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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	Hisun Pharmaceutical (Nantong) Co., Ltd.,
Corporate address of manufacturer	Zhejiang Hisun Pharmaceutical Co., Ltd. 46 Waisha Road, Jiaojiang District, Taizhou, Zhejiang, 318000, P. R. of China
Inspected site	
Address of inspected manufacturing site if different from that given above	Hisun Pharmaceutical (Nantong) Co., Ltd 18, 4th Haibin Road, Rudong Coastal Economic Development Zone, Nantong, Jiangsu, 226407, P. R. of China DUNS: 421314476 Longitude; $121^{0}04.941$ Latitude; $32^{0}32.479$
Unit / block / workshop number	Block P10 and Block P08
Manufacturing license number	SU20160252
Inspection details	
Dates of inspection	28 to 30 January 2019
Type of inspection	Routine reinspection
Introduction	
Brief summary of the manufacturing activities	Manufacturing and quality control of APIs.
General information about the company and site	Hisun Pharmaceutical (Nantong) Co., Ltd was founded in 2011 and production started in 2014. It is a subsidiary company wholly-owned by Zhejiang Hisun Pharmaceutical Co., Ltd. A pharmaceutical production license has been issued by Jiangsu FDA. The site is focused on APIs and Pharmaceutical intermediates manufacturing. The company employed 448 people on the site at the time of inspection including 17 in QA, 30 in QC and 232 in production department.

History	This was the third WHO GMP inspection at this site. The Praziquantel API facilities have previously been inspected by the WHO in July 2016 and January 2017. The site had been inspected by USFDA in June 2016.
Brief report of inspection activities undertaken	
Scope and limitations	
Areas inspected	Quality management system including documentation and data review Production Blocks P10 and Block P08 Block P10 (Quality control laboratories) API and starting material warehouses Shared purified water plant
Restrictions	N/A
Out of scope	Other process than the submitted in APIMF301Praziquantel to WHO Micronization of Praziquantel
WHO product numbers covered by the inspection	Praziquantel (APIMF301)

Abbreviations

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

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

Part 2	Brief summary of the findings and comments

1. Quality management

A formal documented system for quality assurance was established, with procedures covering all key quality elements being in place. Operations were specified in a written form and GMP requirements were essentially being met. The procedures that were reviewed and discussed during the inspection were generally of a satisfactory standard. Managerial responsibilities were appropriately specified in written job-descriptions. Product and processes were monitored, and these results considered during batch release; regular monitoring and reviews of the quality of pharmaceutical products were being conducted according to documented schedules and procedures.
The Quality Unit was divided into QA and QC. The Unit was separate from the production department.

Product quality review (PQR)
PQRs were performed according to a written procedure. The Praziquantel PQR for 2017 was reviewed. The Praziquantel PQR for 2018 was not complete at the time of inspection. The required elements had been considered and documented and were found mostly acceptable.

Quality Risk Management
Quality risk management procedures and a number of specific risk assessments were available for inspection. Risk assessment associated with change control was checked and acceptable.

Deviations
Deviations were handled according to written procedures. A deviations log book was kept. Deviation management were spot checked and found acceptable.

Internal audits
Internal audits were not covered in this inspection.

2. Personnel

Personnel qualifications
The key personnel met during the inspection were suitably qualified through qualifications and experienced. There appeared to be a sufficient number of personnel for the site activities performed and these too were qualified through qualifications, experience and training.

Personnel hygiene
Personnel in the Pharma Plant were required to wear protective clothing suitable for the type and stage of manufacturing. Suitable sanitation and change room facilities were available. The Hisun Chemical Plant previously located on the same site has now been separated by segregation of personnel movement, however the catering and some other facilities e.g. QC lab were in a shared building. Although some hygiene requirements and procedures on the movement from the Chemical Plant to the shared areas have been established, the company was reminded of its responsibility to continuously monitor and control the potential risk of cross contamination caused by personnel movement.

3. Buildings and facilities

Design and construction

The buildings and facilities inspected were designed and constructed to facilitate cleaning, maintenance and operations as appropriate to the type and stage of manufacture. Manufacturing areas were spacious to allow placement of equipment without risk of mix up or confusion between operations.

