

Downstream process:

The ampoules are washed in automatic ampoule-washing machine, sterilized and depyrogenated in dry-heat sterilizer.

Filling the liquid bulk vaccine into ampoules is carried out using filling and sealing machine under laminar air flow of grade A.

During the filling process, the formulated bulk of the vaccine is cooled and mixed in the vessel. At the beginning, in the middle and at the end of the filling process, ampoules are collected and sealed to be tested for sterility.

Filled ampoules are collected into stainless steel trays under laminar airflow of grade A. The trays are labeled according to the sequence of filling process and loaded into the chamber of automatic freeze-dryer.

Lyophilization of the vaccine is carried out using automatic freeze-dryer.
Filling and sealing machine provides the sealing process in flame of propane-butane and oxygen mixture under laminar air flow of grade A. Prior to sealing, the ampoules are blown with sterile dry inert gas (argon or nitrogen). After sealing, sealed ampoules are sampled for quality control testing on the vaccine. The ampoules are visually examined and checked for integrity. Labeling of ampoules of YF vaccine and the solvent (lot number, date of release, expiry date) is carried out using automatic labeling machine Bausch-Strobel. Labeled ampoules are packed in modular cardboard boxes, 10 ampoules in each.

**Production batch record review:**
Batch record of lot of YFV 10D presentation was spot checked.

### 3. Facilities and equipment system

Zone segregation principles based on cleanliness grades were considered for the premises. Production unit has individual HVAC system, assuring the balance of pressure difference and air exchange frequency rates. Pressure differentials between the premises with different cleanliness grade are provided. Regular environmental monitoring is carried out. Cleaning and disinfection of premises and equipment are considered.

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 and contained manufacturing areas were in place. Smoking, eating, drinking, chewing, and keeping plants, food, drinks, smoking material and personal medicines was not permitted in production, laboratory and storage areas. Wrist-watches, cosmetics and jewelry were not observed as being worn in clean areas. Cleaning, disinfecting and decontaminating procedures along with the environmental monitoring program were in place to control the non-viable and viable contamination levels in the production areas.

The Company has production lines equipped with automatic machines for filling in ampoules and vials (including ultrasound treatment & washing, sterilization and depyrogenation), freeze-drying, sealing and labelling the products.

The main production facility is a four story building where all four vaccines are being produced. Glassware washing and preparation, nutrient media production, filling, lyophilisation, labelling and packaging of the preparations take place in the same building.

Ground floor comprises the following units:
- Warehouse for in-coming materials (chemicals);
- Labelling & packaging facilities;
- Warehouse for finished products (vaccines and nutrient media) including:
  - Cold rooms/chambers (4°C) for storage of final product products;
  - Freezer rooms/chambers (minus 20°C) for storage of final product;
  - Premises for pre-shipment preparation of the products
- Glassware washing and preparation unit.

Second floor comprises the following units:
- Nutrient media production unit;
- Filling, freeze-drying, labelling and packing unit.

On the third floor the following units are located:
- YF vaccine bulk production department;
• Rabies vaccine bulk production department,

On the fourth floor other vaccine production units are located.

• Tick-born encephalitis vaccine bulk production department,

OPV bulk production department is located in separate and dedicated facility.

Each unit is located in a separate area independent functionally and technically and has separate HVAC system.

Details of the water system production, capacity and sanitization were provided in the site master file.

➢ *Qualification and validation:*

Provisions for qualification and validation were found to be well defined in the Validation Master Plan and related study protocols. The most recent Validation Master Plan 2018 was reviewed.

The qualification and validation of equipment and processes were spot-checked as the following:

  • Validation of sterilisation by filtration of nutrient media,
  • HVAC,
  • Autoclave qualification,
  • Depyrogenation Tunnel,
  • Freeze Driers,
  • Media Simulations,
  • Validation of inoculation,
  • Validation of cleaning of egg shell of embryonated egg.

4 Laboratory control system

QC laboratories are separated from production areas and located in production building (analytical laboratories) or in separate building (virology or in vivo, not covered during this inspection). In general, provisions are in place for sampling and testing of starting materials, packaging materials, intermediate products, bulk products and finished products. Testing methods are validated and equipment are in general terms qualified and calibrated. OOS methodology is in place and described in a specific procedure.

The premises of QC Division are located separately from the production unit. The analytical laboratory is located in the main production building, but it is equipped with a separate HVAC system and separate access (other than for access to production area).

*Analytical*

The equipment is temperature controlled manually once a day. The qualification is performed annually by QA department. Equipment in laboratory are appropriately identified, qualified and maintained. The micropipettes are calibrated annually in house. The calibration of analytical balances is outsourced. A pre-use calibration by calibrated standard weight is in place for the analytical balances.

The performances of the following tests were spot checked: ovalbumin content, residual moisture by weighing and bacterial endotoxin content. There was no trending of the positive control for ovalbumin content is in place.

