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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, Ruodong 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	16 - 19 January 2017
Type of inspection	Follow-up inspection
Introduction	
Brief summary of the manufacturing activities	Manufacturing and quality control of APIs.

General information about the company and site	Hisun was founded in 1956. Hisun Pharma was established in 1998. Hisun Nantong site was set up in 2011. Headquarters are located in Taizhou. The Hisun Pharmaceutical Nantong site was starting to be developed in 2011 and production started in 2014. At the time of the present inspection, the product list included about 10 APIs produced on the site. No Penicillin and beta lactam antibiotics were manufactured on this site.
History	The site has been inspected by USFDA in June 2016 and by WHO in July 2016. The site has not been inspected by the CFDA at the time of this inspection.
Brief report of inspection activities undertaken	
Scope and limitations	
Areas inspected	• Quality management • Personnel • Buildings and facilities • Process equipment • Documentation and records • Materials management • Production and in-process controls • Packaging and identification labelling of APIs and intermediates • Storage and distribution • Laboratory controls • Validation • Change control • Rejection and reuse of materials • Complaints and recalls • Contract manufacturers (including laboratories) Site visit: Warehouses for starting materials and finished API products, Block P10 and P08 for Praziquantel production QC laboratories 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 (where applicable)**

Brief summary of the findings and comments

1. Quality management

Product quality review (PQR)

The Praziquantel 2015 PQR was reviewed during the last inspection.

The PQR 2016 for Praziquantel was not yet available at the time of inspection.

Management review (MR)

Quality Management Review Procedure was reviewed, including the management review reports in 2015 and 2016 and considered acceptable.

Quality risk management

An SOP for Risk Management Procedure and Cross contamination risk assessment in Hisun Group (Nantong site) were reviewed. Hisun Pharma and Hisun Chemical Plant were separated according to the company's statement and physically segregated with a fence barrier for material and personnel movement. Production of API Fipronil had been terminated in the chemical plant according the agreement signed by the General Manager of Nantong plant of Hisun Pharma. Non-compliances observed during the inspection that was listed in the full report regarding risk management were addressed by the manufacturer to a satisfactory level.

Deviations

Deviations are managed according to the company procedure. Deviations in 2015 and 2016 were reviewed during the inspection.

2. Personnel

Personnel qualifications

Personnel met during the inspection were suitably qualified through qualifications, experience and training in general.

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 provided. Hisun Chemical Plant was located on the same site now with segregation for personnel movement, however the catering and some other facilities e.g. QC lab were still in a shared building. Although some hygiene requirements regarding the movement from the Chemical Plant to the shared area have been established, it remains the company's responsibility to continuously monitor and control the potential risk of cross contamination caused by personnel movement.

Training

An SOP for training had not been changed since the last WHO inspection. An example of records for the training of a new warehouse SOP was reviewed. No comments were made.

3. Buildings and facilities

The site was initially shared with Hisun Chemical (Nantong) Co., Ltd. After the last WHO inspection the two sites were physically segregated with fence barrier. Production of Fipronil API at the Hisun Chemical plant had been terminated after the 2016 WHO inspection as claimed by the company.

Design and construction

Building P10, dedicated to the production of crude Praziquantel, was inspected. The areas on the different floors were clean and well maintained.

Building P08 had several clean areas, each dedicated to different products. P08-01 was dedicated for final stage production of Praziquantel.

Utilities

The Purified Water System, Nitrogen plant and other utilities were installed in a separate building.

A dedicated HVAC system provided filtered air to the controlled area of Praziquantel production in Building P08. The pressure-drop was recorded according to a specified schedule. Records for primary and secondary filters were checked and were up-to-date with the readings within limits.

Water System

A purified water (PW) system were inspected and the associated documentation was reviewed. The pre-treatment of PW remained the same as during the last inspection. A change control was raised regarding the addition of two loops to the PW distribution system. The design of PW system and monitoring data reviewed were acceptable.

Nitrogen

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.

4. Process equipment

Design and construction

Process equipment in Building P10 and P08 for Praziquantel were inspected. They 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 maintenance. Manufacture and material transfer as well as sampling took place in closed systems wherever possible.

Material of product in contact 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 and cleaning

In the gowning areas giving access to the Grade D area of P08, hands wash facility was available. De-gowning was with a separate airlock.

Equipment maintenance procedure was available for inspection. Operation and maintenance procedure for a gas membrane filter and its maintenance record were reviewed and found acceptable.

Calibration

Calibration of balance used for sampling of raw material was spot checked and found acceptable.

Computerized systems

A computer system was used in QC lab for HPLC, GC and IR networking.

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

5. Documentation and records

Labels on Praziquantel final product in the warehouse had tick boxes to indicate the quality of the final product. Until the material was packaged in customer specific drums usually all grades (US, EU, WHO) were ticked. From the sample request forms seen in the QC lab it was clear that to verify compliance with the three grades all tests were done.

Praziquantel batch manufacturing records (BMR) at the purification stage were reviewed. Analytical data were noted in a separate batch testing document at the laboratory. In the BMR the batch numbers of all materials used are well recorded. Product yield was calculated from the packaging activity.

6. Materials management

Receipt and quarantine

Incoming material receipt procedure was described in an SOP on raw material, packaging material receiving and handling procedure. The supplier approval status was checked with the current version of a qualified supplier list. Incoming materials were placed in quarantine by labelling them as such and placing a yellow ribbon around the shipment. A white belt was used for material from suppliers that were on a list of suppliers to be approved. On the containers a yellow, green or red sticker was put, depending on their status. These labels were printed by QC and a reconciliation document is kept at the QC lab.

