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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	Hisun Pharmaceutical (Hangzhou) Co., Ltd.
Corporate address of manufacturer	46 Waisha Road, Jiaojiang District, Taizhou City, Zhejiang Province, 318000, The People´s Republic of China
Inspected site	
Name & address of inspected manufacturing site if different from that given above	Xialian Village, Xukou Town, Fuyang District, Hangzhou City, Zhejiang Province, 311404, P. R. of China
Unit / block / workshop number	Building C06, Line 5
Inspection details	
Dates of inspection	02-06 September 2019
Type of inspection	Routine inspection
Introduction	
Brief description of the manufacturing activities	Production and quality control of APIs and FPPs including sterile injections.
General information about the company and site	Hisun Pharmaceutical (Hangzhou) Co. Ltd. is a 100% subsidiary of Zhejiang Hisun Pharmaceutical Co., Ltd and is in Fuyang District, Hangzhou City, Zhejiang Province, South Eastern China. Two other pharmaceutical companies, i.e. Hanhui Pharmaceutical Co., Ltd (Joint Venture) and Hisun Biopharmaceutical Co., Ltd, are performing manufacturing activities at the same. Approximately 1613 employees are employed at the Hisun Hangzhou site. The site included production of API for human and veterinary use, OSD, lyophilized powder for injection, biological products and Dietary supplements. An antineoplastic FPP product including Penam API and FPP were manufactured on site. Capreomycin lyophilized powder for injections under WHO PQ programme, were manufactured on production line 5 in Building C06. This line was non-dedicated with various other products also produced on the line.

	Supply of prequalified Capreomycin sulfate for injection commenced early 2016.
History	This was the 5th WHO inspection with the previous inspection conducted in August 2017. The site has also been inspected by the USFDA, April 2019 and is regularly inspected by the Chinese authorities.
Brief report of inspection activities undertaken – Scope and limitations	
Areas inspected	• Pharmaceutical quality system • Documentation system • FPP production system of Line 5 • Facilities and equipment System • Laboratory control system
Restrictions	Nil
Out of scope	Products not submitted to WHO for prequalification
WHO products covered by the inspection	Capreomycin Sulfate 1g /vial (lyophilized powder for injection) [TB261]
Abbreviations	**Meaning**
AHU	Air handling unit
ALCOA	Attributable, legible, contemporaneous, original and accurate
API	Active pharmaceutical ingredient
APR	Annual product review
APS	Aseptic process simulation
BMR	Batch manufacturing record
BPR	Batch production record
CC	Change control
CFU	Colony-forming unit
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
GPT	Growth promotion test
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
LAF	Laminar air flow

LIMS	Laboratory information management system
MB	Microbiology
MBL	Microbiology laboratory
MF	Master formulae
MFT	Media fill Test
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
SIP	Sterilization in place
SMF	Site master file
SOP	Standard operating procedure
URS	User requirements specifications
UV	Ultraviolet-visible spectrophotometer
WFI	Water for injection

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

1. Pharmaceutical quality system

A system for quality assurance was established, with policies & procedures covering key quality elements supporting investigations of complaints, deviations and OOS/OOT's. Root causes were identified, and corrective and preventative actions are taken. It also reviews, approves, notifies and follows up all change controls to ensure the change is scientifically justified, and the risk assessment was well conducted. Control on materials, calibrations, and validations are performed adequately with internal audits conducted as per a predefined plan.

Quality risk management

A quality risk management (QRM) process was available, with product cross contamination risk assessments documented. Management procedure of new product introduction was in place. A risk assessment plan for new product introduction was assessed and found acceptable.

Annual product quality review (APQR)

An APQR procedure was reviewed and found acceptable. The APQR of Capreomycin Sulfate 1g /vial for 2018 was prepared as per the procedure and available. It included all batches manufactured during 2018 and reviewed all CPPs & CQAs. No recall or complaint was recorded during 2018.