Building P10, dedicated to the production of crude Praziquantel, was inspected. The areas on the different floors were clean and well maintained. The room on the top floor where reactors are loaded has adequate dust extraction. A dedicated Grade D clean area in P08 was used for final stage of Praziquantel production.

Purified Water System

The Purified Water (PW) System and the distribution system were inspected, and the associated documentation was reviewed. The pre-treatment of PW remained the same since the last inspection. A change control had been raised regarding the addition of an additional loop to supply a further workshop, to the PW distribution system.

The design of PW system and monitoring data reviewed were acceptable. The water system is well engineered and appeared well maintained. The personnel running the plant were experienced and able to explain fully the operation and controls. The water system is controlled at specified temperature.

Nitrogen

A Nitrogen separation plant was installed in Building P03. Nitrogen system remains the same as during the last inspection. A schematic drawing of Nitrogen supplied to reactors in the clean area was briefly reviewed and discussed. No deficiencies were raised.

HVAC

A dedicated HVAC system provided filtered air to the controlled area of Praziquantel production in Building P08. This was a recirculation system. The periodic qualification of HEPA leakage testing was checked and discussed.

Containment

Praziquantel API was manufactured in dedicated facilities.

Lighting

The lighting in all warehouses, production areas, and the QC laboratory was suitable.

4. Process equipment

Process equipment in Building P10 and P08 for Praziquantel were inspected. These were dedicated to the Praziquantel production. Equipment used in the manufacture appeared to be of appropriate design and size for its intended use, cleaning and well maintained. Manufacture and material transfer as well as sampling took place in closed systems wherever possible.

Product contact material was either stainless steel or glass. Equipment was installed satisfactorily with process and utility pipework adequately supported. Standards of housekeeping and maintenance were observed to be satisfactory.

Equipment maintenance procedure was available for inspection. Equipment appeared maintained in good conditions. Access to and the protection of the glass lined vessels during entry for maintenance and checking were discussed and considered satisfactory.

Calibration

Equipment was calibrated, and calibration status was up to date and labelled on the equipment. No deficiencies were noted.

Computerized systems

Computerized systems were used in the QC lab for HPLC, GC and IR control and data acquisition.

Other than Programmable Logic Controller (PLC) systems used to control some limited equipment (e.g. the water system), computerized systems were not used for material or production control.

5. Documentation and records

Activities were documented in SOPs and other appropriate documents such as batch manufacturing records (BMRs) and logs. Those reviewed were seen to be appropriately approved and version controlled. All records and other documentation requested during the inspection were promptly available.

Master production instructions (master production and control records)

Approved master production instructions were available. Master BMR Praziquantel API was reviewed and discussed.

Laboratory control records

Laboratory logs were in place for receipt of samples and appropriate testing records were kept and available for review.

Batch manufacturing record review

Batch manufacturing record was reviewed, and these results considered during batch release.

6. Materials management

General controls

Manual systems were in place for the receipt and tracking of inventory. Raw materials and finished goods were stored in dedicated areas of the warehouse. There was a tank farm for the receipt of solvents. These appeared to be tidy and well managed and appropriately labelled.

Receipt and quarantine

Solid materials were required to be checked on receipt, including for damage and verification that the supplier was approved. They were then placed in quarantine and labelled with the storage location. Bulk liquids were received from either dedicated tankers or tankers accompanied by a cleaning certificate. Bulk materials were tested before discharge from the road tanker and a new lot number assigned to the combined content in the receiving tanks.

7. Production and in-process controls

Production in P10 and P08 were in operation at the time of inspection. Final purification, crystallization, drying and packaging was performed in Grade D clean area. Different grade Praziquantel API for human or veterinary use were manufactured. Process used for WHO and EU grade of Praziquantel API was specified and documented. Blending was not performed for Praziquantel API production.

In-process sampling was performed at defined and documented stages during processing. In-process samples were tested in the QC laboratory.

Deviation management following a written procedure was documented, explained and investigated.

