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

Part 1	**General information**
Manufacturers details	
Company information	
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	
Address of inspected manufacturing site if different from that given above	Xialian Village, Xukou Town, Fuyang City Hangzhou City, Zhejiang Province, 311404, P. R. of China
Unit / block / workshop number	Building C06, Line 5
Manufacturing license number, (delete if not applicable)	ZHE20000291
Inspection details	
Dates of inspection	31 July to 3 August 2017
Type of inspection	*Follow up inspection*
Introduction	
Brief summary of the manufacturing activities	Production and Quality Control of API and FPP
General information about the company and site	Hisun Pharmaceutical (Hangzhou) Co., Ltd. is a 100% subsidiary of Zhejiang Hisun Pharmaceutical Co., Ltd. and is located in Fuyang, Hangzhou City, Zhejiang Province, in South Eastern China. Approximately 2100 employees are employed at the site. The site manufactures API and finished product for human and veterinary use, OSD, solution for injection, lyophilized powder for injection and biological products. The

	site also housed a Hisun/Pfizer joint venture facility. The site supports a wide range of multinational pharmaceutical customers. Antineoplastic FPP product and Penem API and FPP were manufactured on site. Capreomycin and Kanamycin powder for injection, under consideration by WHO, were manufactured on production line 5 in Building C06. This line was non-dedicated with up to 7 different products manufactured on the line. Supply of prequalified Capreomycin Sulphate Injection commenced in early 2016.
History	This was the 4th WHO inspection with the last being in October 2016. The site has also been inspected by the USFDA (October 2016) and is regularly inspected by the CFDA.
Brief report of inspection activities undertaken	
Scope and limitations	
Areas inspected	Production and QC laboratories including: • Product starting material, Packaging components, product intermediates and finished product warehouses. • Production facilities in Building C06, particularly Line 5. • QC facilities including Analytical Chemistry Laboratories in building C02
Restrictions	Nil
Out of scope	Products not submitted to WHO for Prequalification
WHO product numbers covered by the inspection	Capreomycin Sulfate 1 g , Powder for injection (TB261) Kanamycin Acid Sulfate 500m g, Powder for injection (TB300) Kanamycin Acid Sulfate 1 g, Powder for injection (TB 301)

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. Pharmaceutical quality system

A system for quality assurance in general was established, with procedures covering key quality elements. The quality system was managed individually for FPP, API and Biologicals respectively and was not harmonized on the site. The procedures for quality system and CAPAs to the deficiencies made in the last inspection were reviewed. The system ensured that as examples:

- Production and quality control operations were generally specified in approved documentation.
- Controls on materials, calibrations, and validations were performed acceptably.
- Internal Audits appraised the effectiveness and applicability of the QA system.
- A Quality Risk Management (QRM) process was generally available, with product cross contamination risk assessments documented.
- Product Quality Reviews within the scope of the inspection were conducted and appeared generally comprehensive and were generated in a timely manner.

Product quality review PQR
Product Quality Reviews (PQR), within the scope of the inspection, were conducted for the year 2016. SOP on Annual Product Review Procedure was available. Trend analysis was performed on critical process parameters, test results of intermediates and finished products, batch size and yield. The PQR for Capreomycin Sulfate for Injection 1g, was available. The PQRs were generally comprehensive and were generated in a timely manner.

Quality risk management
Risk management procedure and Management procedure of new product introduction procedures were reviewed. The risk assessment report for cross contamination risk with an API production block next to the Building C06 was reviewed and generally acceptable.

Quality management review
Quality management review procedure was available for review. Management review was performed quarterly. Annual review in 2016 and OOS review for the second quarter of 2017 were reviewed and discussed.

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

Aseptic processes on Line 5 were required to be re-validated by media fill every 6 months. The documented procedure for this was reviewed and found to be detailed and satisfactory. The last media fill was performed in November 2016. The media fill report for Injection Workshop Line 5 was available. The study was performed using vials with a specified size with sterile media. The results of the media fill study met the acceptance criteria and the line was appropriately qualified.

Two new products had been introduced onto line 5 since the last inspection as per the company SMF. The change control regarding a new product manufacturing in the production line 5 was reviewed. Cleaning validation management procedure and the cleaning validation data were reviewed.

Revalidation for HEPA filter leakage verify in Line 5 was reviewed and acceptable.

5. Complaints

Complaints were handled according to a documented procedure and a risk-based classification of complaints was in place. The QA department was responsible for management of complaints. Provision was made for consideration of the possible effect of systematic problems that may be carried through and affect other products, as well as, the possible effect of the complaint on previous or subsequent batches. A sample of 2016 complaint records was reviewed and they were generally satisfactory.

6. Product recalls

The product recall procedure for the overseas market has not been changed since last inspection. There had been no recalls for injectable products manufactured on line 5 since last inspection.

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

GMP internal audit management procedure, was available and described that inspections were performed at least twice per year. Internal auditors were required to have at least 5 years of quality or production experience and were qualified in terms of the formal internal auditor qualification process. The inspection plan for 2017 was available. The last inspection was performed in May 2017 and the inspection report was available. CAPA progress and efficacy was managed by QA.