Sampling of raw materials was done by QC in a sampling room in the warehouse. Sampling instructions and procedure were available.
For products produced on site procedure warehousing and distribution procedure of finished product applies. Separate inventory logbooks for raw and auxiliary materials and finished products showed the goods movement between production and warehouse.

Supplier approval

A SOP on supplier approval was reviewed. It contained a flowchart for the supplier qualification. Information and test samples were requested and QA assessed the results. A supplier was included in the Qualified Supplier List after approval. The qualification status of each supplier was reviewed annually. Requalification of a supplier takes place periodically, unless there was an earlier need. An example was review and the process looked adequate.

7. Production and in-process controls

Production operations

Production of Praziquantel took place in the following workshops. There were two processes for Praziquantel manufacturing. Process B was for WHO grade Praziquantel. Final drying, milling and packaging were performed in a Grade D clean area.

Building 10 and 8 were in operation at the time of inspection. Production areas were inspected and found to be of good standard, clean and logically organized to suit their intended purpose.

In Building P10 wet crude Praziquantel was filled from the centrifuges into drums. These have been numbered to allow for an individual tare weight to be deducted from the gross weight that is recorded on the label. In Building P08 the Praziquantel relevant workshop was inspected where the purification of crude Praziquantel took place and found acceptable.

In-process sampling and controls

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

Blending batches of intermediates or APIs

The company stated that no blending was carried out. Tailing material handling procedure was checked. Non-compliances observed during the inspection that was listed in the full report regarding procedure for handling tailing materials were addressed by the manufacturer to a satisfactory level.

Contamination control

API synthesis, purification, crystallization, drying and packaging was performed in facilities dedicated to Praziquantel. Batch packaging record and the record in the packaging room were checked. The deficiencies regarding the line clearance between batches were discussed.

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 this inspection.

Packaging and labelling operations

The packaging process had two stages. SOPs for using and cleaning record for packing area and the record were reviewed. Non-compliances observed during the inspection that was listed in the full report packaging operation were addressed by the manufacturer to a satisfactory level.

Labels for all stages were produced and issued by QC except for the final product, where QA issues labels. The applicable procedure for QC was Management Procedure of Certificate. For raw materials labels were managed according to a SOP on sample analysis logbook of raw materials/packaging and showed that the data on the label have been checked by a second analyst. Blank labels for the packaging operation were issued in bulk to the packaging room.

9. Storage and distribution

Warehousing procedures

The warehouses for incoming materials (dry, acid and basic substances) were inspected. Dedicated rooms were used for the storage of Praziquantel material (requirement less than 30^{o}C). Packaging materials was stored in a temperature controlled area.

Distribution procedures

Finished API products were released for distribution after they had been released by QA according to a written procedure.

Product release

The release management procedure for APIs was reviewed. The release process of a Praziquantel batch was reviewed and found acceptable.

10. Laboratory controls

Sample management

The QC lab was visited to inspect sample management. Logbooks per product were available to log in the samples. Sample request forms were made by production department.

Reference substances management

Secondary reference standards were prepared by the Hisun head quarter in Taizhou, Zhejiang. For this activity a QA agreement was drawn up between Hisun Nantong and Taizhou site. A logbook for reference standards in QC laboratory showed that record was made of the incoming vials of Praziquantel reference standard with batch number and vial numbers. Their use was also recorded. Traceability to pharmacopoeial standards was achieved by CoAs that were shipped with the vials. As an example a certificate document was checked and acceptable.

Reserve/retention samples
This subject was covered in the last inspection therefore was not reviewed in detail in this inspection.

Stability study
This subject was covered in the last inspection and was not reviewed in detail in this inspection.

Handling of out of specification/out of trend (OOS/OOT) results
OOS handling procedures were reviewed. An OOS regarding a Praziquantel batch was reviewed and the investigation was ongoing at the time of the inspection.

Microbiological testing
Microbiological testing took place in a separate and suitably equipped laboratory. Corrective action regarding the autoclaves in the micro laboratory was made since the last inspection. PW sampling and testing records as well as the plates in incubation were checked. Non-compliances observed during the inspection that was listed in the full report regarding microbiological testing were addressed by the manufacturer to a satisfactory level.

11. Validation

Process validation
A process validation was triggered by a new supplier of a key starting material for Praziquantel production via a change control. The process validation was ongoing. This new validation had not been submitted to WHO at the time of inspection.

Cleaning validation
Cleaning validation was not reviewed in detail in this inspection. The production facility and equipment were dedicated to Praziquantel.

Equipment qualification
In the previous inspection deficiencies for this subject were noted. During the present inspection the corrective actions were checked and no comments were made.

12. Change control

Change control was managed according to a SOP. Changes were classified as minor or moderate or major.
A Major change regarding a new supplier for key starting material for Praziquantel production was reviewed. The change related supplier approval, process validation and regulatory were checked. At the time of the inspection, the change control was ongoing.

13. Rejection and re-use of materials

Reprocessing and Reworking
A study was set up to support the application of a change in the API Master File to re-introduce material into the Praziquantel manufacturing process. Since the study was not yet completed no comments were made.
CAPAs to deficiencies regarding the reprocessing were made since the last inspection.

Recovery of materials and solvents

Solvents and mother liquors were recovered and used in the Praziquantel manufacturing process. Both fresh and recovered materials were used in the process validation batches.

14. Complaints and recalls

Complaints were managed according to a complaint management procedure. An overview of all complaints in 2014-2017 including complaints on Praziquantel was reviewed in a document. No comments were made.

15. Contract manufacturers (including laboratories)

No contract manufacturers were used for Praziquantel production. It was understood that X-Ray Powder Diffraction and heavy metal testing were contracted to the laboratory at the company's headquarters in Taizhou, but not for routine test of Praziquantel API.

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-eight 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-six 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. Fifties 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. Fifties 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. Fifties 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. Fifties 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