## Prequalification Team Inspection services
### WHO PUBLIC INSPECTION REPORT
#### of the Vaccines manufacturer

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<th>General information</th>
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<tr>
<td>Manufacturers details</td>
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<td><strong>Company information</strong></td>
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<tr>
<td><strong>Name of manufacturer</strong></td>
<td>Beijing Bio-Institute Biological Products Co., Ltd. (BBIBP)</td>
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</table>
| **Address of manufacturer** | No. 6 (east part) and No. 9 (west part), Bo Xing 2nd Road, Economic and Technological Development Area, 100176 Beijing, P.R. China.  
GPS for bOPV Block: Longitude 116.530571, Latitude 39.751189  
GPS for YF Block: Longitude 116.529367, Latitude 39.750558 |
| **Contact person** | Dr Hui Wang, Vice General Manager  
wh6247@126.com |
| Inspection details | |
| **Dates of inspection** | 6 to 10 March 2017 |
| **Type of inspection** | Initial |
| **Representative from the National Regulatory Authority** | Representatives from the Centre for Food and Drug Inspection (CFDI) and Beijing Food and Drug Administration (BFDA) of Republic of China took part in the inspection. |

### Introduction

**Brief summary of the manufacturing activities**

Beijing Tiantan Biological Products Co., Ltd. previously TiantanBio (BIBP) is registered with the China Food and Drug Administration (CFDA) to manufacture sterile parenteral drugs, biological and animal products at the E-Town site.

BBIBP manufacturing campus contains a total of twenty-two buildings: six independent biological production buildings, with an individual Quality System (QA/QC) building, Warehouse Storage Building, and Animal Testing Building along with other supporting facilities.

For the vaccines in scope of this inspection (bOPV and Yellow Fever Vaccine (YFV)) activities on site included working cell and seeds establishment, drug substance manufacturing, drug product formulation, filling, visual inspection, labelling, packaging, Quality Control and distribution.

**General information about the company**

BBIBP is a state-owned listed company for high technologies, involved in research, manufacturing and marketing of biological products including
BBIBP, as the largest vaccine products industry base in China, total have 39 kinds of products. The current site of TiantanBio is a newly constructed production campus in the outskirt of Beijing called “E-Town Vaccine Industry Base” with an area of more than 165,000 square meters and a total investment of about 560 million CNY. Transfer of production activities to this site was from 2014. This newly constructed production campus has been the largest manufacturing base for vaccines in China.

History

The list of CFDA GMP inspections for BBIBP during the last 5 years are presented below:

<table>
<thead>
<tr>
<th>No.</th>
<th>Register address</th>
<th>Inspection duration</th>
<th>Authority</th>
<th>Purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>Beijing economic and technology development area BOXING second road, No.6 and No.9</td>
<td>2014/03/27-31</td>
<td>CFDA, China</td>
<td>GMP compliance and site inspection for bOPV Product</td>
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<tr>
<td>6</td>
<td>Beijing economic and technology development area BOXING second road, No.6 and No.9</td>
<td>2015/01/22-25</td>
<td>CFDA, China</td>
<td>GMP compliance inspection for MMR and OPV</td>
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<tr>
<td>7</td>
<td>Beijing economic and technology development area BOXING second road, No.6 and No.9</td>
<td>2015/10/9-10/13</td>
<td>CFDA, China</td>
<td>GMP compliance inspection for Yellow Fever Product</td>
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Brief report of inspection activities undertaken

Scope and limitations

Areas inspected: Buildings 103, 105, 107 and 201.

Restrictions: Not applicable

Out of scope: The inspection was limited to bOPV and YFV manufactured in the building mentioned above.

