## Part 1: General information

<table>
<thead>
<tr>
<th>Name of Manufacturer</th>
<th>Institute of Technology on Immunobiologicals - Bio-Manguinhos Oswaldo Cruz Foundation – Fiocruz</th>
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<tbody>
<tr>
<td>Production Block</td>
<td>Henrique Aragão Pavilion for YF API Production. DEPFI/CTV for formulation Filling and Freeze Drying. DIEVA PRF for Filling and Freeze Drying and Finishing.</td>
</tr>
<tr>
<td>Physical address</td>
<td>Av. Brasil, 4365 / Manguinhos - Rio de Janeiro - RJ – BRAZIL</td>
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| Contact person and email address | Dr Maria da Luz F. Leal  
Malu@bio.fiocruz.br |
| Date of inspection   | 15 – 19 February 2016 |
| Type of inspection   | Routine GMP Inspection |
| Dosage forms(s) included in the inspection | Sterile Injectable |
| WHO Vaccines covered by the inspection | Yellow Fever Vaccine: 5, 10 and 50 doses, lyophilised active component to be reconstituted with diluent before use Intramuscularly or Subcutaneously. Water for injection as diluent |
| Summary of the activities performed by the manufacturer | Manufacturing of drug substance, formulation, filling, lyophilisation, capping, visual inspection, labelling, packaging, Quality Control and distribution. |
PART 2: SUMMARY

General information about the company and site
The Institute of Technology on Immunobiologics – Bio-Manguinhos is the Unit of Oswaldo Cruz Foundation – Fiocruz, dedicated to the technological development and production of vaccines, laboratory diagnosis reagents and biopharmaceuticals demanded by the Ministry of Health of Brazil Public Health Programs.

The Bio-Manguinhos Institute facilities are located in the “campus” of Oswaldo Cruz Foundation, with approximately 1 square kilometre area, 5 km far from Rio de Janeiro downtown. It is constituted of 21 buildings with 57.893m² of total constructed area, where there were independent laboratories for production, quality control, warehouse, storage and distribution, administrative and support activities.

The production in this site comprises:
- Biological active pharmaceutical ingredients: Attenuated Live virus of the yellow fever (17DD strain) and *Haemophilus influenzae b*.
- Sterile Products: lyophilized powders, solutions (with aseptic preparation), parenteral solutions of small volume (with aseptic preparation) and parenteral suspensions of small volume (with aseptic preparation).

The above manufacturing facilities have a valid Manufacturing License, No. 062/2015, issued by the national DRA and valid until May/2016.

Around 40 million doses of Yellow Fever vaccines were produced annually. Around 10 million doses of Yellow Fever vaccine were supplied to UN Agencies in 2015.

History of WHO and/or regulatory agency inspections
WHO site visit for the prequalification of Yellow Fever Vaccine took place from 29 May to 01 June 2012.

In March 2013, Bio-Manguinhos received ANVISA’s inspection aiming to renew the GMP certificate. In order to address the outcomes and the recommendations from the inspection, Bio-Manguinhos has prepared an Action Plan, and during 2013 and 2014, worked in the implementation of the corrective actions.

In 2015, Bio-Manguinhos received two additional ANVISA inspections, the first one was carried out from 26th January to 02nd February 2015 and focused on the Final Process Department (DEPFI), where is performed the formulation, filling, lyophilization, capping and visual inspection of 5 and 10 doses yellow fever vaccine. The second one was performed from 30th November to 2nd December and the focus was the Rockefeller Pavilion facility (DIEVAPRF) dedicated to the filling, lyophilization, capping and visual inspection of 5 and 10 doses yellow fever vaccine.

Focus of the inspection
The inspection focused on the production and control of Yellow Fever 5, 10 and 50 doses. Yellow Fever 50 doses was not filled since 2009. The Polysaccharide Meningococcal A and C 10 doses vaccines is no more manufactured nor supplied through
UN Agencies. The 26th February 2016 the Company has requested from WHO Prequalification Vaccine Assessment Team the temporary suspension of Polysaccharide Meningitides Vaccine prequalification.

The inspection covered all the sections of the WHO GMP text, including premises, equipment, documentation, materials, validation, sanitation and hygiene, production, quality control and utilities.

**Inspected Areas**
- Quality Assurance
- Sanitization and hygiene
- Qualification and validation
- Complaints
- Recalls
- Self-inspection
- Personnel
- Training
- Personal hygiene
- Premises
- Equipment
- Materials
- Documentation
- Production
- Quality control

**PART 3: INSPECTION OUTCOME**

3.1 PHARMACEUTICAL QUALITY SYSTEM (PQS)

Bio-Manguinhos’ Quality Policy states: “Our commitment is through the pursuit of continuous improvement, develop and produce vaccines, reagents for diagnosis and biopharmaceuticals within the quality standards, constantly motivating our employees, so that we meet the expectations of our customers, with social responsibility and preservation of the environment”.

