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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	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	East Factory Campus 1 Haizheng Avenue, Jiaojiang District Taizhou City, Zhejiang Province People´s Republic of China 318000 Waisha Campus 46 Waisha Road, Jiaojiang District Taizhou City, Zhejiang Province People´s Republic of China Postal code: 318000
Unit / block / workshop number	E03
Manufacturing license number, (delete if not applicable)	ZHE 20000291
Inspection details	
Dates of inspection	13 - 15 December 2017
Type of inspection	Follow up inspection
Introduction	
Brief summary of the manufacturing activities	Production and quality control of FPPs and APIs.

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 verify 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 E03 • QC laboratories
Out of scope	The scope of the inspection was restricted to the FPPs in the WHO PQ programme. There were other products and processes of the same dosage form in operation at the time of the inspection and whilst these processes were spot checked as part of the general GMP review of the production area, these products were outside the scope of WHO product prequalification.
WHO product numbers covered by the inspection	TB289 Moxifloxacin (as hydrochloride) Film Coated Tablets, 400mg TB305 Cycloserine Hard Capsules, 250mg

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. Pharmaceutical quality system

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 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 the company had done, and progress was considered generally satisfactory

Product quality review

Annual product quality review was performed according to a documented procedure. The commercial manufacturing has not been started for the two FPPs inspected and the PQRs were restricted mainly to the review of the stability data of validation batches and the implementation of regulatory commitments The stability study CAPAs to the deficiency in last inspection were reviewed. The data were checked in QC labs and discussed. The company has provided a satisfactory response to the matters raised.

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 weaker than that expected. In its CAPA the company committed to sustaining its continuing efforts to consolidate its improvements to date and further improve the overall consistency of the robustness of its processes and records. The follow up of these matters will be one focus in future inspections so as to verify that the promised improvements made to date have been sustained and further enhanced where necessary.

Change and deviation management

The company has SOPs in place for change and deviation management. The procedures as described were generally of a good standard. Examples of change control and deviations were reviewed. Non-compliances observed during the inspection are listed in the full report. Subsequent CAPAs by the manufacturer addressed these points to a satisfactory level

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. Good manufacturing practices for pharmaceutical products

Good manufacturing practices generally were implemented. Necessary human and physical resources were provided, including qualified and trained personnel, adequate premises, suitable equipment and services, appropriate materials, containers, approved procedures and instructions, laboratories and equipment for in-process and other controls. Qualification and validation activities were generally being performed. Manufacturing steps were recorded in batch manufacturing and packaging records. Manufacturing processes were defined and reviewed. Product was released by the authorized persons.

3. Sanitation and hygiene

Premises and equipment were maintained at a satisfactory level of cleanliness. Personal hygiene and sanitation in its production facility, with appropriate hand washing required, appeared satisfactory. Clean areas were cleaned frequently in accordance with an approved written programme.

Personnel were seen to be performing their duties in an organized manner. No gowning violations in production were noted during the periods of inspection. Procedures were in place for the preparation and control of sanitizing materials used in production areas.

4. Qualification and validation

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

For equipment and process validation the company had identified the qualification and validation work to be done. Revalidation was required to be performed periodically. The key elements of a qualification and validation programme were defined. There has been no new process validation of the two FPPs in the scope of the inspection as the product has not yet been qualified by PQ.

A worst-case approach was used in cleaning validation. Risk assessment reports for cross contamination in Workshop 302 were reviewed.

The new computerized systems used in QC labs and those for material management were reviewed and found acceptable.

5. Complaints

Procedure for handling product complaints was available for review. Responsibilities were described and a responsible person in QA was coordinating complaint handling. Complaint register was kept, and investigation was performed as required by the procedure.

6. Product recalls

The procedure for handling of recalls was available for inspection. There was no recall for the products in the inspection scope as the commercial batches are not yet available.

7. Contract production, analysis and other activities

No production or quality control operations for the FPPs in the inspection scope were contracted to any third party. The company uses some specialist service providers for work, such as, HVAC qualification and where these were reviewed, quality and service agreements were found to be in place.

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

Self-inspection was not covered in detail by this inspection. This inspection focussed on CAPA from the previous inspection and where reviewed audits of CAPA effectiveness had been performed.

9. Personnel

The key senior personnel in both production and quality assurance of the Taizhou site had been changed since the last inspection.

The manufacturer had an adequate number of personnel with the necessary qualifications and practical experience. Responsibilities of staff, and their specific duties were recorded in written job descriptions generally. Personnel interviewed during the inspection were aware of the principles of GMP in general. An organization chart was available and considered acceptable.

10. Training

Training was not covered in detail by this inspection.

11. Personal hygiene

Smoking, eating, drinking, chewing, and keeping plants, food, drink; smoking material and personal medicines was prohibited in production, laboratory and storage areas.

The approach to sanitation and hygiene was in general acceptable. Non-compliances observed during the inspection that was listed in the full report regarding the gowning requirement for access the microbiological laboratory were addressed by the manufacturer to a satisfactory level.

12. Premises

The OSD FPP production within the inspection scope was located in Workshop 302 (Building E03) at the East campus. Corrective actions had been implemented since previous inspection in the layout and design of the premises to further minimize the risks of possible cross-contamination.

The production facilities and equipment were multipurpose. The inspected areas used for staging, weight check, shifting, granulation, tray drying, compression, capsulation and blistering were at the acceptable standard for this type of production activity.

13. Equipment

The equipment installed for the OSD production line was multi-purpose and had unique identification numbers. The equipment usage logs were available and acceptable. Most of the equipment was as per the previous inspection. The operational procedures of a new milling machine in the OSD line of Workshop 302 was inspected and discussed.

Laboratory equipment and instruments were in a high standard and suited to their intended testing purpose. Equipment qualification and maintenance were undertaken according to written procedure.

14. Materials

Incoming materials and finished products were quarantined after receipt until they were released for use or distribution by QA. Where inspected the materials and products spot checked were stored under their required specified conditions.

The APIs used for the two FPPs in the inspection scope were made in house. The other starting materials and packaging materials were purchased from approved suppliers. There was a raw material qualification programme in place.

15. Documentation

The production documentation system was paper based and controlled by the site QA department. Excel sheets were used for registers, e.g. change control, deviation and so on. The company documents were categorized into different types including corporate procedure, site level API procedure 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 recorded up to the time as checked during the inspection.

16. Good practices in production

The manufacturing processes inspected were found to be performed and recorded according to the required BMRs and in general batch production records were satisfactory. The production of the two FPPs in the inspection scope was not in operation at the time of inspection. There were, however, other products of the same dosage form in operation, allowing the inspection of the production facilities in an operational state. Manufacturing records of the products under processing were reviewed in situ and considered generally acceptable and reflected the operational state observed. The processes spot checked appeared stable and under control.

The IPC testing (e.g. blister leakage test, friability, disintegration, LOD, weight) was performed in the IPC laboratory located within the processing area. These were inspected and found satisfactory.

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

17. Good practices in quality control

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 was 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 considered 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 the proportion of incidents with a conclusion of the root cause due to human error appeared to be increasing.

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. located at East Factory Campus, 1 Haizheng Avenue 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

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