World Health Organization

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
WHO PUBLIC INSPECTION REPORT
(WHOPIR)
Active Pharmaceutical Ingredient Manufacturer

Part 1	**General information**
Manufacturers details	
Company information	
Name of manufacturer	Shangyu Jingxin Pharmaceutical Co., Ltd.
Corporate address of manufacturer	No.31, Weisan Road, Hangzhou Bay Shangyu Economic and Technological Development Area, Zhejiang Province, P.R. China.
Inspected site	
Address of inspected manufacturing site if different from that given above	No.31, Weisan Road, Hangzhou Bay Shangyu Economic and Technological Development Area, Zhejiang Province, P.R. China. Post code : 312369 GPS coordinates : 30°09'37 N ; 120°45'55 E D-U-N-S No.: 527982528
Unit / block / workshop number	Workshop 515, 518
Manufacturing license number	Zhe 20050427 Scope: APIs
Inspection details	
Dates of inspection	21 - 24 January 2019
Type of inspection	Routine re-inspection
Introduction	
Brief summary of the manufacturing activities	Production, quality control of APIs
General information about the company and site	Shangyu Jingxin Pharmaceutical Co., Ltd. was founded in December 2004 and is wholly owned by Zhejiang Jingxin Pharmaceutical Co., Ltd. It is a stock market listed company. Zhejiang Jingxin Pharmaceutical Co., Ltd. has five manufacturing sites in different locations for dosage form, APIs, intermediates and traditional Chinese medicines respectively. No penicillin or cephalosporin APIs were manufactured on the site.

History	This was the third WHO GMP inspection at this site. The Levofloxacin API facilities have previously been inspected by the WHO Prequalification of Medicines Programme in August 2014 and August 2015. The site had been inspected by EDQM in March 2015. However, the inspection scope in terms of facilities and the APIs for CEPs were different from this inspection.
Brief report of inspection activities undertaken	
Scope and limitations	
Areas inspected	• Pharmaceutical Quality System • Documentation system • Warehouses: solid and liquid raw materials finished APIs, packaging materials. • Workshop 515 Production of intermediate • Workshop 518 Production including finishing and packaging • QC Laboratory: Chemical and Physical Lab
Restrictions	Other products and/or processes outside of WHO pre-qualification were not inspected during this inspection.
Out of scope	The scope of the inspection was restricted to the API in the WHO PQ programme.
WHO product numbers covered by the inspection	APIMF 245 Levofloxacin hemihydrate (used for non-sterile FPP)

Abbreviations

AHU	air handling unit
ALCOA	attributable, legible, contemporaneous, original and accurate
API	active pharmaceutical ingredient
APQR	annual product quality review
BDL	below detection limit
BMR	batch manufacturing record
BPR	batch packaging record
CAPA	corrective actions and preventive actions
CC	change control
CFU	colony-forming unit
CoA	certificate of analysis
CpK	process capability index
DQ	design qualification
EM	environmental monitoring
FAT	factory acceptance test
FBD	fluid bed dryer
FMEA	failure modes and effects analysis
FPP	finished pharmaceutical product
FTA	fault tree analysis
FTIR	Fourier transform infrared spectrometer

GC	gas chromatograph
GMP	good manufacturing practice
HACCP	hazard analysis and critical control points
HPLC	high-performance liquid chromatograph
HVAC	heating, ventilation and air conditioning
IR	infrared spectrophotometer
IQ	installation qualification
KF	Karl Fisher
LAF	laminar air flow
LIMS	laboratory information management system
LoD	limit of detection
LOD	loss on drying
MB	microbiology
MBL	microbiology laboratory
MF	master formulae
MR	management review
NMR	nuclear magnetic resonance spectroscopy
NRA	national regulatory agency
OQ	operational qualification
PHA	process hazard analysis
PM	preventive maintenance
PpK	process performance index
PQ	performance qualification
PQR	product quality review
PQS	pharmaceutical quality system
QA	quality assurance
QC	quality control
QCL	quality control laboratory
QRM	quality risk management
RA	risk assessment
RCA	root cause analysis
SOP	standard operating procedure
TAMC	total aerobic microbial count
TFC	total fungi count
TLC	thin layer chromatography
URS	user requirements specifications
UV	ultraviolet-visible spectrophotometer