Vaccines covered by the inspection: bOPV 20 dose (2.0 mL/vial) and YFV 1 dose (0.5 mL/vial).
## Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AHU</td>
<td>air handling unit</td>
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<tr>
<td>ALCOA</td>
<td>attributable, legible, contemporaneous, original and accurate</td>
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<td>APQR</td>
<td>annual product quality review</td>
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<td>AQL</td>
<td>Acceptance quality limit</td>
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<td>BMR</td>
<td>batch manufacturing record</td>
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<td>bOPV</td>
<td>bivalent oral polio vaccine</td>
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<td>BPR</td>
<td>batch packaging record</td>
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<td>CAPA</td>
<td>corrective actions and preventive actions</td>
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<td>CC</td>
<td>change control</td>
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<td>CFU</td>
<td>colony-forming unit</td>
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<td>CoA</td>
<td>certificate of analysis</td>
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<td>CpK</td>
<td>process capability index</td>
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<td>DQ</td>
<td>design qualification</td>
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<td>EM</td>
<td>environmental monitoring</td>
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<td>FAT</td>
<td>factory acceptance test</td>
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<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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<td>GMP</td>
<td>good manufacturing practice</td>
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<td>HACCP</td>
<td>hazard analysis and critical control points</td>
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<td>HPLC</td>
<td>high-performance liquid chromatograph</td>
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<tr>
<td>HVAC</td>
<td>heating, ventilation and air conditioning</td>
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<td>ID</td>
<td>identity</td>
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<tr>
<td>IPC</td>
<td>In process control</td>
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<td>IQ</td>
<td>installation qualification</td>
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<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>
<td>microbiology</td>
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<td>MBL</td>
<td>microbiology laboratory</td>
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<td>MF</td>
<td>master formulae</td>
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<td>MR</td>
<td>management review</td>
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<td>NRA</td>
<td>national regulatory agency</td>
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<td>OQ</td>
<td>operational qualification</td>
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<td>PHA</td>
<td>preliminary hazard analysis</td>
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<td>PM</td>
<td>preventive maintenance</td>
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<td>PQ</td>
<td>performance qualification</td>
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<tr>
<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>PSF</td>
<td>product summary file</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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<td>QC</td>
<td>quality control</td>
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<td>QCL</td>
<td>quality control laboratory</td>
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<td>QMS</td>
<td>Quality management system</td>
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<tr>
<td>QRM</td>
<td>quality risk management</td>
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<td>RA</td>
<td>risk assessment</td>
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<td>RCA</td>
<td>root cause analysis</td>
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<tr>
<td>Acronym</td>
<td>Description</td>
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<td>--------------------------------------------------</td>
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<td>RH</td>
<td>relative humidity</td>
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<td>RM</td>
<td>raw materials</td>
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<td>RS</td>
<td>reference standard</td>
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<tr>
<td>SOP</td>
<td>standard operating procedure</td>
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<td>TAMC</td>
<td>total aerobic microbial count</td>
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<td>TFC</td>
<td>total fungal count</td>
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<tr>
<td>TMC</td>
<td>total microbial count</td>
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<tr>
<td>TOC</td>
<td>Total organic carbon</td>
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<tr>
<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>VMP</td>
<td>Validation Master Plan</td>
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<td>WFI</td>
<td>water for injection</td>
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<tr>
<td>YFV</td>
<td>Yellow Fever Vaccine</td>
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Part 2: Brief summary of the findings and comments (where applicable)

1. Pharmaceutical quality system (PQS)
Production and control operations were specified in written form and GMP requirements were essentially being met. Managerial responsibilities were appropriately specified in written job-descriptions. Product and processes were monitored and the results taken into account during batch release; regular monitoring and reviews of the quality of bOPV and YFVs were being conducted according to documented schedules and procedures.

- Quality Risk Management:
The procedure for “Risk assessment and control” and its flow chart were spot checked. Failure modes and effects analysis (FMEA) was mainly used as risk assessment tool, other tools listed were hazard operability analysis (HAZOP), risk classification and screening, FAT, control charts, experiment design, Metrix, Pareto diagram and process capability analysis

Using the FMEA process risk was defined as Risk = Probability x Severity x Detectability (scoring from 1 to 10).
Risk assessment (RA) was carried out by the team. The following discrete steps were performed during the risk assessment:
- Risk identification
- Risk analysis
- Risk assessment
- Risk control
- Risk evaluation
- Risk mitigation
- Risk review

A risk assessment for the multiproduct facility building 103 was performed in July 2016. The product contact equipment was dedicated for YFV, MMR and varicella respectively. Before, July 2016, the product contact equipment were not dedicated and underwent the implemented procedures for decontamination and cleaning. Procedures for campaign change for YFV, MMR and varicella were in place.

