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20, AVENUE APPIA – CH-1211 GENEVA 27 – SWITZERLAND – TEL CENTRAL +41 22 791 2111 – FAX CENTRAL +41 22 791 3111 – WWW.WHO.INT

Prequalification Team Inspection Services
WHO PUBLIC INSPECTION REPORT
(WHOPIR)
Vaccine manufacturer

Part 1	**General information**
Manufacturers details	
Company information	
Name of manufacturer	**Beijing Institute of Biological Products (BIBP) Co., Ltd.**
Corporate address of manufacturer	No. 6 (East Part) and No. 9 (West Part), Boxing 2nd Road, Beijing Economic and Technological Development Area, Beijing, the People's Republic of China, 100176
Inspected site	
Address of inspected manufacturing site if different from that given above	The same as above. Latitude and longitude of the manufacturing facility: 39.89642931344263, 116.4276408097534 North latitude (N): 39°53′47.15″ East longitude (E): 116°25′39.51″
Inspection details	
Dates of inspection	31 October to 3 November 2022
Type of inspection	Routine GMP inspection
Introduction	
Brief summary of the manufacturing activities	BIBP currently has about 10 vaccines being manufactured in E-town site, mainly including COVID-19 Vaccine (Vero Cell), Inactivated; Poliomyelitis Vaccine (Vero Cell), Inactivated, Sabin Strains (sIPV); Poliomyelitis (Live) Vaccine Type I and Type III (Human Diploid Cell), Oral (bOPV) and Yellow Fever Vaccine, Live (YF).
General information about the company and site	BIBP is a state-owned listed company for high technologies, involved in research, manufacturing and marketing of biological products such as vaccines and diagnostic kits. The current site of BIBP 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.
History	The WHO PQ had inspected the BIBP in 2017 for bOPV and in 2021 for Inactivated COVID-19 (EUL) and sIPV vaccines.
Brief report of inspection activities undertaken	
Scope and limitations	
Areas inspected	• Building 107: bOPV bulks, formulation, filling, and packaging and sIPV bulks and formulation area.

	• Building 103: filling of sIPV, packaging and labelling. • Building 201: QC labs. • Building 103: Warehouse
Restrictions	Not applicable
Out of scope	The inspection was limited to bOPV and sIPV vaccines and to WHO PQ approved facilities and did not include any other vaccine or other activity.
Vaccines covered by the inspection	• Poliomyelitis Vaccine (Vero Cell), Inactivated, Sabin Strains (sIPV) • Poliomyelitis (Live) Vaccine Type I and Type III (Human Diploid Cell), Oral (bOPV)

Abbreviations

AHU	Air Handling Unit
ALCOA	Attributable, Legible, Contemporaneous, Original and Accurate
APR	Annual Product Review
APS	Aseptic Process Simulation
BMR	Batch Manufacturing Record
bOPV	Bivalent Oral Polio Vaccine
BPR	Batch Production Record
CA	Compressed Air
CAPA	Corrective Actions and Preventive Actions
CC	Change Control
CFU	Colony-Forming Unit
CIP	Cleaning In Place
CoA	Certificate of Analysis
CpK	Process capability
CPV	Continued Process Verification
CQA	Critical Quality Attribute
DQ	Design Qualification
EDI	Electronic DeIonization
EM	Environmental Monitoring
FMEA	Failure Modes and Effects Analysis
FTA	Fault Tree Analysis
GMP	Good Manufacturing Practices
GPT	Growth Promotion Test
HEPA	High Efficiency Particulate Air
HVAC	Heating, Ventilation and Air Conditioning
IQ	Installation Qualification
LAF	Laminar Air Flow
LIMS	Laboratory Information Management System
LSP	Lot Summary Protocol
MB	Microbiology
MBL	Microbiology Laboratory
MF	Master Formulae
MFT	Media Fill Test
MR	Management Review

MR	Measles vaccine
NCA	National Control Authority
NCL	National Control Laboratory
NRA	National Regulatory Agency
OOE	Out of Expectation
OOS	Out of Specification
OOT	Out of Trend
OQ	Operational Qualification
PHA	Process Hazard Analysis
pH	(negative) logarithm of H^+ concentration
PLC	Programmable Logic Controller
PM	Preventive Maintenance
PQ	Performance Qualification
PQR	Product Quality Review
PQS	Pharmaceutical Quality System
PW	Purified Water
QA	Quality Assurance
QC	Quality Control
QCL	Quality Control Laboratory
QMS	Quality Management System
QRM	Quality Risk Management
RA	Risk Assessment
RCA	Root Cause Analysis
RO	Reverse Osmosis
SIP	Sterilization In Place
sIPV	Sabin Inactivated Poliovirus Vaccine
SMF	Site Master File
SOP	Standard Operating Procedure
UN	United Nations
UNICEF	United Nations Children's Fund
URS	User Requirements Specifications
UV	Ultraviolet-Visible Spectrophotometer
VVM	Vaccine Vial Monitor
WFI	Water for Injection
WHO	World Health Organization

Part 2	Summary of the findings and comments

1. Pharmaceutical quality system (PQS)

A pharmaceutical quality system (PQS) was established and documented, covering the essential GMP principles and procedures for the site. The PQS covered the important elements that could have an impact on pharmaceutical products, including organization and personnel, premises and facilities, equipment, materials and products, qualifications and validations, documentation management, production management, quality control and quality assurance, distribution, self-inspections and recalls.