Bio-Manguinhos has a Quality Assurance System in place. This system is documented and monitored for its effectiveness. Overall, the Quality Assurance responsibilities were defined as following:

- Plan and manage Quality Assurance System implemented, disclosing the policy and philosophy of Bio-Manguinhos Quality based on current Good Practices (GMP, GLP) and Standards NBR ISO 9001 (Requirements for Quality Management Systems) and NBR ISO 17025 (General Requirements for Competence of Assay and Calibration Laboratories).
• Coordinate and elaborate the documents of Quality Assurance System (Quality Manual, Standard Operational Procedures, Working Instructions, Production Protocols, and Validation Protocols), so that guidelines are compiled by Bio-Manguinhos Organizational Units.
• Assure that products are planned and developed complying with GMP, GLP and GCP.
• Assure that production and control activities are documented, in clear and accurate written procedures (specific SOP), complying with GMP.
• Assure, with Quality Control Department and other Departments, specifications for products, raw materials and packing materials used in manufacturing processes.
• Assure correct manufacturing, supply and usage of raw materials and packing materials.
• Assure that all controls are performed on the raw materials, packing materials, intermediary products and finished products, as well as controls in process and calibration and validation.
• Assure labelling, packaging and checking of finished product based on documentation, which is defined and registered in adequate protocols.
• Assure that lots of products are not sold or supplied before they are tested and approved for quality according to relevant registration and regulations for production, control and release.
• Assure that products are stored, distributed and handled, so that their quality is guaranteed until their expiry date.
• Assure that any deviation is investigated, the root cause is identified and the lot released only after impact analysis.
• Assure self-inspection procedure and/or internal and external audit for quality assessing regularly effectiveness and application of Quality Assurance System.

In general the Pharmaceutical quality system and all of the elements was in place however these elements vary in their maturity and some needed further attention and improvement. The company has provided the remedial corrective and preventive actions adequately addressing the raised issues regarding the change control management.

**Quality risk management**
This aspect of the QMS was fairly basic and this element of the QMS required further utilisation for fuller maturity and to make best use of resources. Although the QRM should be systematic, the company performed only few assessments. The company has provided the remedial corrective and preventive actions adequately addressing the raised issues regarding the quality risk management.

**Product quality review**
Provisions for product quality review (PQR) were in place to verify the consistency of the process and the appropriateness of current specifications to highlight the trends and identify product and process improvements. The PQR review was performed for active
pharmaceutical ingredients, finished products, HVAC system and water system. The content, review frequency and approval dates were in place.

The company has provided the PQR (RPP-008-15-3) regarding the attenuated yellow fever 05, 10 and 50 dose presentations, the yellow fever diluent, the EM of Rockefeller Process, the EM of Yellow Fever Diluent, the EM of the formulation process in DEPFI, the EM of the filling, lyophilisation and capping of Yellow Fever Vaccine in DEPFI, the Water monitoring report in Rockefeller and the Water monitoring report in DEPFI.

The PQR (RPP-008-15-3) regarding the attenuated yellow fever 5, 10 and 50 dose presentations covered batches produced from 01.01.2015 to 30 September 2015.

These PQRs were generally acceptable and the company has provided the remedial corrective and preventive actions adequately addressing the raised issues regarding the PQR management.

**Change Control**

Provisions for change control were in place. The change control procedures establishes the impacts of the changes to comply with the quality guidelines. Change control was not covered in details during the present GMP inspection.

The new changes reported for the Campus Manguinhos comprises:

- Rio de Janeiro (RJ) - New Warehouse and Administration Building (Napa). The building will integrate the management and logistic areas, nowadays physically separated, providing modern facilities and better working conditions for the staff. The new warehouse of raw materials complies with Good Manufacturing Practices and other requirements of regulatory agencies.

- Rio de Janeiro (RJ) - Integrated Prototypes, Biopharmaceuticals and Reagents for diagnosis Center (CIPBR). A prototype plant to increase the range of developed products and manufacturing batches for clinical trials. Largest plant for production of laboratory diagnosis reagents in Brazil.

- Rio de Janeiro (RJ) - Building Rotavirus. The Technological Vaccines Complex (CTV) concentrates the main industrial activities of the Institute and also the laboratory of Rotavirus vaccine.