- Management review (MR):
The procedure “Quality system management review” was reviewed. According to the SOP quality system review shall be performed yearly. The SOP was applicable, but not limited to:
  - Quality management system
    - Achievements for the quality targets
    - Deviations
    - CAPA
    - Change control
    - Audits/external inspections
    - Process performance
    - Production compliance
    - Resources, equipment and facilities
    - Internal quality audits
The first Management review was performed in December 2016. It was recommended to include in the next Management review follow-up actions from previous reviews. MR minutes were not signed by the participants, however participant’s signature list was available (stored in human resource department) and presented to the inspectors. It was advised to keep together MR minutes/report and signature list.

- **Product Quality Review (PQR):**
The procedure “Product annual quality review” was discussed. PQRs were prepared annually, covering the period September – August. This period was set to coincide with regular production shutdown in summer for maintenance.

Statistical tools were used for data presentation and analysis. Process capability was calculated using Cpk.

The PQR 2015-2016 bOPV 2.0 mL (20 doses), PQR 2015-2016 bOPV 1.0 mL (10 doses) and PQR 2015-2016 YFV were spot checked.

In the YFV PQR it was indicated that in 2015-2016 YFV was produced at two different scales. Process validation was stated to cover both sizes and choice could be made based on market demand.

- **Deviations:**
The procedure “Deviation management” and its flow chart were reviewed. The SOP was applicable to planned and unplanned deviations. Unplanned deviations were classified as:
  - Critical
  - Major
  - Minor
  - Incident (event that does not have impact on product quality, SOPs or GMP). There was separate incidents register.

Ishikawa diagram and 5 Why’s were used for root cause analysis. It was indicated that root cause analysis was only initiated for “significant” (critical and major) deviations.

- **Corrective actions and preventive action (CAPA)**
The procedure “Corrective actions and preventive actions” and its flow diagram were discussed. CAPAs were proposed by manager or supervisor of each department. The QA manager was responsible for reviewing and approving CAPAs as well as follow up. CAPA register 2016 was spot checked.

- **Change control (CC)**
The procedure “Change control” and its flow chart were discussed. The SOP was applicable to:
  - Specifications
  - Analytical methods
  - Packaging materials
  - Manufacturing process
  - Computerizes system
  - Organization and personnel
  - Premises, facilities and equipment
  - Raw materials and excipients
  - documents
Changes were classified:

- **Major**
- **Minor**

- **Release Procedure of vaccines**

Qualification requirements of the Authorized Person/Qualified Person responsible for batch certification and release were in place. The BBIBP Qualified Persons for batch certification are the vice president of Quality and the manager of Quality Assurance. BBIBP has the responsibility to test and release finished products, perform sampling, and ensure that product is manufactured, packaged, QC tested and released in compliance with cGMPs, applicable procedures and product specifications. In addition to BBIBP internal release tests, the products are also sent to National Institutes for Food and Drug Control (NIFDC) for testing and release. When product is approved for release, the Qualified Person will issue the certificate for final release to the commercial market.

2. **Good manufacturing practices for pharmaceutical products**

Manufacturing processes were defined and reviewed. Qualifications and validations were performed. Necessary resources were provided. Operators were instructed to carry out procedures, and records were made for the production operations. Significant deviations were recorded and investigated, root causes were determined and corrective and preventive action were implemented. Systems were in place for handling complaints and recalling any batch of product from sale or supply.

3. **Sanitation and hygiene**

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 are provided with airlocks for personnel and materials entries and exits. There were locations with movement from grade E to grade C. Gowning procedures for access to the classified manufacturing areas were in place. 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.

4. **Qualification and validation**

Provisions for qualification and validation were in place and covers premises, equipment, utilities and systems, processes and procedures at periodic intervals and when changes have been made. Validation and qualification protocols and reports were spot checked as presented below. Validation Mater Plan summarizing validations performed in YFV and bOPV departments in 2016 and including validation and qualifications schedule for 2017 were spot reviewed. The list of cleaning validations, changeover, campaign and process validations were not included in these VMPs. The validation and qualification reports were spot checked as presented below.

