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Prequalification Team Inspection services
WHO PUBLIC INSPECTION REPORT
(WHOPIR)
Finished Product Manufacturer

Part 1	**General information**
Manufacturers details	
Name of manufacturer	Zhejiang Jiangbei Pharmaceutical Co., Ltd.
Corporate address of manufacturer	Dongdai Zhang'an Street, Jiaojiang District, Taizhou City, 318017, Zhejiang Province, The People's Republic of China
Inspected site	
Name & address of inspected manufacturing site if different from that given above	Same as above
Synthetic unit /Block/ Workshop	FPP workshop, Building 37
Inspection details	
Dates of inspection	9 to 11 September 2019
Type of inspection	Follow up inspection
Introduction	
Brief description of the manufacturing activities	Production and quality control of FPP, API and API intermediates.
General information about the company and site	Zhejiang Jiangbei Pharmaceutical Co., Ltd. is a privately-owned company founded in 1993 as Jiangbei Chemical Factory. In 2004 the site was established as Zhejiang Jiangbei Pharmaceutical Co., Ltd. The site has workshops for both API and FPP operations. There were approximately 420 staff employed at the time of inspection. The company produces several FPPs products including Efavirenz tables. The Efavirenz tablet is not currently registered with Chinese NMPA. APIs and intermediate are also produced at the site. No toxic or hazardous substances such as antibiotics, hormones or cytostatics are manufactured on the site.

History	This was the second WHO inspection for FPP. The first one was conducted 26 to 29 November 2018. Two earlier WHO inspections for API were conducted in May 2016 and August 2018. The site had also been inspected by the UK MHRA in September 2018 for a non-WHO PQ tablet.
Brief report of inspection activities undertaken – Scope and limitations	
Areas inspected	• CAPA review • Pharmaceutical quality management system • FPP production system Building 37 • Laboratory quality control management system
Restrictions	This follow up inspection mainly focus on verification of the CAPA implementation.
Out of scope	The inspection was performed for the operations relevant to the tablet production supporting the PQ programme. Although the company had facilities for other solid dosage forms, these were not inspected.
WHO APIs covered by the inspection	Efavirenz Film coated tablets 600mg (HA700)
Abbreviations	**Meaning**
AHU	Air handling unit
ALCOA	Attributable, legible, contemporaneous, original and accurate
API	Active pharmaceutical ingredient
APR	Annual product review
BMR	Batch manufacturing record
BPR	Batch production record
CC	Change control
CIP	Cleaning in place
CoA	Certificate of analysis
CpK	Process capability
DQ	Design qualification
EDI	Electronic deionization
EM	Environmental monitoring
FMEA	Failure modes and effects analysis
FPP	Finished pharmaceutical product
FTA	Fault tree analysis
GMP	Good manufacturing practices
HEPA	High efficiency particulate air
HPLC	High performance liquid chromatography (or high performance liquid chromatography equipment)
HVAC	Heating, ventilation and air conditioning
IQ	Installation qualification
KF	Karl Fisher
LAF	Laminar air flow

LIMS	Laboratory information management system
MB	Microbiology
MBL	Microbiology laboratory
MR	Management review
NC	Non conformity
NRA	National regulatory agency
OQ	Operational qualification
PHA	Process hazard analysis
PLC	Programmable logic controller
PM	Preventive maintenance
PQ	Performance qualification
PQR	Product quality review
PQS	Pharmaceutical quality system
PW	Purified water
QA	Quality assurance
QC	Quality control
QCL	Quality control laboratory
QMS	Quality management system
QRM	Quality risk management
RA	Risk assessment
RCA	Root cause analysis
RO	Reverse osmosis
SMF	Site master file
SOP	Standard operating procedure
URS	User requirements specifications
UV	Ultraviolet-visible spectrophotometer

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

1. Pharmaceutical quality system

A system of quality assurance was established, with procedures covering the key quality elements being in place. The procedures that were reviewed and discussed during the inspection were generally acceptable. Operations were specified in written form in SOPs and the master batch manufacturing record. Product and processes were generally monitored appropriately.