APQR conducted during 2017 was reviewed. No return or recall for WHO grade Capreomycin injections was recorded. Packaging process validation and cleaning validation were performed during 2017.

Change control (CC) management

Change control was managed according to a written procedure. Several CCs including withdrawal of Kanamycin 500 mg, 1000gm from WHO PQ programme, CCs of CoA of starting material, alarm system, lyophilizer's pump and microbiological testing method of media etc. were reviewed during the inspection and found acceptable.

Deviation management

Several deviations including filter's prefiltration integrity test, deviation of air pressure during vial unloading and vial transferring etc. were reviewed and discussed. Non-compliances observed during the inspection that was listed in the full report on deviation and CAPA management have been addressed by the manufacturer satisfactory.

2. Good manufacturing practices for pharmaceutical products

Good manufacturing practices were generally implemented and followed. Required staff and system resources were provided. Manufacturing processes were clearly defined and documented. Qualification and validation were performed.

3. Sanitation and hygiene

In general, the premises and equipment were maintained at an acceptable level of cleanliness. The company had a standard operating procedure as the basis for its approach to personal hygiene and sanitation in its production facility.

Clean areas were cleaned frequently in accordance with approved written procedures. Rotation of disinfectants in clean areas was established. Environmental monitoring of microbial status was regularly undertaken. Disinfectants used in Grade A and B areas were sterilized before use.

4. Qualification and validation

Process validation

Aseptic processes on Line 5 were required to be re-validated by media fill every 6 months. Updated process validation protocol & report of Capreomycin sulfate 1g vial, and media fill protocol and report in workshop line 5 were reviewed.

The following documents were reviewed and found acceptable:

- Revalidation protocol & report for cold storage in C06 storage room.
- Tunnel revalidation protocol and report of line 5.
- Revalidation protocol & report of an autoclave in line 5.
- Revalidation of SIP vacuum freeze dryer of injection workshop line 5.
- A holding time study for Capreomycin sulfate starting material after package opened.
- Trend analysis of EM data for 2018 of line 5.
- Trend analysis of WFI for 2018 of line 5 and sampling plan for PW/WFI in 2019.

Cleaning validation

Cleaning validation was performed according to an SOP. The following documents reviewed.

- Cleaning validation: protocol with three cleaning validation batches.
- Management procedures for clean area temporarily shut down and resume of production.

5. Complaints

A procedure for complaints handling was in place. No complaints were received during 2019.

6. Product recalls

A procedure for product recall was in place with three levels of actions according to risk. A protocol and report of a mock recall for Capreomycin sulfate 1g for a proposed defect were available and found acceptable.

7. Contract production, analysis and other activities

According to the company, there was no use of external scientific, analytical or other technical assistance in relation to the products in the inspection scope.

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

A GMP internal audit management procedure was revised and updated to include a GMP checklist, GMP internal auditor qualifications, self-inspection plan template & modified inspection report template.

The 2018 annual self-inspection plan for injection was revised to include two internal inspections on production line 5.

9. Personnel

During inspection of warehouse, some deficiencies were noted regarding the use of monitoring system of cold rooms. Training records of warehouse manager and warehouse supervisor were reviewed. Non-compliances observed during the inspection that was listed in the full report were addressed by the manufacturer to a satisfactory level.

10. Training

Training management system and annual training plan for 2019 was revised and training planned and records on cross contamination for QA & QC were checked and found acceptable.

11. Personal hygiene

Personnel were required to undergo initial health examination by the local hospital and this was repeated periodically at a frequency determined by the type of work environment. This had not changed since the last inspection.

Changing and washing before entry production areas followed a written procedure. Direct contact was avoided between the operator's hands and starting materials, primary packaging materials and intermediate or bulk product. The protective clothing washing and sterilization operations followed standard operating procedures. Sterile garment washing operations were validated. Extensive hand washing was required of visitors as they entered the various areas.