A system of supplier approval was in place and followed a documented procedure. This has not been changed since last inspection.

9. Personnel

Personnel generally appeared aware of the principles of GMP and received initial and continuing training, including hygiene instructions, relevant to their needs. Steps were taken to prevent unauthorized people from entering production, storage and QC areas. An organization chart was available. Job responsibilities were recorded in written job descriptions. In response to the findings from the last inspection the company recruited a Corporate Senior Vice President for QA and a site QA manager.

10. Training

Training was provided in accordance with a written programme for all personnel whose duties take them into manufacturing areas or into control laboratories. Newly recruited personnel received training appropriate to the duties assigned to them. Approved training programmes were available. Training records were filed appropriately. Training records for a sample of personnel in the validation team were reviewed and appeared generally satisfactory.

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 been changed since the last inspection.

Changing and washing before entry to the 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, where used.

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 in the 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.

HEPA filters for Grade A areas were required to be leak and integrity tested every 6 months. The SOP and record of the last test for Line 5 were reviewed and generally found satisfactory.

13. Equipment

The equipment installed was of a high standard and supplied by well known, industry recognized EU and US manufacturers. The facility was well designed and appeared to operate effectively.

The manufacturing/compounding vessel and filter system were equipped with automated CIP and SIP systems. These systems had been suitably validated.

The Filling line was designed using Restricted Access Barrier System (RABs) principles and the Lyophilisers were automatically loaded and unloaded. All fixed pipe-work was clearly labeled to indicate the contents and the direction of flow. Production equipment was cleaned on a scheduled basis.

A new secondary packaging line has been procured and installed since the last WHO inspection as an implementation of corrective actions. Equipment qualification was reviewed and was acceptable.

Laboratory equipment and instruments were suited to the testing procedures undertaken.

14. Materials

APIs, Capreomycin Sulphate concentrate solution and Kanamycin Sulphate non-sterile, were supplied by Hisun Pharma, Taizhou site. Starting materials in the storage area were appropriately labelled.

Packaging materials were purchased from approved suppliers. Vials and Rubber stoppers were stored in separate rooms. Printed packaging materials were stored in secure conditions.

Finished products were held in quarantine until their final release, and stored under appropriate and monitored conditions. Several batches of WHO grade Capreomycin Sulfate injection 1 g were stored in the warehouse at the time of inspection.

Rejected materials and products were marked as such and stored in designated secure areas. Recalled products and returned goods were required to be stored separately in designated secure areas.

A SAP system was used for material management. SAP system materials and products release operating procedure was reviewed. Deficiencies observed during the inspection that was listed in the full report regarding SAP management were addressed by the manufacturer to a satisfactory level.

15. Documentation

In general, documentation was designed, prepared, reviewed and distributed according to a documented procedure. Non-compliances observed during the inspection that was listed in the full report regarding testing record management in QC laboratory were addressed by the manufacturer to a satisfactory level.

Authorized master formulae were available for both Capreomycin and Kanamycin Sulphate injections. Batch manufacturing records (BMRs) were retained for each batch processed. A batch number of product management procedure was checked and considered acceptable.

BMRs and BPRs were retained for each batch processed. Line clearance and equipment status was confirmed and recorded before processing began. BMRs and BPRs of Capreomycin 1 g, as an example, were reviewed and observed to be generally satisfactory.

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

16. Good practices in production

Clean areas for the manufacture of sterile products were classified according to the required characteristics of the environment. Clean rooms and clean-air devices were routinely monitored while in operation. For Grade A and B zones, particle monitoring was undertaken for the full duration of critical processing, including equipment assembly. To control the microbiological cleanliness of Grades A–D in operation, the clean areas were monitored using settle plates, airborne plates and surface plates. Appropriate alert and action limits were set for the results of particulate and microbiological monitoring were available.

Bulk Capreomycin and Kanamycin Sulphate solutions were filtered through sterile filters into a previously sterilized container for filling. The handling of sterile components and filling of aseptically prepared products was performed with a Grade A environment.

The implementation of CAPAs in response to the last inspection was reviewed in relation to the Autoclave operating procedure and its loading pattern. Smoke test in the Grade A area with existence of the stainless steel box was also reviewed.

During the time of the inspection, it was confirmed that it was permitted to fill another product on the same production line while a different product was in the lyophilizer. Deficiencies observed during the inspection that was listed in the full report regarding the line clearance and segregation were addressed by the manufacturer to a satisfactory level.

PART 3
Conclusion

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 City, Hangzhou City, Zhejiang Province, 311404, P. R. of China,** was considered to be operating at an acceptable level of compliance with WHO good manufacturing practices for pharmaceutical products.

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

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.
   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.
   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
   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
   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, 2011 (WHO Technical Report Series, No. 961), Annex 5
   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
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
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
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
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
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
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
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
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
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
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
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
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
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
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
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
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
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
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
http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex03.pdf