The deficiencies raised in this section have been adequately addressed, and will be verified during future PQ inspections.

Management review (MR):

The SOP for quality management system review was presented, as well as the last MR minutes. The review included the PQS assessment, external inspections, client audits, key performance indicators, compliance assessment, CAPA effectiveness, resource including knowledge management. The MRs were carried out at least once per year. In general, the procedure appeared to be adequate.

Product quality reviews (PQR):

The PQR reports for bOPV and sIPV were spot-checked.

The deficiencies raised in this section have been adequately addressed, and will be verified during future PQ inspections.

Quality risk management (QRM):

The risk assessment and control procedure was discussed. The procedure was prepared in accordance with ICH Q9 and applied to all departments covering all aspects of quality. A process flowchart was part of the procedure and a cross-functional team was responsible for risk assessment using both a proactive and reactive approach. Various tools were described and detailed in the procedure. In general, the procedure appeared to be adequate. A typed summary of the risk assessments performed in 2022 was provided and some risk assessments were spot-checked during the inspection.

Contamination control strategy (CCS):

The company had in place a CCS by product. The CCS for sIPV bulk and vaccine were presented however they were not reviewed in detail during this inspection.

Deviation management:

An SOP for Deviation was in place. Deviations were categorized as critical, major, minor, or incidents. Periodical review reports of deviations were prepared every quarter. Some deviation records were spot-checked during the inspection.

Change control:
A change control procedure was in place. The changes were classified as general and major, which were further divided into temporary changes (that will be limited by time or production batches due to some reason and changed back to the original state after specified time or completion of production batches) and permanent changes (changes that will be implemented for a long time after approval). The major changes were further categorized as changes involving registration and not involving registration documents. The impact/risk assessment was performed on proposed changes before acceptance/rejection. The procedure described how changes were tracked. In general, the procedure appeared to be adequate. Some change control records were spot-checked.

CAPA management:
A SOP for Corrective Actions and Preventive Actions (CAPA) was in place. The SOP was referenced to various QMS elements such as CAPA raised due to management review meeting, internal audit, external audit, deviations, annual product quality review, risk assessments, OOS/OOE, trend analysis, adverse reaction/complaints, recall and other works. The process flow chart for CAPA was part of the procedure. Quarterly review was performed by the QMS administrator. In general, the procedure appeared adequate. Some of the CAPAs were reviewed as part of the deviations, complaints and change control procedures.

Complaints:
The product complaints management procedure was in place. The complaints for finish products were classified into 3 different types based on defects: Major quality complaint, quality complaint and invalid quality complaint. The overseas complaint process was established. Sinopharm International sale personnel was responsible for receiving and reporting abroad quality complaint information and was responsible for following up or participating in on-site investigation and feedback to customers. The procedure stated according to customer demands, the quality investigation report/explanatory statement should be provided within 30 working days after receiving the quality complaint, a phased quality investigation report should be provided if it was postponed.
The Complaint List for 2021 and 2022 was spot checked. There was no complaint related to PQ vaccines in 2021. Some investigation records were reviewed.

Product recalls:
The management procedure for product recall was in place. The SOP applies to all products sold by the company (including domestic and international markets). According to the severity of drug safety hazards, the recall was classified as follows:

- Level I recall: the use of the drug may cause serious health hazards.
- Level II recall: the use of the drug may cause temporary or reversible health hazards.
- Level III recall: the use of the drug generally will not cause health damage, but the drug is required to be recalled due to other reasons.

The company stated that there has been no batch recall of vaccines for this site in the last 5 years. Provisions for mock recall were in place.

Self-inspection:
Self-inspection management procedure was discussed. A self-inspection master plan for 2022 was available. The self-inspections were performed at least once a year. The internal auditor's related skills and knowledge were defined.

Quality audits and suppliers' audits and approval:
Supplier management including qualification and disqualification, vendor audit and monitoring were reviewed and discussed.

Contract production, analysis, other activities, and Quality agreement:
It was stated by the company that no production activities are outsourced for the sIPV and bOPV for purposes of the PQ.
The Contract laboratory management procedure was reviewed. The contract analysis laboratories were divided into high, medium, and low risks based on the risk assessment. Some audit reports and quality agreements were spot-checked.