Part 2	Brief summary of the findings and comments

1. Quality management

A formal documented system for quality assurance was established, with procedures covering key quality elements being in place. Operations were specified in written form and critical GMP requirements were essentially being met. Regular monitoring and reviews of the quality of pharmaceutical APIs and intermediates were being conducted according to documented procedures. The Quality Department was divided into QA and QC units, which were separate to the production department. The procedures that were reviewed and discussed during the inspection were generally of an acceptable standard. Non-compliances observed during the inspection that was listed in the full report regarding the job responsibility of vice General manager/QP and the risk of conflict of interest between the quality and operations units were addressed by the manufacturer to an acceptable level.

Product quality review (PQR)

PQR was performed according to an SOP. The 2017 and 2018 PQRs for Levofloxacin hemihydrate were reviewed. The 2016 PQR for Levofloxacin hemihydrate was also spot checked. There were several grades of Levofloxacin API all manufactured by a single synthesis process.

Several of the listed OOS/OOTs, complaints, changes and deviations in 2017 and 2018 PQRs were checked. No batches had been recalled since the last WHO inspection.

Starting from 2018, WS511 was also used to produce Levofloxacin API. The company stated that the WHO grade with code DK25 was only manufactured in WS515 for intermediates and WS518 for finished API.

Quality risk management

Quality risk was managed according to an SOP. Risk assessment report for Levofloxacin and the Levofloxacin potential genotoxic impurity assessment report were briefly checked. These were generally acceptable. Whilst there was evidence of risk assessments being performed in certain cases, the overall approach, consistency and overall extent of assessments need further enhancement before the programme could be mature and comprehensive. The deficiency was addressed in the CAPA by the manufacturer to an acceptable level.

Product release

Finished API product release procedure was available and reviewed. Deficiencies was noted. See observation below in Part 3.

Deviation Management

Deviation management following a written procedure were documented, explained and investigated. A major deviation regarding for an unqualified operator operated in the final purification step was reviewed. No observation was made.

2. Personnel

Personnel qualifications

There were an adequate number of personnel who were suitably qualified through qualifications, experience and training. Job description and responsibilities of DGM for quality were reviewed and discussed.

Personnel hygiene

Personnel were required to wear protective clothing suitable for the type and stage of manufacturing. Suitable sanitation and change room facilities were provided. Smoking and eating was not permitted in manufacturing areas.

3. Buildings and facilities

Design and construction

Buildings and facilities used in the manufacture of the API were dedicated to the Levofloxacin APIs. Levofloxacin carboxylic acid was manufactured in Workshop 515. Levofloxacin Hemihydrate, Levofloxacin HCl and Levofloxacin lactate were manufactured in the workshop 518 where final crystallization, centrifuging, drying and packaging took place in the classified Grade D clean area.

Manufacturing areas were generally designed, and constructed to facilitate cleaning, maintenance and operations as appropriate to the type and stage of API manufacture.

Water

Purified water (PW) was produced by a double RO system. Distribution was through a SS loop at ambient temperature. Monthly sanitization was performed by pasteurization. Conductivity, pH and return flow rate were monitored on-line. Endotoxin was not tested for PW although that Levofloxacin API could also be used for injectable FPP. WHO assessment team has raised a discussion of endotoxin testing of the Levofloxacin hemihydrate API in dossier assessment.

Containment

Levofloxacin API was manufactured in dedicated facilities.

Lighting

Lighting in all areas visited was acceptable.