- **Aseptic process validation**

YFV:

The aseptic process validation was in place as per the procedure “Media fill”. Media fills started from final bulk preparation. The final sterile bulk in stainless steel tank is transferred to the building 103 where the aseptic filling and the lyophilisation of YFV take place. The media fill procedure and protocols were spot checked and found appropriate. The bulk preparation and filling is carried out in one day.
Worst case interventions were listed. The list of persons who participated in the media fills was attached to the protocol.

According to the report, vials were incubated in the inverted position. Vials were first incubated at 20-25 °C (7 days) and thereafter at 30-35 °C (7 days). Visual checks were performed during incubation and after by microbiologists.

bOPV:
Aseptic media simulation for Building 107 filling line for bOPV: the media fill tests for this line for both 1.0 mL/vial and 2.0 mL/vial presentations from July 2015 were spot checked.

- Bulk transportation tank validation
  The procedure “Facility and equipment validation and qualification management” was discussed. According to the SOP new bulk tank sterility and pressure holding validation should be performed for 3 consecutive runs. Bulk transportation tank validation Performance report was discussed. The aim of this study was to validate sterility and pressure holding of the tank. This validation study was performed every two years for 1 run.

- Autoclave qualification
  The autoclave and dry heat oven qualification was performed as per the procedure in place. The qualification is performed yearly considering all loads.

  Autoclave performance re-qualification record was spot checked. This autoclave was used for:
  - Rubber stoppers
  - Al caps
  - Gowns
  - WFI used for detergents preparation

- Pure steam qualification
  The procedure “Pure steam quality testing kit” was spot checked. Pure steam generation and distribution system re-qualification report was discussed. Samples were taken from generation and distribution system. The following tests were carried out:
  - Non-condensable gases
  - Dryness
  - Superheat
  - pH
  - Nitrates
  - Ammonia
  - Conductivity
  - TOC
  - Non-volatile mater
  - Heavy metals
  - Microbial limit
  - Bacterial endotoxins

- Dry heat oven/ depyrogenation tunnel qualification
  According to the SOP qualification was performed once a year for all loading patterns.
Vials depyrogenation tunnel qualification report was checked. Qualification was carried out for both vial sizes, the following tests were performed:

- Air velocity
- HEPA integrity
- Particle counts
- Heat penetration/distribution
- Endotoxin reduction after depyrogenation

➢ Clean room qualification
The procedure “HVAC system qualification” was discussed. According to the SOP HVAC system and ULAF qualification should be carried out once per year, including HEPA filters integrity. A change control has been initiated to increase the integrity test of filters of grade A, Grade B and unidirectional air flow (UDAF) every 6 months.

The air to the vial filing room was supplied by the AHU. Performance re-qualification report “at rest” and “in operation” were reviewed. The following tests were carried out:

- Air flow/air changes per hour
- Air flow pattern
- Air volume
- Pressure differentials
- Temperature and relative humidity (RH)
- Microbial counts
- Particulate counts
- Recovery tests
- HEPA filters integrity

➢ Temperature mapping
✓ The procedure “Storage system qualification” was discussed. According to the SOP mapping should be repeated every two years.

✓ The last temperature revalidation of the -20°C storage room was reviewed. The temperature mapping was done according to Chinese GSP (2013) guideline.

✓ Incubation room where the embryo is checked and eggs marked for inoculation site. Temperature mapping is performed yearly and the last was performed in April 2016. The record was reviewed. Additionally, if production was increased to supply through UN agencies, there would presumably be more locations of eggs in the room. Future temperature mapping should be more comprehensive.