Product quality review

Annual product quality review was performed according to a documented procedure.
APQR of Efavirenz coated tablets 600 mg for year 2018 was reviewed. As commercial manufacturing has not been started for the PQ FPP, inspected data was limited and consisted of the review of the production and the stability data of validation batches. The CAPA made to the observation made in last inspection was reviewed and found acceptable.

Quality risk management

Risk assessment for introduction of new product into the FPP production block was reviewed. The revision to address the risk assessment, implementation action plan and cleaning validation protocol & report were closed.

The CAPAs to the deficiencies regarding the material transfer after dispensing in the production area was checked and found acceptable.

Change control

Change control procedure and change evaluation form have been updated. The company reviewed the changes according to the updated SOP. The inspection team verified change records and found in compliance with SOP with the action plan reviewed completed. CAPA accepted and closed.

Deviation

A deviation record in response to the previous inspection observation addressing the cleaning of tablet coating machine was revised. The CAPAs regarding updating cleaning procedure and other equipment as well as cleaning records were revised and found accepted.

CAPA management

CAPA management procedure as part of quality system was in place. The CAPAs to the deficiencies made in last inspection were in detailed reviewed with the review comments documented.

OOS investigation

OOS/OOT investigation procedures, OOS log books of 2018 and 2019 and several OOSs were reviewed. CAPAs to OOS/OOT investigation were inadequate in certain aspects. Non-compliances observed during the inspection that was listed in the full report regarding OOS were addressed by the manufacturer to a satisfactory level.

2. Good manufacturing practices for pharmaceutical products

Good manufacturing practices were generally implemented. Necessary human and physical resources were provided, including sufficient qualified and trained personnel, adequate premises, suitable equipment and services, appropriate materials, containers, approved procedures and instructions, laboratories and equipment for in-process and other controls, for the current operational level of FPP activity. Product was released by the authorized persons.

The product within this inspection scope had been developed and then was transferred to the site by an external institute. The company has established its own small R and D department for FPP to facilitate the process development and troubleshooting since last inspection.

Product block was visited. The secondary packaging of Efavirenz tablets 600mg was in operation at the time of inspection. Some deficiencies were noted. They have been addressed by the manufacturer in CAPAs to a satisfactory level.

3. Sanitation and hygiene

FPP workshop in Building 37 was completed in 2014. Premises and equipment were maintained at a satisfactory level of cleanliness at the time of inspection. Personal hygiene and sanitation in production facility, with appropriate hand washing facilities appeared satisfactory.

Personnel were seen to be performing their duties in an organized manner. No gowning violations in production were noted during the periods of inspection.

4. Qualification and validation

The company approach to validation was explained in the Validation Mater Plan (VMP).

Process validation

A supplement Process validation report for Efavirenz tablets 600mg and BMRs of PV batches were reviewed. Process validation protocol for Efavirenz Tablets 600mg was revised with respect to the raised deficiencies in the last inspection and found accepted. Risk assessment in process validation protocol for Efavirenz Tablets 600mg to the process and production was revised and found acceptable.

CAPAs to process validation and qualification packaging process were inspected. A secondary packaging machine for Efavirenz 600 mg tablets was newly installed and IQ, OQ & PQ reports were available and reviewed. While inspection of packaging line, some deficiencies were noted. Additional CAPAs regarding the secondary packaging operation have been addressed by the manufacturer at a satisfactory level.

Cleaning validation

Cleaning validation protocol and report for Efavirenz Tablets 600mg were reviewed and found updated. Non-compliances observed during the inspection that was listed in the full report regarding cleaning validation were addressed by the manufacturer to a satisfactory level.

Risk Assessment for tools, equipment in direct contact with Efavirenz Tablets and related method of sampling after cleaning was reviewed which included sampling using swab & rinse method. CAPA was accepted and closed.

Cleaning validation protocol and report for equipment used in manufacturing Efavirenz Tablets were reviewed and found acceptable.