4. Process equipment

Design and construction

Equipment used for the APIs within the scope of the inspection was generally of a good standard and suitable for their intended use. The equipment for manufacturing Levofloxacin hemihydrate was dedicated.

Equipment maintenance and cleaning

Equipment maintenance and cleaning were performed according written procedures. Equipment maintenance SOP regarding the inspection of glass line reactors was reviewed and discussed.

Computerized systems

Computerized systems were not used for material or production control of Levofloxacin API.

A computerized system was used in QC lab with HPLC and GC equipment being networked. Basic data integrity controls were in place.

5. Documentation and records

Documents were originated and managed according to written procedures. Activities were documented in SOPs and other appropriate documents such as specifications, protocols and batch manufacturing records (BMRs). These were all approved, and version controlled. All records and other documentation requested during the inspection were readily available.

Batch production record and batch testing records were kept and available. They were reviewed, and results were considered during batch release. The approved master formula of the Levofloxacin Hemihydrate were available, comprehensive and reflected dossier requirements. The BMRs in process during the inspection and reflected the stage of production that was on-going at the time the completed BMRs reviewed were generally acceptable.

6. Materials management

General controls

Written procedures describing the receipt, identification, quarantine, storage, handling, sampling, testing and approval or rejection of materials were available. All materials in warehouse were managed manually.

Warehouses for solid starting materials, liquid tank farm and finished API products were visited. They were managed according to written procedure and generally in good order, with the exception of the warehouse for wastes and recoverable materials for sale to third parties. One of these areas was also being used for materials storage for sister company. These operations were outside the site QMS and were not managed to appropriate GMP standards. Non-compliances observed during the inspection that was listed in the full report regarding material management and warehousing were addressed by the manufacturer to an acceptable level.

Sampling and testing of incoming production materials

Materials were sampled by QC following documented sampling procedures before release. The tank farm for solvents delivered by trucks was inspected and it was noted that the hoses for connecting truck and tank were dedicated. The hoses of the tank vehicle were not used. Acceptable documented procedures and controls were in place for handling deliveries and the subsequent batch number changes.

Supplier approval

A supplier management SOP was reviewed. Quality agreement with an ethanol supplier and the audit report were reviewed and found acceptable.

7. Production and in-process controls

Production operations for levofloxacin APIs were carried out in two workshops (WS) - 515 and 518. Production was in operation in both WS515 and WS518 at the time of inspection. Starting from crystallization step the production operations were carried out in classified rooms (class D). Non-compliances observed during the inspection that was listed in the full report regarding Production and packaging operations were addressed by the manufacturer to a satisfactory level.

8. Packaging and identification labelling of APIs and intermediates

Final API packaging and labelling were not in operation at the time of inspection.

The packaging and labelling operations were inspected. Label control, labelling and line clearance was reviewed and discussed. Improvements need to be made in the several aspects of these operations where a number of basic GMP failings were noted. Non-compliances observed during the inspection that was listed in the full report were addressed by the manufacturer to a satisfactory level.

9. Storage and distribution

Warehousing procedures

Finished APIs were stored in a designated warehouse and held until released by an authorized person. This warehouse was well ordered and clean and tidy. A manual bin card system was used to control stock. The company has two different kinds of drum labelling approaches.

Distribution procedures

APIs were released for distribution following release by the Quality department.

Non-compliances observed during the inspection that was listed in the full report regarding Finished API labelling and release operations were addressed by the manufacturer to an acceptable level.

10. Laboratory controls

Sample receiving and distribution

Sample receiving procedures and corresponding registers were available for inspection. They were reviewed and discussed. Non-compliances observed during the inspection that was listed in the full report regarding sample release and distribution procedure were addressed by the manufacturer to a satisfactory level.

Testing of intermediates and APIs

QC testing was conducted as specified in the relevant specifications and according to documented testing methods.