➢ Cleaning validation
The manual cleaning validation of the product contact vessels was spot checked. The revalidation is considered every three years. The manual cleaning report of the filling parts of the filling machine performed in August/September 2015 was spot checked. Clean hold time was established. The dirty time was mentioned in the validation protocol however not documented in the validation report.
Process validation
The PSF submitted to WHO was a simplified PSF (format agreed in context of the 2016 YFV not including the process validation of Yellow Fever Vaccine). The clinical data submitted for PSF review were based on batches not produced in the present manufacturing building of YFV building 103 and 105. Previously, the manufactured batch size of the formulated bulk to fill was 15000 mL and around 25000 vials (0.5 mL in 2 mL vials). Since August 2016, the manufactured batch size of the formulated bulk to fill was 30000 mL and around 50000 vials (0.5 mL in 2 mL vials). A comparative study of the manufacturing process of YFV in the new campus E-Town between the batch sizes 15000 mL and 30000 mL was available.

Fumigation process
Fumigation of filling area: there was a gap analysis presented regarding the shared facility used for multiple products filling. There was an indication of a planned replacement of current procedure with a vaporisation hydrogen peroxide (VHP) system (by July 2017). The most recent revalidation of the current procedure was reviewed. At risk monitoring points were identified. In addition to biological indicators, at these points, agar plates to which virus had been added were placed. After fumigation these were sampled and tested on cell culture for cytopathic effect (as an indication of live virus).

5. Complaints
The procedure “Product complaint” and its flow chart were discussed. This document relates to Adverse Events following Immunisation (AEFIs). A separate SOP and staff deals with quality related complaints. Complaints were received, registered and categorized by adverse events monitoring manager. There are three physicians in the pharmacovigilance area. The Chinese regulations require reporting to the government only when there is a death or clustered AEFIs. For YFV it was indicated that all listed AEFIs were retrieved from the literature and none came from direct reporting to the company by recipients, physicians or from CFDA. However, the company does have a telephone number for complaints, which is included in the package insert. From 2009-2014 (YFV produced in old facility), there were 2364 AEFIs. 2337 were considered as expected general reactions. 27 were considered abnormal, of which one case (haemolytic jaundice) was considered serious. The quality complaint registers for 2015 and 2016 were presented to the inspectors. 4 complaints were registered in 2015 and 3 were registered in 2016.

6. Product recalls
The procedure “Product recall” and its flow chart were discussed. Recalls were classified as per National Agency of Drug and food Control guidelines:
- Level I - recall within 24 hours, report to CFDA 1 day
- Level II – recall within 48 hours, report to CFDA 3 days
- Level III – recall within 72 hours, report to CFDA 7 days

Adverse events monitoring manager was responsible for dealing with recalls. Qualified Person had overall responsibility for dealing with recalls. Up to the date of inspection there was no product recall recorded. According to the recall procedure, the mock recall in performed every three years. Last level I mock recall was performed in 2015 for China market (YFV). It was advised to perform mock recall also for international markets.
7. **Contract production, analysis and other activities**

The activities involved in the bOPV and YFV bulk production, formulation, and filling & packaging are performed by BBIBP. Certain activities related to product testing, equipment validation and maintenance, calibration of instrument, and international shipping of the product are subcontracted. The complete list of the contracted companies and their services was provided in the PSF however this was not inspected in detail.

8. **Self-inspection, quality audits and suppliers’ audits and approval**

The procedure “Self inspection” was discussed. According to the SOP comprehensive audit should be performed at least once per year.

According to the SOP the following should be covered by the self-inspection:

- Personnel
- Facilities
- Utilities
- Equipment
- Raw materials
- Production
- Labelling
- Hygiene, cleaning
- Documentation
- QC laboratory
- QA

Inspection was carried out by a self-inspection team of selected individuals drawn from relevant disciplines. Before inspection, inspection plan was prepared and listed critical points to be covered.

Inspection report was written by the team and CAPAs addressed by the inspected department. CAPA implementation was monitored by the quality management system administrator.

Self-inspection schedule for 2017 was presented to the inspectors.

**Suppliers’ audits and approval:**

The procedure “Major material supplier qualification” and its flow chart were discussed. SOP covered:

- Materials in direct contact with the product
- Packaging materials
- Excipients
- Starting materials

Existing eggs supplier “Merial Vital Laboratory Technology” qualification documents were discussed.

According to the SOP animal source material suppliers, primary packaging materials suppliers should be qualified (documents and on-site audits) once in two years. Labels suppliers’ qualification was performed based on documents evaluation once in 5 years.