The new changes reported for the new Campus Santa Cruz (RJ) comprises:

- Bio-Manguinhos/Fiocruz, Campus Santa Cruz (RJ). For expanding the supply of biological products: production up to 120 million of vaccine vials and biopharmaceuticals.

The new changes reported for the new Campus CTPV comprises:

- Technology Center of Plant Platforms - Eusebio (CE). New manufacturing capacity of biopharmaceutical products for human use, supported by plant-based technology platforms.
Deviations Management
Provisions for deviations handling were in place according to the implemented procedures. The list of deviations was spot checked and did give rise to concerns. The company has provided the remedial corrective and preventive actions adequately addressing the raised issues regarding the deviations management.

CAPA Management
Provision for CAPAs handling were in place according to the implemented procedures. The company has presented the CAPA generated from previous ANVISA and WHO GMP inspections.

3.2 GOOD MANUFACTURING PRACTICES (GMPs) FOR PHARMACEUTICAL PRODUCTS
Overall, the level of implementation of good manufacturing practices was considered continuously improving. In general terms, necessary resources were available, including qualified and trained personnel, premises, equipment and services, appropriate materials, containers and labels, approved procedures and instructions, laboratories and equipment for in-process and other controls. Manufacturing processes were generally defined and reviewed. Instructions and procedures were generally available. Qualification and validation of equipment, manufacturing processes and quality control testing methods were performed. Operators were trained to carry out procedures, and records were made during manufacture. Key elements of GMP were available.

3.3 SANITATION AND HYGIENE
Most of the premises were generally maintained at an acceptable level of cleanliness. The company had provisions for personal hygiene and sanitation in its production facility. Smoking, eating, drinking, chewing, and keeping plants, food, drinks, smoking material and personal medicines was not permitted in production, laboratory and storage areas. Wrist-watches, cosmetics and jewellery were not observed as being worn in clean areas. Manufacturing areas were provided with airlocks for personnel and materials entries and exits. Gowning procedures for access to the classified and contained manufacturing areas were in place. Changing rooms were provided with photos describing the gowning procedures. During the inspection the gowning procedures appeared to be complied with no dress code violations noted. The level of hygiene observed and the measures taken to maintain this were considered satisfactory.

3.4 QUALIFICATION AND VALIDATION
The Validation Team was in charge of systems, equipment qualifications and process validations as following:
• Process Validation: media simulation for aseptic process (since bulk production, formulation, filling, Freeze-drying, until capping process), concurrent validation, cleaning validation, sterilization process validation, validation of vapour Hydrogen
peroxide sterilization, validation of formaldehyde fumigation and validation of the sterilizing filtration process with the filter supplier.

- Validation of Utility Systems: WFI, PW, Clean Steam, Clean Compressed Air.
- Validation of analytical methodology: microbiological, biological and physical/chemistry assays.
- Qualification of the Operators: Qualification of Person for Access to the Cleanroom.
- Personal manual visual inspection certification: Validation team was responsible to certificate the person who execute manual visual inspection for liquid or freeze dried products.
- Calibration: Temperature, Pressure, Flow, Balance, Volume, pH, Conductivity and Humidity. The calibration laboratory is accredited by the National Metrology Authority (INMETRO) according to NBR ISO/IEC 17025 for balances and volume calibrations. A multidisciplinary team evaluate if the equipment and computerized systems were constructed according to User Requirement Specification (URS) and design. The initial Installation Qualification (IQ) and Operational Qualification (OQ) were performed by the manufacturers. The Performance Qualification and re-validations were carried out by the internal Validation team.

Provisions were in place for Information Technology System (IT) and Automation Technology Systems (AT).

The Validation Master Plan (VMP) was available. The Re-validation and Re-qualification Policies and Frequencies were considered. The company has provided the remedial corrective and preventive actions adequately addressing the raised issues regarding the qualification and the validation.

3.5 COMPLAINT and PRODUCT RECALL

Complaint: The Post-Marketing and Customer Service Division from the Market Relations Department was responsible for registering all the complaints about vaccines, reagents for diagnosis and biopharmaceuticals. In the case of any quality or safety complaint related to YF, the NRA of the received country (international or ANVISA) will inform the Bio-Manguinhos company and immediately a deviation will be initiated by the QA and QP officers. Further investigation to be followed to identify the risk of safety issue and a decision of a recall will be made accordingly. A list of complaints for the last 3 years was spot checked.

Recall: is managed through the implemented procedures. The Quality Department has the responsibility of coordinating the recall. The recalled products are stored in a segregated and secure space identified with a plate “RECALL” until the receipt of the discharge authorisation.