5. Complaints

A written complaints management procedure was in place. The product complaint procedure mentioned the possibility of a complaint triggered recall. This was not checked in detail during the inspection.

Return management

A returned products disposal procedure was reviewed and found updated in response to the previous inspection observation to include testing for retuned products on request by QA, checking supply chain condition for retuned products and introducing a return product batch numbering management procedure. CAPA closed.

6. Product recalls

A drug recall management Procedure was revised and to include the consideration of an international recall and notifying the drug regulatory authority i.e. FDA, WHO, MHRA etc. of the importing products. CAPA closed. There had been no recall for the products in the inspection scope as commercial batches are not yet available.

7. Contract production, analysis and other activities

Production for the FPP in the inspection scope was not contracted out.

QC testing of HDPE bottle and cap were contract out to an external laboratory. This was not verified during this inspection.

8. Self-inspection, quality audits and suppliers' audits and approval

Self-inspection

A self-inspection plan and SOP was in place. They were not inspected during this inspection.

Suppliers' audits

The WHO grade Efavirenz API manufactured in house was inspected by WHO in 2018 and has been qualified by PQ programme.

9. Personnel

The manufacturer had an adequate number of personnel with the necessary qualifications and practical experience. Personnel interviewed during the inspection in general were aware of the principles of GMP.

An organization chart was available and reviewed. Job descriptions of FPP Director, FPP QA manger and FPP QA personnel were reviewed. Deficiencies observed during the inspection that was listed in the full report regarding the company organogram were addressed by the manufacturer to a satisfactory level.

10. Training

Training systems and procedures were in place. Training records and job descriptions of production and FPP validation personnel were verified. Deficiencies were noted and have been addressed by the manufacturer to a satisfactory level.

11. Personal hygiene

Smoking, eating, drinking, chewing, and keeping plants, food, drink and personal medicines was prohibited in production, laboratory and storage areas. No violations were noted during the inspection.

12. Premises

The OSD FPP production within the inspection scope was in Building 37. This is a multi-floor building including tablet and capsule production lines as well as packaging facilities.

The facility is generally well designed and well-ordered with a high degree of containment systems in place. The CAPAs to the observations made during the previous inspection were checked and satisfactory.

13. Equipment

Equipment installed in building 37 was multi-purpose and each piece of equipment had a unique identification number. Logbooks were kept.

There are two production lines for tablets, one small and one large capacity; and reserved one production line for capsulate in the FPP production block. Efavirenz tablets PV was performed with the equipment line of small capacity.

During inspection of production line, the compress machine and coating machine used in the Efavirenz tablets PV was checked.

14. Materials

Excipients, raw material, packaging material for drug product were stored in a warehouse on the ground floor in Building 37; finished drug products were stored in a warehouse in a different building. Material was managed by a manual system with bin cards and issuance logs.

A material management procedure and a starting material distribution procedure were reviewed. Incoming materials and finished products were quarantined after receipt until released for use or distribution.

15. Documentation

The documentation system was paper based and controlled by QA department. The company documents were categorized into different types including API procedure and FPP procedure respectively. The documentation was managed at acceptable level. The following documents were reviewed:

- An SOP on batch number management
- An SOP on review and release for finished products
- A finished product release form and check record for finished product release
- An SOP on test record management and a batch testing record review form
- An SOP on molds management and a record for punch and dies check
- Efavirenz 600mg updated master BMRs and BMRs of the PV batches.
- A batch packaging record was spot checked during inspecting of the new installed packaging line

Non-compliances observed during the inspection that was listed in the full report regarding documents were addressed by the manufacturer to a satisfactory level.

16. Good practices in production

The manufacturing processes were performed and recorded according to instructions in the batch manufacturing records. The production line layout and flow of personnel and material was complying with GMP. Production equipment logbooks for production and cleaning were kept in place and were checked during inspection.

The packaging equipment line was established following the previous inspection. At the time of inspection, the production of the FPPs in the inspection scope was not in operation except secondary packaging.

