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Prequalification Team
WHO PUBLIC INSPECTION REPORT
(WHOPIR)
Active Pharmaceutical Ingredient Manufacturer

Part 1	**General information**
Manufacturers Details	
Company information	
Name of manufacturer	Zhejiang Hisun Pharmaceutical Co., Ltd.
Corporate address of manufacturer	46 Waisha Road, Jiaojiang District Taizhou City, Zhejiang Province People´s Republic of China Postal code: 318000
Inspected site	
Address of inspected manufacturing site if different from that given above	Yantou Campus 56, Binhai Road, Jiaojiang District Taizhou City, Zhejiang Province People´s Republic of China Postal code: 318000 Waisha Campus 46 Waisha Road, Jiaojiang District Taizhou City, Zhejiang Province People´s Republic of China Postal code: 318000
Unit / block / workshop number	Yantou Campus : Y10, Y11, Y31, Y22, Y28, Y55, Y66 and Y58
Manufacturing license number	ZHE 20000291
Inspection details	
Dates of inspection	7 - 12 December 2017
Type of inspection	Follow up inspection

Introduction	
Brief summary of the manufacturing activities	Production and quality control of APIs and FPPs.
General information about the company and site	Zhejiang Hisun Pharmaceutical Co., Ltd. (hereinafter Hisun) was founded in 1956; the company was listed on the Shanghai A Share Stock Exchange in 2000. Hisun produces a wide range of products: active pharmaceutical ingredients (antineoplastic, anti-parasite, antibiotics, cardiovascular, endocrine regulation, immunosuppressant and antidepressant drugs), and finished products including injectable preparations, tablets, hard capsules, granules and suspension preparations. Hisun is licensed by the Zhejiang Provincial FDA and inspected regularly by the provincial inspection authorities. A pharmaceutical production license has been issued by Zhejiang Provincial FDA. Licensing covers both pharmaceutical APIs and FPP.
History	The company has been regularly inspected by WHO and other regulatory agencies. The site was inspected by USFDA in August 2017, Health Canada and TGA. Australia in May 2017. This inspection from WHO is a follow up inspection to follow-up on the corrective action and non-compliant outcome to the joint inspection performed by WHO PQT together with the Spanish and Danish inspectorates in May 2016.
Brief report of inspection activities undertaken	
Scope and limitations	
Areas inspected	• Quality management system • CAPAs and changes made since last inspection • Validations including cleaning validation, process validation, analytical method validation • Data management • Production Blocks Y31, Y22, Y28 QC laboratories
Restrictions	The scope of the inspection was restricted to the APIs in the WHO PQ programme.

WHO product numbers covered by the inspection	APIMF169 Capreomycin Sulfate Concentrate APIMF257 Kanamycin Acid Sulfate APIMF238 Moxifloxacin Monohydrochloride APIMF252 Linezolid APIMF262 Cycloserine

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 (where applicable)**

Brief summary of the findings and comments

1. Quality management

A system for quality assurance was established, with procedures covering the key quality elements of WHO GMP in place. These procedures were reviewed and discussed during the inspection. Managerial responsibilities were specified in written job-descriptions. Operations were specified in written form. Product and processes were monitored, and the results taken into account during batch release; regular monitoring and reviews of the quality of pharmaceutical products were being conducted according to documented schedules and procedures.

The procedures reviewed were generally adequately designed and operated. Areas, such as the processes for management review, were considered to require enhancement and these areas for improvement are documented in the following discussion and were fully listed in the observations section of the confidential inspection report to the company. The matters raised were satisfactorily addressed in the CAPA provided by the company.

QC operations have been established and had recently been consolidated into a new multistory laboratory block on the Waisha campus. The QC lab is operated under a common set of general management procedures and systems but with respective heads of the individual groups responsible for different testing activities, e.g. the API and FPP testing labs located on different floors. The groups were similarly equipped and operated the same core procedures, sample and data management systems and software. There were some common areas, e.g. microbiology operations where the one group served both API and FPP operations. This consolidation of operations into a single laboratory complex is expected to assist in further harmonization between the different product streams which were previously operating over several sites and previously exhibited some site differences in the detailed procedures followed.