*Virology*

The cells used for quality control tests are derived from PS cells obtained in 1995 from the Robert Koch Institute. The maximum passage of use is 20-25. However, management of cell banks is not done according to the traditional seed lot production system: for each year, a cell stock is derived from the cell stock of the
previous year. Aliquots of cells for quality control are stored in a tank of liquid nitrogen in a dedicated room. The nitrogen is added automatically to maintain the required level. Detailed content of main tank is recorded manually in a logbook.

The performances of the following tests were spot checked: identity by sero-neutralisation and potency determination by plaque forming unit assay.

**Stability**

At the time of inspection, three stability studies were ongoing:

- **Endpoint of shelf life** since 2010 for 19 batches at 2-8°C with testing at time points 0 and 24 months. No issue was raised during data analysis.
- **27 month at 2-8°C** for 3 batches produced with eggs coming from the current supplier with testing time points 0-3-6-9-12-18-24-27 months. No issue was raised during data analysis.
- **27 month at 2-8°C** for 6 non-commercial batches produced with eggs coming from a new supplier with the same testing time points as previously mentioned. No issue was raised during data analysis.

**Environmental monitoring for downstream and upstream:**

The environmental monitoring program was in place. The media used are supplied from suppliers and containing adequate neutralizers. The test results of non-viable particles environmental monitoring from January to December 2017 for aseptic rooms of grade B was spot checked. All test results presented were within the established limits.

The test results of microbial environmental monitoring for 2017 were presented and found within the established specifications.

**Water monitoring:**

Only WFI is used in YFV production facility. The test results on WFI for the year 2017 were presented and found within the established specification.

5 Materials system

Raw and packing materials are procured from qualified vendors. The incoming materials are verified on receipt and are stored at appropriate storage conditions. Materials are received, sampled and tested according to implemented procedures.

Packaging materials and finished products are sampled as per the sampling plan. Rejected materials are stored in segregated rejected material area.

Labels are stored under locked area in the warehouse. Labels are printed out on line during labelling operations.

6 Distribution and shipping

Shipping validation has been previously submitted to and reviewed by WHO as satisfactory. Final product storage and packing procedure was observed and considered satisfactory during the last inspection. These were not reviewed further during this inspection.
Part 3: Conclusion

Based on the areas inspected, the people met and the documents reviewed, and considering the findings of the inspection, including the deficiencies listed in the Inspection Report, as well as the Corrective Actions taken and planned, and committed to be implemented, The *Federal State Budgetary Scientific Institution «Chumakov Federal Scientific Center for Research & Development of Immune-and-Biological Products», Russian Academy of Sciences (FSBSI), Moscow* was considered to be operating at an acceptable level of compliance with WHO GMP guidelines.

All the non-conformances observed during the inspection that were listed in the full inspection report as well as those reflected in the WHO Public Inspection Report (WHOPIR), were addressed by the manufacturer, to a satisfactory level, prior to the publication of the WHOPIR.

This WHOPIR will remain valid for 3 years, provided that the outcome of any inspection conducted during this period is positive.
PART 4

List of GMP guidelines referenced in the inspection report


   **Short name: WHO TRS No. 986, Annex 2**


   **Short name: WHO TRS No. 970, Annex 2**


   **Short name: WHO TRS No. 929, Annex 4**

   [http://whqlibdoc.who.int/trs/WHO_TRS_929_eng.pdf?ua=1](http://whqlibdoc.who.int/trs/WHO_TRS_929_eng.pdf?ua=1)


   **Short name: WHO TRS No. 937, Annex 4**

   [http://whqlibdoc.who.int/trs/WHO_TRS_937_eng.pdf?ua=1](http://whqlibdoc.who.int/trs/WHO_TRS_937_eng.pdf?ua=1)


   **Short name: WHO TRS No. 961, 957), Annex 1**


   Short name: WHO TRS No. 957, Annex 2


   Short name: WHO TRS No. 961, Annex 6
   http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1


   Short name: WHO TRS No. 961, Annex 7
   http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1


   Short name: WHO TRS No. 961, Annex 9
   http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1


   Short name: WHO TRS No. 943, Annex 3
   http://whqlibdoc.who.int/trs/WHO_TRS_943_eng.pdf?ua=1


   Short name: WHO TRS No. 961, Annex 2
   http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

*Short name: WHO TRS No. 981, Annex 2*

http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_981/en/


*Short name: WHO TRS No. 981, Annex 3*

http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_981/en/


*Short name: WHO TRS No. 961, Annex 14*

http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1


*Short name: WHO TRS No. 992, Annex 4*


*Short name: WHO TRS No. 992, Annex 5*


*Short name: WHO TRS No. 996, Annex 3*


*Short name: WHO TRS No. 996, Annex 5*


*Short name: WHO TRS No. 941, Annex 2*


*Short name: WHO TRS No. 978, Annex 5*

[http://www.who.int/biologicals/areas/vaccines/TRS_978_Annex_5.pdf?ua=1](http://www.who.int/biologicals/areas/vaccines/TRS_978_Annex_5.pdf?ua=1)