Suppliers re-audit schedule for 2017 was presented to the inspectors.
9. Personnel
There were an adequate number of personnel qualified to perform and supervise the manufacturing and quality control. The organograms were provided in the site master file. Duties of the responsible staff are recorded in written descriptions. Steps were taken to prevent unauthorized people from entering production, storage and QC areas.

10. Training
The procedure “GMP training management” was discussed. This was general SOP and explained the following training levels:
- Company
- Department
- Group

According to the SOP new employees had to receive the following training:
- Basic GMP
- Regulations
- Company management procedures
- On-job training

Training effectiveness was evaluated by:
- Oral questions and answers
- Written exam: open questions and multiple choice questions
- Practical performance

The procedure “Visual inspectors training and qualification” was discussed. According to the SOP visual operators were re-qualified once in two years.

New visual operator’s on-job training consisted of 3 steps.

Eyesight checks were carried out every 6 months by ophthalmologist.

The procedure “QC laboratory analysts training” was discussed. Analyst qualification was performed once per year. Several analysts were performing the same analysis and results were compared.

11. Personal hygiene
Formal procedures were in place governing personal hygiene aspects for staff and visitors entering into the production premises. Training and gowning procedures and qualification were a requirement for staff entering into classified areas including aseptic rooms. During the inspection the gowning procedures appeared to be complied with and no dress code violations noted.
12. Premises and equipment
Exposed surfaces of the production areas were smooth, impervious and unbroken. Changing rooms were
designed as airlocks and used to provide physical separation of the different stages of changing. Changing
rooms were flushed with filtered air. Premises were cleaned and disinfected according to written procedures.
Dedicated manufacturing facility and utilities were in place for bOPV and for YF manufacturing up to sterile
final bulk. The YFV downstream processes including filling and lyophilisation were performed in multiple
product facility on campaign basis. Changeover procedures were implemented.

The manufacturing site for the oral bivalent poliomyelitis (live) Vaccine Type I and Type III (Human
Diploid Cell), 2 mL/vial is located in the third floor of Building 107. The quality control testing to release
the related materials, intermediates and bOPV final products are performed in Building 201 and 205.

- Building 107 dedicated to manufacturing and in-process testing of bOPV. Building 107 included
  separate manufacturing units for cell culturing, virus inoculation, single harvest, monovalent
  preparation, bivalent formulation, filling and capping, packaging, etc.
- The cell culture manufacturing unit (without virus) and the OPV virus production unit (with virus) are
  separated by physical barriers and using separated and dedicated air handling units (AHU) systems and
designed at some extent as a containment facility handling live viral materials and equipped with
decontaminating autoclave for infected materials. Procedures for fumigation of the bio-positive rooms
  by formaldehyde were in place.
- Building 201 is used for microbial, biological, physical/chemical testing for the release of related
  materials and intermediate products of bOPV. The basement is used for storage polio virus seeds,
cells, raw materials and OPV samples. The first floor of the building is used for sterility testing and
decontamination and cleaning, the second floor is used for microbial testing and biological testing.

Finished product storage:
The room 3 for finished product storage at -20°C. This contained cartonned vaccine separated on pallet by
batch. This contained both released material and batches (of bOPV) quarantined awaiting either internal
release of NIFDC release. For bOPV labelling and packaging is done at risk (awaiting results). For YFV it
was indicated that batches are stored unlabelled awaiting internal clearance before packaging.
Released batches indicated by green strap around cartons (at pallet level). Quarantined batches by a yellow
strap, with status of which level of release awaited based on inventory card only.

14. Materials
The reception, sampling, testing, storage and releasing or rejecting of starting materials, packaging
materials, bulk and finished products is performed according to implemented specifications and SOPs.
Controls are in place at receipt, checking, sampling, storage, release, storage of approved materials in
segregated areas (quarantine, approved and rejected) with adequate labelling.

The current seed lot systems for cell substrate and poliovirus seeds (type 1 and 3) were discussed. The
storage locations were visited and the draft SOPs (for cell banks) for the preparation and QC testing of new
seed lots were spot checked. Each of the seed system includes pre-master, master and working seeds. The
QC testing was in line with relevant WHO TRS.
The SOPs for QC testing of calf serum and trypsin were reviewed, and both comply with Eur. Ph.
monographs.
15. Documentation
A provision for documentation management was in place. Master Documents including SOPs, forms, master batch records are maintained in an electronic system with access control.