This inspection spent a significant proportion of the available inspection time on the review of the implementation and effectiveness of the CAPAs to the critical and major deficiencies made in the previous joint inspection with other EU agencies in 2016. In general, CAPAs provided and reviewed were acceptable and adequately addressed the key aspects of the points raised in the last inspection. Some areas were discussed including those of management review, quality risk management, OOS trend analysis and review which should be further enhanced. During this inspection, the key quality system processes were reviewed with examples chosen from both API and FPP operations particularly where there was a common corporate procedure. In this respect, the report reflects the overall findings on these systems and not only the specific observation illustrating an issue from either the API or FPP process stream. In these areas, the company was expected to report its responses and CAPA holistically and not to restrict them to the specific observation in either the API or FPP area alone. This was that the company has done, and progress was considered generally satisfactory

Product quality review

Annual product quality review was performed according to a documented procedure. The 2016 PQR for Capreomycin Sulfate concentrate solution was reviewed and considered to be generally acceptable. Two product complaints in the PQR were investigated and discussed.

Quality Risk Management

The company's procedure on "Quality risk management" was reviewed. This SOP discussed a risk assessment tool similar to failure modes and effects analysis (FMEA). There were a number of documented assessments in place. Non-compliances observed during the inspection that was listed in the full report regarding risk assessments procedure and practice were addressed by the manufacturer to a satisfactory level.

Whilst the company's overall approach to QRM and to aspects of root cause analysis, e.g. in the management of investigations and risk assessments, has improved over the period since the last inspection, there still remained some examples of inconsistency and weakness in the robustness of QRM implementation. In some of the cases reviewed, records lacked adequate detail either in the detailed documentation of the work performed or in its analysis and review. In some other cases, the detail and/or depth of the assessments performed was inadequate.. In its CAPA the company committed to sustaining its continuing efforts improve the overall consistency of the robustness of its processes and records.

CAPA management
CAPA was managed according to a SOP. The CAPAs to the critical and major deficiencies were reviewed in detail during the inspection. Non-compliances observed during the inspection that was listed in the full report regarding CAPAs were addressed by the manufacturer to a satisfactory level.

Management review
A management review procedure and meeting records for 2017 were available and reviewed. Non-compliances observed during the inspection that was listed in the full report regarding management were addressed by the manufacturer to a satisfactory level.

2. Personnel

Both production and quality senior management staff changes had been made on the site since the last WHO inspection. 3875 persons were employed by the company at the time of inspection. In general, people met during the inspection had good understanding and experience to GMP.

3. Buildings and facilities

General

The API production and storage facilities were located in the Yantou campus, while the QA and QC in the Waisha campus. The production blocks of Yantou Campus for Kanamycin and Capreomycin were inspected. The production of Kanamycin Acid Sulfate was not in operation at the time of inspection.

Production blocks used to produce Moxifloxacin, Cycloserine and Linezolid were not inspected due to the focus of the inspection being a follow up of the CAPA to the last inspection (2016).

Design and construction
The workshops for the production and packaging of the inspected APIs were generally located, designed, and constructed to facilitate cleaning, maintenance and operations as appropriate to the type and stage of manufacture of the APIs.

Adequate space was provided for production and QC activities. Contamination during the final stages of production, including packaging, was minimized by these activities taking place in a suitably controlled Grade D environment.

Utilities
Adequate ventilation, air filtration and exhaust systems were provided. The HVAC system providing filtered air to the Grade D cleanrooms was reviewed and found acceptable.

Purified Water

Purified water system has not been changed since last inspection. User points were monitored at specified intervals for appearance, conductivity, TOC, microbiology, endotoxin. The test results were available, and trends were satisfactory investigated.

Containment

The APIs in the inspection scope were produced in non-dedicated facilities except the final processing stage of Capreomycin.

Lighting

Lighting was considered to be adequate in all areas visited during the inspection.

Sanitation and maintenance

All areas visited appeared to be clean. Cleaning procedures were available, and records maintained. Pest control measures throughout the premises were in place.

4. Process equipment

Majority process equipment installed for API manufacturing was of multi-purpose design. The equipment qualification program was described in written SOPs and found acceptable.

The procedure for preventive maintenance program/policy was available for review. Cleaning procedures were available, and records maintained. An equipment cleaning procedure for Kanamycin Acid Sulfate was reviewed and discussed.

5. Documentation and records

The documentation system was paper based and controlled by the site QA department. Excel sheets were used for registers, e.g. change control, deviation management. The company documents were categorized into different types including corporate procedures, site level API procedures and FPP procedure respectively. Non-compliances observed during the inspection that was listed in the full report regarding document review and management were addressed by the manufacturer to a satisfactory level.