Acceptable reference standards(RS) management procedures were in place. Secondary working reference standard (WRS) were prepared against the primary reference standards. Each vial of the secondary WRS of Levofloxacin was one-time use.

Reserve/retention samples

There was a designated temperature-controlled area for storage of retention samples inside of a warehouse. Access to this area was restricted to approved personnel. Sufficient samples of each batch of API manufactured were kept. Retention samples were stored in a container system that were comprised of the same materials as those used for the final API.

Handling of out of specification (OOS) results

OOS/OOT was managed according to an SOP. The procedure, OOS flow chart and two examples were reviewed and found acceptable.

Stability monitoring of APIs

A range of stability chambers were available. Stability monitoring programme and samples of the relevant WHO batches were checked. Non-compliances observed during the inspection that was listed in the full report regarding stability study were addressed by the manufacturer to an acceptable level.

Data management

The company was operating networked HPLC and GC equipment using Open Lab software. Basic system and data integrity controls were in place.

11. Validation

Validation and qualification were performed according to written procedures. A change control to process validation had been made since last WHO inspection to separate different quality grades of Levofloxacin hemihydrate. The relevant validation protocol and report were reviewed. Material hold time studies were spot checked, and satisfactory.

12. Change control

Change Control (CC) was managed according to an SOP and classified into critical, medium and minor, as well as permanent or temporary change. The CC log book was in excel sheets. Several change controls were reviewed. Non-compliances observed during the inspection that was listed in the full report regarding change control were addressed by the manufacturer to an acceptable level.

13. Rejection and re-use of materials

Reprocessing

Reprocessing was managed according to an SOP. A log book for reprocessed batches was available and reviewed. It was noted that a Levofloxacin batch was reprocessed because of “other single unknown impurity” was OOS. The investigation performed was reviewed and found acceptable.

Reworking

Reworking was not allowed by the company procedure.

Recovery of materials and solvents

Recovery was performed according to written procedures. There were several recovered materials from several steps of the Levofloxacin process stages.

Solvent recovery is performed within the specific synthesis process with appropriate specifications set where performed. These systems remained the same as in the last inspection.

14. Complaints and recalls

The company has procedures to manage complaints and recalls. A customer complaint regarding batch number error on the label of Levofloxacin API was reviewed. Non-compliances observed during the inspection that was listed in the full report regarding the finished API labelling operation were addressed by the manufacturer to a satisfactory level.

15. Contract manufacturers (including laboratories)

There was no contract manufacturing of Levofloxacin API or key starting materials. External contract laboratory testing was used for limited number of specialist analytical procedures using qualified specified laboratories.

PART 3

Conclusion

Based on the areas inspected, the people met and the documents reviewed, and considering the findings of the inspection, including the deficiencies listed in the Inspection Report, as well as corrective actions taken and planned. APIMF 245 Levofloxacin hemihydrate (used for non-sterile FPP) manufactured at Shangyu Jingxin Pharmaceutical Co., Ltd. located at No 31, Weisan Road, Zhejiang Hangzhou Bay Shangyu Industrial Area, Shangyu City, Zhejiang Province, P.R. China-312369 was manufactured in compliance with WHO GMP for Active Pharmaceutical Ingredients.

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

2. 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/
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. WHO guidelines on good manufacturing practices for heating, ventilation and air-conditioning systems for non-sterile pharmaceutical dosage forms. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 1010), Annex 8
   Short name: WHO TRS No. 1010, Annex 8 Annex 8, TRS 1010.
   http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

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 TRS No. 961, 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 prosecution 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. WHO good manufacturing practices for biological products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fiftieth Report Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 3
Short name: WHO TRS No. 996, Annex 3
http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex03.pdf

22. 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 TRS No. 996, Annex 5
http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex05.pdf

23. 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

24. WHO good manufacturing practices for biological products. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fiftieth Report* Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 3
Short name: WHO TRS No. 996, Annex 3
http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex03.pdf