The following procedures were spot checked. The procedure “Reprocessing” was discussed. Reprocessing was allowed in case of wrong or mistaken labels. The procedure “Time limit for YF process steps” was discussed. The procedure “Returns” was discussed. The procedure “Finished product visual inspection” was discussed. According to the SOP pass rate should be NTL 98%. If the pass rate is less deviation should be initiated and investigated.

16. Good practices in production
In general production operations followed defined procedures. Deviations from procedures were recorded and investigated. Access to production premises was restricted to authorized personnel.

Manufacturing process of bOPV:
Cell expansion and control cells
Cell expansion area was visited and the manufacturing steps were spot checked. There are a total of seven cell expansion steps, and all of which are performed under LAF in Class C background. The cell substrate used for manufacturing bOPV is well characterized cell line and based on seed-lot system. Considering the extensive QC testing of the cell bank, as well as additional downstream testing, the setup of the control cells and the tests performed are considered satisfactory.

Several trains of cell expansions can be performed at the same time to enhance manufacturing capacity.

Gentamicin was only added when preparing the working virus seed. Calf serum is added to cell expansion media, but not viral amplification media.

Multiplicity of infection (MOI)
The procedure indicates that MOI will be re-established for each new virus working seed lot.

Formulation
The addition of the diluent, following the addition of the two antigens, was observed. The operation was performed under LAF within Grade B background. The diluent bottle was wiped with disinfectant before being moved inside the curtain under the LAF.

Time out of refrigerator (TOR)
Filling, inspection, labelling and packaging are performed at room temperature (not more than 25°C). As specified in the procedure, the operation for each of these four steps is completed within 8 hours for each lot (≤ 50,000 vials per lot). The cumulative time out of cold chain is no more than 40 hours, and is supported by the available stability results at 25°C.

The manufacturing date is the date of formulation and filling, as there is no hold time of the final bulk.

Procedures for change from virus type 1 to virus type 3 and vice versa are performed according to the general procedure for clearance and to the procedure for disinfection. Fumigation by formaldehyde is performed for change from type I to III of the manufacturing area where live virus are manipulated and vice versa.
Manufacturing process of YFV:
SPF eggs are routinely monitored for adventitious agents in accordance with WHO recommendations.
One seed storage location was spot checked. It was indicated that seed is also maintained at another company location. Deep freezers for seed storage also had a system to inform the responsible person by SMS when local alarm occurred. There was appropriate control of access, storage and log of material.
Inoculation occurs under a UDAF in a grade C background.
Inoculation is performed manually using a 5mL. There were differences observed in practice of the staff in performing the inoculation. It was indicated that consideration was being given to use an automated system to more consistently deliver the required dose (but no documentation yet available concerning this change).
Eggs are wax sealed following inoculation and transferred to the incubation room.
The simulation of formulation process was viewed. This occurs in grade A with a grade B surround.
The company has indicated a plan to move the final bulk filtration to the filling premises. Connection of the tank to the filling line was via a tube passed from A/B filling suite through a port into grade C with aseptic connectors. There is planned (but not documented) further modifications to pressure differentials at connect room to reduce possible contamination to general facility.
Visual Inspection is currently a manual process. The company indicated that they use an automated system for MMR inspection. It was indicated that if production volume increased the machine could also be set up for checking of YFV, including container integrity.
The area for final packaging in insulated shippers was seen but there were no activities in progress. The shipping validation report was reviewed (dated August 2106). It cited the WHO Guideline as the reference and conducted the test with ambient temperature of 43°C.
The shipping validation study demonstrated compliance with type B criteria (no low temperature requirement and <30°C internal temperature for 48 hours at 43°C ambient temperature). Although the labelled storage temperature for the vaccine is -20°C, there is accelerated stability data at 5°C for 24 months showing no significant loss of potency and shipment is not packed with dry ice but uses cold packs conditioned to -20°C. In fact, temperature was maintained at <8°C throughout the validation study period. This is acceptable.