Personnel:
Approximately 1640 full-time staff were working at the time of inspection, including 43 employees in QA, 160 employees in QC, more than 900 employees in production and workshop, and more than 40 employees in the Warehouse. Personnel met during the inspection appeared to have knowledge of GMP principles and showed that they received initial and ongoing training.
The Company's Organizational Chart showing relationships between different areas including Quality Assurance, production and Quality Control were reviewed. There was a clear separation between the quality control and production departments. Job descriptions of personnel were available, and some job descriptions were spot-checked.

Training:
The GMP Training Management procedure was reviewed. The training was divided into Orientation training, Induction training, Job-transfer training, and Ongoing training. It was specified that re-training and testing were necessary for personnel on extended vacation/absence for more than 6 months. Training was required for newly issued or revised SOPs. Training was categorized as: face to face training, discussion, self-learning, and online learning.

Qualification of aseptic operators in Grade B:
According to Management procedures for aseptic operator training, qualification requirement for Grade A/B, need to execute 3 successful gowning tests. The frequency for aseptic operator qualification is annual. Media fill test specified that all aseptic operators (including EM QC and maintenance personnel) in filling room must join and pass MFT every 6 months at least. A list of qualified aseptic operators was provided, including name, expiry date, position, qualified area, effective date of MFT.

Visual inspectors' qualification:
Management procedures for Visual inspector qualification were in place. According to the training and examination, the visual inspector should be granted the visual inspection certification of corresponding similar products. Some visual inspectors' training and qualification records were spot-checked

Personal hygiene:
The SOP for Personnel Health and Hygiene Management was spot checked. A walk-through during the inspection verified that appropriate signs were in place that instructed personnel to wash their hands and overall to wear clothing appropriate to their duties.

Documentation:
The documentation system was controlled by QA department. In general, documentation was designed, prepared, reviewed and distributed according to a documented procedure. Approved, signed, and dated testing procedures and specifications were available for starting and packaging materials and for finished products.

Batch numbering system:
A Batch numbering system was in place and discussed. Batch manufacturing records (BMRs) were retained for each batch processed.

Batch Release Process:
This was not inspected in detail during this inspection. A general procedure describes the procedures and responsibilities for batch release.

Lot Summary Protocol (LSP)
This was not inspected in detail during this inspection, however LSP was in place.

2. Production system

In general terms, 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. 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 in place. Operators were instructed to carry out procedures, and records were made for the production operations.

3. Facilities and equipment system

Access to production premises was restricted to authorized personnel. Overall, dedicated facilities were in place for manufacturing drug substances. Cell banks and Seed lots were stored in qualified equipment with adequate temperature monitoring and inventory system. The premises were generally maintained at an acceptable level of cleanliness. The company had provisions for personal hygiene and sanitation in its production facility. Manufacturing areas were provided with airlocks for personnel and materials entries and exits. Gowning procedures for access to the classified manufacturing areas were in place. A difference of 15 Pa between rooms of different grade is maintained. 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.

Qualification and validation:
Procedures 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. The general policy and strategy for the validation and qualification was defined in the VMP. Some qualification and validation protocols and reports were spot-checked.

4. Laboratory control system

The QC function was independent from other departments. Adequate resources were available to ensure that the QC arrangements were carried out. 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. QC personnel had access to production areas for sampling and investigations as appropriate. Some QC test results were spot-checked.

Physico-chemical:
The Physico-chemical lab（including sample receiving and distribution was visited during the inspection, and it was found clean and in good order, with necessary analytical equipment.

Microbiology:
Micro labs for bioburden and water testing and for sterility test were visited. EM samples were incubated in incubators located in each workshop.

Management of OOS test results:
A procedure for OOS, OOT and OOE handling was in place. The list of OOS for 2022 was presented.

Trending:
Trend Analysis was in place. According to the VMP, the continued process verification (CPV) of the critical quality attributes (CQAs) should be trended in the APQR.

Qualification and use of reference standard:
Reference standard management procedure was in place. There were two types of reference standards, purchased and self-made. The reference standard management procedure indexed several standards calibration and quality control documents.

Analytical methods and their validation:
Analytical method validation SOP was in place, it basically followed ICH Q2.

Stability:
Stability SOP was presented. The cumulative hold time (maximum intermediate hold times) is considered as well as the maximum TOR. Stability studies for bOPV were spot-checked.

Environmental monitoring results:
The trend report for bOPV Workshop from January 2022 to September 2022 was reviewed. The sampling locations were based on a risk assessment. Recovery studies were performed for the validation of exposure time for settle plates.