The IPC testing (e.g. friability, leak test, weight) was performed in the IPC laboratory located within the processing area, were spot checked and found acceptable. The observations related to the previous inspection for pressure gauges, windows in corridors and curtains were checked. CAPA closed.

17. Good practices in quality control

QC laboratory was in a separate building and was visited. The QC function was independent of other departments. QC laboratories including microbiological laboratory were separated from production areas. The Microbiology Laboratory was segregated from the Chemistry Laboratory.

Sufficient space had been allocated to avoid mix ups and cross-contamination. Adequate storage space was provided for samples, reference standards, solvents, reagents and records. Sample receiving, and distribution procedure and registers were in place.

Retention and retained samples were kept in a secured and temperature-controlled room. CAPA has been implemented for the sample's appearance check of the Efavirenz tablets.

Stability chamber room was visited. Stability study protocol for Efavirenz tablets were in place and the samples of Efavirenz tablets under stored at 30^0C/RH75%. The stability study register was available and checked. A deviation for power failure was reviewed and discussed. CAPA closed.

The reference substance used in QC and log book were checked. The validity of primary Efavirenz RS was checked regularly. The working reference substance was recharacterized according to a specified time period.

HPLC, GC and IR were networked. The CAPAs to the finished product testing and data management procedure were checked. The following documents were reviewed.

- An SOP on data integrity management system
- An SOP on QC computer management
- An analytical revalidation report of Efavirenz tablets 600mg
- CAPA to IR data security.

The above procedures were updated and appeared acceptable. Non-compliances observed during the inspection that was listed in the full report regarding stability study were addressed by the manufacturer to a satisfactory level.

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, ***Zhejiang Jiangbei Pharmaceutical Co., Ltd.***, located at ***Dongdai Zhang'an Street, Jiaojiang District, Taizhou City, 318017, Zhejiang, 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 GMP 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***
   http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_986/en/
2. WHO good manufacturing practices for active pharmaceutical ingredients. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957), Annex 2. ***Short name: WHO GMP for APIs*** or ***TRS No. 957, Annex 2***
   http://www.who.int/medicines/publications/44threport/en/
3. WHO good manufacturing practices: water for pharmaceutical use. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fourth-sixth Report. Geneva, World Health Organization, 2012 (WHO Technical Report Series, No. 970), Annex 2
   Short name: WHO TRS No. 970, Annex 2
   http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_970/en/
4. 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
   http://whqlibdoc.who.int/trs/WHO_TRS_929_eng.pdf?ua=1

5. Guidelines on heating, ventilation and air-conditioning systems for non-sterile 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 8. **Short name: WHO TRS No. 1010, Annex 8**
   http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_1010/en/

6. 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
   http://whqlibdoc.who.int/trs/WHO_TRS_937_eng.pdf?ua=1

7. 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 GPPQCL Guidelines or ***TRS No. 957, Annex 1***
   http://www.who.int/medicines/publications/44threport/en/

8. 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 2
   Short name: WHO TRS No. 957, Annex 2
   http://www.who.int/medicines/publications/44threport/en/

9. 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
   http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

10. 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
    http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

11. 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 9***
    http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

12. 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***
http://whqlibdoc.who.int/trs/WHO_TRS_943_eng.pdf?ua=1

13. 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
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

14. 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***
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_981/en/

15. 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***
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_981/en/

16. 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***
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

17. WHO Guidelines on good manufacturing practices: validation, Appendix 7: non-sterile process validation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 3. ***Short name: WHO TRS No. 992, Annex 3***
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

18. 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***
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

19. 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***
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

20. WHO Recommendations for quality requirements when plant – derived artemisin is used as a starting material in the production of antimalarial active pharmaceutical ingredients. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 6
Short name: WHO TRS No. 992, Annex 6
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

21. Guidance on good data and record management practices. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fiftieth Report Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 5
Short name: WHO GDRMP or ***WHO TRS No. 996, Annex 5***
http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex05.pdf

22. 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 TRS No. 996, Annex 10
http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex10.pdf

23. 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
http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex10.pdf