Batch manufacturing records (BMRs) were retained for each batch processed. They were spot checked and appeared satisfactory.

6. Materials management

The procedure on vendor qualification and the lists of the approved suppliers were available for inspection. It was not reviewed in detail in this inspection. A spot check was made during the product PQR review and these checks generally satisfactory.

7. Production and in-process controls

The production blocks for Capreomycin fermentation, extraction, Kanamycin extraction and drying were visited. The fermentation hall contains reactors and fermenters for a number of different products. Production of Capreomycin was not in operation at the time of inspection in all of these blocks. The access control of the fermentation process parameters in the control system had been enhanced since the last inspection and were reviewed and considered acceptable.

8. Packaging and identification labelling of APIs and intermediates

The packages of intermediates and finished products were labelled reflecting the material name, manufacturing step and the dates. The controls reviewed appeared acceptable.

9. Storage and distribution

The raw materials (solids, liquids) were stored in warehouses of the Yantou campus. The CAPA documents to the warehouse deficiencies were reviewed and acceptable

10. Laboratory controls

The QC function was independent of other departments. QC laboratories including microbiological laboratory were separated from production areas. The Microbiology Laboratory and Microbiology QC test was segregated from the Chemistry Laboratory. Adequate resources were available to ensure that the QC arrangements are effectively and reliably carried out in general.

A new building had been brought into full operation in 2017 and this was a significant change from the situation at the last inspection when the new laboratory was still under commissioning, and testing activities were distributed over several locations. The new lab is very well equipped both with instruments and space as well as software tools for managing analysis. HPLC, GC and IR systems were networked and data integrity controls in place. Sufficient space was given to avoid mixups and cross-contamination. Adequate storage space was provided for samples, reference standards, solvents, reagents and records.

Sample receiving, and distribution procedure and registers were available, inspected and discussed.

Microbiological laboratories were inspected from the corridor. Visibility into the controlled areas is generally very good. These laboratories were seen to be of a good standard.

Updated data management and control procedures were in place. Examples of the stability testing data and integration parameters of the data processing method were reviewed and discussed as part of CAPA review and improvements implemented since the previous inspection. The situation is much improved reflecting the investments made by the company in specialist advice and the software and hardware implemented since the last inspection.

A number of consultants had been used to assist the company in improving its data management procedures and assurance since the last inspections by US FDA and WHO/EU. Contracts and task lists and review documentation were available and a programme of third party specialist audit of data integrity had been performed and was on going.

OOS handling procedure and OOS registers were available and reviewed. The inspectors noted that several of the cases where the company had concluded that there was an invalid OOS, were not adequately, investigated and documented in sufficient detail. The company trend data indicated that a significant proportion of incidents where due tohuman error which is found unacceptable.

11. Validation

The company approach to validation was documented in the Validation Mater Plan (VMP). A validation schedule was available, and spot checked by inspectors.

Cleaning validation procedures had been revised since the last inspection. The PDE criteria had been introduced and the products were assessed and classified into different potency groups. A worst-case approach was used in the cleaning validation.

Analytical method validation of related substance of Kanamycin API in house testing method validation protocol was reviewed and discussed.

12. Change control

The company has SOPs in place for change and deviation management. The procedures as described were generally of a good standard. Deviations were managed by and in hard copy reporting documents. Examples of change control and deviation were reviewed. Non-compliances observed during the inspection that was listed in the full report regarding risk assessment of change control and deviation investigation as well as root cause analysis were addressed by the manufacturer to a satisfactory level.

13. Rejection and re-use of materials

Reprocessing and reworking management procedure were available for review. This was not checked in detail during this inspection.

14. Complaints and recalls

Procedure for handling product complaints was available for review. Responsibilities were described and a responsible person in QA was coordinating complaint handling. Examples of complaints and batch return were reviewed. Investigation was performed as required by the procedure.

15. Contract manufacturers (including laboratories)

Contract manufacturing and testing were not utilized by the Hisun Taizhou API site.

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***, Zhejiang Hisun Pharmaceutical Co., Ltd.(API) located at Yantou Campus 56, Binhai Road, and Waisha Campus, 46 Waisha Road, Jiaojiang District, Taizhou City, Zhejiang Province, 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 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.
   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.
   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
   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