12. Premises

Manufacturing areas were of a good standard and suitable for the activities conducted therein. Exposed surfaces were smooth, impervious and unbroken to minimize the shedding or accumulation of particles or microorganisms and permitted the repeated application of cleaning agents and disinfectants.

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. The final stage of the changing room was at-rest state, the same grade as the area into which it leads. Changing rooms were equipped with mirrors. Airlock doors did not open simultaneously.

Storage areas were of sufficient capacity. Receiving and dispatch bays were separated and protected materials and products from the weather. Segregation was provided for the storage of rejected, recalled or returned materials or products.

QC laboratories were separated from production areas. Adequate storage space was provided for samples, reference standards, solvents, reagents and records. Separate air-handling units were provided for microbiological laboratories.

13. Equipment

Production line 5 was generally properly equipped and maintained, logbooks were kept in place.
The Preventive maintenance report for the sterilizing tunnel on line 5 was reviewed. Preventive maintenance reports for PW system and pure steam and WFI were revised and found acceptable. Operation procedure of power failure in injection workshop was revised and found acceptable.

14. Materials

Materials were managed via a SAP system. An SAP system management procedure was available for review. A unique material code was assigned to each material.

An SOP for receipt and storage of production and packaging raw material was available. APIs Capreomycin sulfate concentrate solution was supplied by Zhejiang Hisun Pharmaceutical Co., Ltd. located in Taizhou. Quality specification of Capreomycin sulfate concentrate issued in 2019 was revised and included storage conditions which was reviewed during the inspection. Non-compliances observed during the inspection that was listed in the full report regarding the material management were addressed by the manufacturer satisfactory.

15. Documentation

Documentation was designed, prepared, reviewed and distributed according to a documented procedure. Authorized master formulae were available for Capreomycin sulfate injections. Batch manufacturing records (BMRs) were retained for each batch processed. Batch manufacturing & packaging records of Capreomycin sulfate 1g /vial were checked and found detailed and acceptable.

Approved, signed and dated testing procedures and specifications were available for starting material, packaging materials and finished products.

16. Good practices in production

Production Line 5 was not dedicated to Capreomycin injection. Several products were manufactured on Line 5 on a campaign basis. Procedures for cross contamination control were in place.

At the time of inspection, the line was in operation. The filling machine set up was observed. The packaging line, visual inspection and in-process control laboratory were visited. Bulk Capreomycin sulfate solutions were filtered through sterile filters into a previously sterilized container. The integrity test of the sterilizing filters was reviewed and discussed.

Clean areas for the manufacture of sterile products were classified according to the required characteristics of the environment. Clean rooms were routinely monitored while in operation. An SOP on environmental monitoring in clean room class A on line 5 was reviewed. Appropriate alert and action limits were set for the results of particulate with microbiological monitoring conducted.

The production line layout and flow of personnel and material is complying with GMP requirement. Production equipment logbooks for production and cleaning were kept in place and were checked during the inspection.

An operating procedure in case of power failure in the injections workshop was reviewed. Some deficiencies regarding the production and environment control that was listed in the full report were addressed by the manufacturer satisfactory.

17. Good practices in quality control

The QC laboratory was briefly inspected. The personnel, premises, and equipment in the laboratory were generally found appropriate.

A sample receiving and handling procedure for testing was verified. Sterile injection samples were required to be taken at beginning, middle and end. The results of the analysis were traceable to reference substances, equipment and instruments used for analysis. The QC procedures, test methods and records were spot checked. The following documents were reviewed and found acceptable:

- Specifications of Capreomycin sulfate bulk solution and the finished product.
- SOP on sterility test method for Capreomycin sulfate injection
- Investigation procedure of OOS/OOT testing results.
- OOS investigation of insoluble particulate testing of rubber stopper.

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, ***Hisun Pharmaceutical (Hangzhou) Co., Ltd.*** located ***at Xialian Village, Xukou Town, Fuyang District, Hangzhou City, Zhejiang Province, 311404, P. R. 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***
   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