Water test results:
The bOPV Workshop Water and Pure Steam Systems trend report from January 2022 to September 2022 was reviewed. Pure Steam is tested for non-condensable gases, superheat, and dryness fraction on critical points in a defined frequency.

5. Materials, packaging, and labelling system

The Management Procedure for Sampling specified that all excipients of WHO PQ vaccine must be tested for ID on every container.
During this inspection, the warehouse was visited on-site and showed in order.
The packaging and labeling workshop was visited, including the 2-8℃ cold storage room, visual inspection room, reject product temporary storage room, packaging material temporary storage room, including refrigerators for VVM label storage, and packaging line. There was no packaging and visual inspection operation during inspection, the equipment and facilities on-site were in good condition.

6. International shipping

This section was not inspected in detail during this inspection.

Part 3	Conclusion – Inspection outcome

Based on the areas inspected, the people met and the documents reviewed, and considering the findings of the inspection, including the observations listed in the Inspection Report, **Beijing Institute of Biological Products (BIBP) Co. Ltd.** located at **No. 6 (East Part) and No. 9 (West Part), Boxing 2nd Road, Beijing Economic and Technological Development Area, Beijing, the People's Republic of China** was considered to be operating at an acceptable level of compliance with WHO GMP Guidelines.

All the non-compliances observed during the inspection that were listed in the full report as well as those reflected in the WHOPIR, were addressed by the manufacturer, to a satisfactory level, prior to the publication of the WHOPIR.

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

Part 4	List of WHO Guidelines referenced in the inspection report

1. WHO good manufacturing practices for pharmaceutical products: main principles. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-eighth Report Geneva, World Health Organization, 2014 (WHO Technical Report Series, No. 986), Annex 2. ***Short name: WHO TRS No. 986, Annex 2***

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

3. WHO guidelines for sampling of pharmaceutical products and related materials. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-ninth Report. Geneva, World Health Organization, 2005 (WHO Technical Report Series, No. 929), Annex 4. ***Short name: WHO TRS No. 929, Annex 4***

4. Supplementary guidelines on good manufacturing practices: validation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fortieth Report. Geneva, World Health Organization, 2006 (WHO Technical Report Series, No. 937), Annex 4. ***Short name: WHO TRS No. 937, Annex 4***

5. General guidelines for the establishment maintenance and distribution of chemical reference substances. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-first Report Geneva, World Health Organization 2007 (WHO Technical Report Series, No.943) Annex 3. ***Short name: WHO TRS No. 943, Annex 3***

6. WHO Good Practices for Pharmaceutical Quality Control Laboratories. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957, Annex 1.
   Short name: WHO TRS No. 957, Annex 1

7. WHO Good Practices for Pharmaceutical Products Containing Hazardous Substances. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957), Annex 3.
   Short name: WHO TRS No. 957, Annex 3

8. WHO good manufacturing practices for sterile pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 6.
   Short name: WHO TRS No. 961, Annex 6

9. WHO guidelines on transfer of technology in pharmaceutical manufacturing WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 7. ***Short name: WHO TRS No. 961, Annex 7***

10. Model guidance for the storage and transport of time-and temperature-sensitive pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 9. ***Short name: WHO TRS No. 961, Annex***

11. WHO good practices for pharmaceutical microbiology laboratories. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 2. ***Short name: WHO TRS No. 961, Annex 2***

12. WHO guidelines for drafting a site master file. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 14. ***Short name: WHO TRS No. 961, Annex 14***

13. WHO guidelines on quality risk management. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-seventh Report Geneva, World Health Organization, 2013 (WHO Technical Report Series, No. 981), Annex 2. ***Short name: WHO TRS No. 981, Annex 2***

14. WHO guidelines on variation to a prequalified product. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-seventh Report Geneva, World Health Organization, 2013 (WHO Technical Report Series, No. 981), Annex 3. ***Short name: WHO TRS No. 981, Annex 3***

15. WHO General guidance on hold-time studies WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 4. ***Short name: WHO TRS No. 992, Annex 4***

16. WHO Technical supplements to Model Guidance for storage and transport of time – and temperature – sensitive pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 5. ***Short name: WHO TRS No. 992, Annex 5***

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

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

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

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

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

22. WHO Recommendations, Guidelines and other documents related to the manufacture, quality control and evaluation of biological products. WHO Expert Committee on Biological Standardization. Seventy-first Report. Geneva, World Health Organization, 2021 (WHO Technical Report Series, No. 1028), Annex 1. ***Short name: WHO TRS 1028, Annex 1***

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

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

25. WHO good manufacturing practices: water for pharmaceutical use. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fifth Report. Geneva, World Health Organization, 2021 (WHO Technical Report Series, No. 1033), Annex 3. ***Short name: WHO TRS 1033, Annex 3***

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