The Company stated that there is no recall of YF vaccine for the last 3 years.
3.6 CONTRACT PRODUCTION AND ANALYSIS

No contract production and analysis is in place for Yellow Fever vaccines as stated by the company.

3.7 SELF INSPECTION AND QUALITY AUDIT

Provisions for self-inspection were in place according to the implemented procedures. Audits and self-inspection were performed at least once a year. Audits were scheduled, planned and prepared in advance and carried out in accordance to an audit plan and checklist. The Audit and Training Division was responsible for internal audits, according to annual plan. Such audits were recorded in proper forms namely audits reports. At the end of audits, reports were made including compliances and non-compliances related to audits.

The corrective actions were defined. These actions were implemented and deadlines were established for its conclusion.

Auditors should be trained in Guidelines for Auditing Management Systems to perform audits and shall have knowledge on management systems, standard NBR ISO 9001:2008, Good Manufacture Practices (GMP), procedures, processes and audit techniques.

Suppliers Quality Audit: provisions for raw material and packaging material supplier were in place according to the implemented procedures as detailed in the provided Site Master file. The company has provided the remedial corrective and preventive actions adequately addressing the raised issues regarding the suppliers management.

3.8 PERSONNEL

Organization chart showing the arrangements for quality assurance, including production and quality control were provided by the company and were parts of the Site Master File.

Bio-Manguinhos established a Training Program with the purpose to invest in training and improvement focussing on institutional goals, developing of human resources (technical and managerial). The Human Resources Department DEREH is responsible for the program coordination and capability of each employee in partnership with other areas as production, for the on job training and Quality assurance Department for GMP training. The DEREH is responsible for the maintenance of training records in an electronic system.

3.9 PREMISES and EQUIPMENT

The Bio-Manguinhos Institute facilities are located in the “campus” of Oswaldo Cruz Foundation, with approximately 1 square kilometre area, 5 km far from Rio de Janeiro downtown. It is constituted of 21 buildings with 57.893m² of total constructed area, where there were independent laboratories for production, quality control, warehouse, storage and distribution, administrative and support activities. Although the premises and equipment were in general terms considered suitable to the manufacturing operations to be carried out at Bio-Manguinhos, deficiencies were raised and the company has
provided the remedial corrective and preventive actions adequately addressing the raised issues.

3.10 MATERIALS
Raw materials including production starting and packaging materials were received and handled by the Warehouse CEADI - Raw Material Storage and Distribution Sector according to the implemented procedures for the inspection of receiving, receiving of materials, storage of the starting materials after the QC analysis and the distribution of starting materials.
Provisions for the handling of rejected materials and products including the rejected starting and packing materials, the rejected eggs from production and Bulk, the intermediate products and returned products were in place.

3.11 DOCUMENTATION
Through the Quality Management System in the management of documents enables communication of purpose and action consistency, contributing to the achievement of compliance and continuous improvement. This management is done through a document control program that establishes guidelines and guides the procedures that describe the process of creation, review, distribution and availability of documents. It is the Documentation Division standardization, filing and distribution of documents.
All documents were prepared by designated production or quality analyst experts; they were reviewed and approved by Division of Documentation; they were distributed in a controlled manner to ensure that the right effective version was used, and any obsolete version was withdrawn and archived. Periodic Review was defined in the related procedures and records were completed in agreement with Good Documentation Practices.
The documents were stored in a secured system and archived in agreement with the archiving procedure which defines in particular: list of documents/records and related retention period and process to retrieve documents. The documents were archived in the quality assurance department of Bio-Manguinhos.

3.12 GOOD PRACTICES IN PRODUCTION
Refer to section 3.2, 3.3, 3.4 and 3.9.
The company has provided the remedial corrective and preventive actions adequately addressing the raised issues regarding the good practices in production.

3.13 GOOD PRACTICES IN QUALITY CONTROL
QC laboratories were separated from production areas. In general terms, provisions were in place for sampling and testing of starting materials, packaging materials, intermediate products, bulk products and finished products as well as environmental monitoring, water systems and gases. Testing methods were validated and equipment were in general terms qualified and calibrated. OOS methodology was in place. The company has provided the
remedial corrective and preventive actions adequately addressing the raised issues regarding the good practices in quality control.

PART 4: CONCLUSION
Based on the areas inspected, the personnel 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, the Institute of Technology on Immunobiologicals - Bio-Manguinhos Oswaldo Cruz Foundation – Fiocruz was considered to be operating at an acceptable level for compliance with WHO GMP guidelines.

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