17. Good practices in quality control
Resources for quality control activities were in place. The testing groups include raw materials testing group, biological testing group, microbiology testing group, sterility testing group, testing groups for each vaccine final product, metrology group and environment monitoring group. The supporting groups include a “Test Control Center” and a “Washing and Deactivation Center”.
The quality control laboratories and activities were spot checked.

Procedures:
The procedure “Materials sampling” was discussed. The scope of the SOP was starting materials and packaging materials. According to the SOP all containers of starting materials were sampled and identity test performed on each individual sample.
The procedure “Purified water (PW) and water for injection (WFI) sampling” and the procedure “YF vaccine process water monitoring” were discussed.
PW and WFI trends from September 2015 - September 2016 for YF production department (building 105) were discussed. Action and alert limits were established based on historical data.
Qualification of media:
All media used for environmental monitoring, water monitoring and QC testing are prepared in house, with the exception of contact surfaces plates purchased from a commercial supplier. In general, the shelf life of media should be based on growth promotion study, the storage condition of the media used during shelf life study should cover the worst case condition used in manufacturing, and the growth promotion should also include in-house isolates. The company has indicated that in-house isolates have been added to growth promotion test since last year.

Contact surfaces plates contain lecithin and tween-80 as neutralizers. The disinfectant used in manufacturing and QC areas are IPA, acid phenolic (pH 1), alkaline phenolic (pH 12.9), and 1% hydrogen peroxide.

The environmental monitoring program:
The procedure for environmental monitoring in Building 107 bOPV was spot checked. The established specifications for non-viable particles at static and dynamic conditions for classified manufacturing areas were according to the current WHO TRS. The alert and the action limits were not based on historical data. Sampling locations were based on RA (FMEA) performed in June 2016.

The environmental results for filling room in Building 107 from January to December 2016 was spot checked. No count was recorded in both grade A and grade B for all microbial samples.

Testing methods:
- Monkey neurovirulence test was discussed and the laboratory was also visited. The reference standards used are the International Standard obtained from NIBSC. The number of animals and the standards used, the tissues examined and the statistical calculations comply with the relevant WHO TRS.
- The potency test (poliovirus titre) was observed, and the SOP was reviewed. The clean cell culture room is surrounded by laboratories handling live virus, and the gowning room is used to enter both cell culture and viral labs. The gowning procedure is cumbersome. The following areas should be improved:
  - Retest policy was discussed, and the deficiency was detailed in Part 3 of the report.
  - The WHO TRS for YFV indicates that labelled virus content should be in IU/dose. The study conducted under aegis of the National Institutes for Food and Drug Control (NIFDC) was reviewed that established the unitage of local standard in IU against the International Reference preparation from the National Institute for Biological Standards and Control (NIBSC). It was noted that the CP 2010 had specification for YFV expressed in pfu/dose and that the later edition of the CP did not include a monograph for YFV. These specifications are currently expressed in IU.

Stability studies for bOPV:
Final product:
The presented stability data support the 24-month storage at -20°C plus additional 6-month at 2-8°C. Given the slight decrease in virus titre at 12-month at 2-8°C, the approval of 12 months storage at 2-8°C may be granted when additional data, e.g. more lots and/or cumulative stability data (lots stored at -20°C for 24 months then stored at 2-8°C for 12 months), are available.
For intermediates:

- Single harvest: It was confirmed that data provided in the PSF were generated using cell factories, and the data support the 6 months hold time at -20°C.
- Monovalent final bulk: The available data was up to 18 months, and the titre remains stable. However, the proposed shelf life is 24 months.
- There was no hold time for monovalent pool or final bulk.

**Stability of YF vaccine:**

Stability data were reviewed.

In conclusion, the limited data set suggests a slightly higher decrease in virus titre for lots manufactured at 30L scale at 2-8°C and 25°C. Nevertheless, the lots from both manufacturing scales are stable at proposed storage temperature of -20°C, and also have the potential for additional storage time at higher temperatures.

**PART 3: 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, Beijing Bio-Institute Biological Products Co., Ltd. (BBIBP) 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 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.