8. Packaging and identification labelling of APIs and intermediates

Packaging and labelling of Praziquantel API and intermediates were not in operation at the time of the inspection. Praziquantel packaging operation procedure was reviewed and discussed.

9. Storage and distribution

Warehousing procedures

Finished APIs were stored in a designated warehouse and held until released by the Authorized Person. The storage condition was monitored and recorded. A manual bin card system was used to control stock, the release procedure and labelling on the API were inspected and found acceptable.

Distribution procedures

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

10. Laboratory controls

The QC laboratories were responsible for physical, chemical and microbiological testing of starting materials, packaging materials, products (API's), environmental monitoring samples and purified water samples.

The QC laboratories was inspected. HPLC and GC have been networked with software and there were no standalone systems. There were dedicated rooms for activities such as sample receipt and storage, wet chemistry, instrumentation, hot areas and balance room. The labs were clean and well maintained. There were adequate pieces of equipment with up to date calibration status.

QC testing was conducted as specified in the relevant specification and according to documented testing procedures. WHO grade Praziquantel was tested with specification and consistent with the version in the dossier assessment report.

Reference substances management

Reference substances management was reviewed and discussed. Secondary reference standards were prepared by the laboratories at the company corporate QC. Records of the receipt of the controlled reference materials were made and available for the incoming vials of Praziquantel reference standard with batch number and vial numbers. Their use was satisfactorily recorded.

Stability study

Stability study was included in the Praziquantel APQR and the data showed was acceptable. The facilities and ovens for stability were inspected and were in good order. Alarm systems were in place.

Handling of out of specification/out of trend (OOS/OOT) results

The OOS/OOT handling procedure and an example of OOS regarding assay testing were reviewed and discussed.

Microbiological testing

Microbiological testing is performed in a dedicated suite of laboratories in the QC building. The facilities were appropriate to the level of controls being performed. Testing consists of TVC estimation on finished API, water testing and the monitoring of the clean rooms for harvesting API and final packaging. There is a programme of endotoxin testing for the water system and results were consistently below the specified limit.

11. Validation

The company had policies, procedures, protocols and reports for validation and qualification of processes, procedures, equipment, utilities etc. The validation status was periodically reviewed.

A change control trigged process validation was reviewed and discussed. The PV had not been completed at the time of inspection.

12. Change control

Change control (CC) was managed according to a written procedure. The change control register for 2017 was checked. Several CC examples were reviewed. Non-compliances observed during the inspection that was listed in the full report regarding change control was addressed by the manufacturer to a satisfactory level.

13. Rejection and re-use of materials

Reworking and reprocessing requirements were described in written procedures. This procedure applied to APIs and intermediates and these activities were properly defined.

Recovery of solvents and materials at different stages of synthesis was done according to documented instructions and were tested to meet predefined specifications. The solvent recovery was done on site.

14. Complaints and recalls

Complaints were managed according to an SOP. A compliant of Praziquantel batch was spot checked. No comments were made.

The company stated that there has been no batch recall of Praziquantel API since last inspection.

15. Contract manufacturers (including laboratories)

There was no contract manufacturing of Praziquantel API. However, external contract testing was used.

PART 3

Conclusion

Based on the areas inspected, the people met and the documents reviewed, and considering the findings of the inspection, including the deficiencies listed in the Inspection Report, as well as corrective actions taken and planned. Praziquantel (APIMF301) manufactured at Hisun Pharmaceutical (Nantong) Co., Ltd. located at 18, 4th Haibin Road, Rudong Coastal Economic Development Zone, Nantong, Jiangsu, 226407, P. R. of China was (were) considered to be manufactured in compliance with WHO GMP for Active Pharmaceutical Ingredients.

All the non-compliances observed during the inspection that were listed in the full report as well as those reflected in the WHOPIR, were addressed by the manufacturer, to a satisfactory level, prior to the publication of the WHOPIR

This WHOPIR will remain valid for 3 years, provided that the outcome of any inspection conducted during this period is positive.

PART 4

List of GMP guidelines referenced in the inspection report

1. WHO good manufacturing practices for active pharmaceutical ingredients. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957), Annex 2.
   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