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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	Minsheng Group Shaoxing Pharmaceutical Co. Ltd.
Corporate address of manufacturer	No.658, Bin'an Road, Binjiang District, Hangzhou, Zhejiang
Inspected site	
Address of inspected manufacturing site if different from that given above	315 Tanggong Road, Paojiang Industrial Zone Shaoxing, Zhejiang Province, China, 312071
Unit / block / workshop number	102 Workshop
Manufacturing license number	Zhe20040270
Inspection details	
Dates of inspection	9-12 January 2017
Type of inspection	Re-inspection
Introduction	
Brief summary of the manufacturing activities	Production, quality control, packaging, storage and distribution of APIs.
General information about the company and site	At the site about 30 APIs and intermediates were manufactured. According to the company no penicillins, cephalosporins were manufactured on this site. The API in the scope for this inspection, Praziquantel (PQT), was manufactured in Workshop 102. Within this workshop a section was dedicated to the two grades of Praziquantel that are manufactured.

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History	This was the second WHO inspection to this site. The previous inspection took place from 19-22 May 2015. The site is regularly inspected by the provincial/city drug regulatory authorities and has also been inspected by USFDA in September 2015 and AGES (Austria) in November 2016 for other products than the product in the scope of this inspection.
Brief report of inspection activities undertaken	
Scope and limitations	
Areas inspected	- Quality management system • 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 • Internal audits (self-inspection) • Contract manufacturers (including laboratories) - Manufacturing areas in Workshop #102 including chemical reaction areas and grade D area for final stage. - QC laboratory - Warehouse raw materials and finished API products
Restrictions	No.
Out of scope	No.
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

The elements of the pharmaceutical quality management systems were established and documented in SOPs which covered the main elements of GMP related activities. QA function was involved and had oversight of activities with impact to product quality. QA was responsible for compliance of systems against their SOPs, as well as GMP and regulatory requirements.

Quality Risk Management
There was a procedure for Quality risk management. Non-compliances observed during the inspection that was listed in the full report regarding the risk management were addressed by the manufacturer to a satisfactory level.

Deviations
A SOP for deviation investigation and handling was available for inspection. The deviations in the Praziquantel PQR 2015 and 2016 were reviewed and discussed.

Internal audits (self-inspection)
Internal audit procedure and plan for 2016 were reviewed and discussed.

Product quality review **(PQR)**
A SOP for product quality review was reviewed and was generally acceptable. PQRs were performed annually. An overview of PQRs for APIs manufactured on the site was presented for review and showed that the review was completed before April of the next year.

PQRs in 2015 and 2016 for Praziquantel API of USP/WHO grade were reviewed. A presentation was given on the CAPAs that were taken after the last WHO inspection and considered acceptable.

2. Personnel

The total number of personnel working at the site in different areas was approximately 590. An organization chart was available and was reviewed. The quality assurance and quality control department were independent from the production department. There were a sufficient number of personnel who were qualified through qualifications, experience and training generally.

Training
The training system was reviewed. There was a training plan for each department and a GMP Annual training plan that offers a different GMP subject each month. Individual's training records were kept in the personal training files. Attendance lists per training activity were available for inspection.

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.

After the last WHO inspection the clean area used for Praziquantel was refurbished, with minor modifications to the HVAC system. The area looked adequate with smooth floors, walls and ceilings.

Purified water system
A modification of the Purified Water (PW) system was done by adding a new loop named Purified Water II. The test results 2015 and 2016 of the PW monitoring and testing results appeared within the acceptance limits.

Containment
Processing took place in closed systems wherever possible. The final synthesis, purification and packaging of PQT produced took place in dedicated facilities to minimize the likelihood of cross-contamination.

Lighting
The lighting in all warehouses and production areas, and the QC laboratory was considered to be suitable.

Sanitation and maintenance
All areas inspected were clean and appeared to be well maintained.

4. Process equipment

Design and construction
Equipment used in the manufacture of PQT API were glass line reactors. They were appropriately designed including the size for its intended use, cleaning and maintenance. Manufacture and material transfer in the process inspected took place in closed systems wherever possible.

Since the last WHO inspection in 2015 a new double cone drier/blender was installed. The qualification and validation documentation for the drier/blender was reviewed, as well as the records of relevant changes.

Equipment maintenance and cleaning
Equipment was maintained according to a SOP. Equipment maintenance schedule was reviewed and discussed.

Calibration
Calibration was spot checked for the pocket balance used for sampling in warehouse.

Computerized systems
Computerized systems were not used for material or production control.
Computerized systems were used in the QC Laboratory.

5. Documentation and records

Documentation system and specifications
Activities were generally documented in SOPs. These were approved and version controlled. Most of the records and other documentation requested during the inspection were readily available.

Equipment cleaning and use record
Equipment was required to be cleaned according to documented procedures. All equipment viewed appeared to be clean and suitably labelled with status.

Batch production records (BMR: batch production and control records)
The BMR for a PQT API was reviewed. The record was well laid out and all entries were clearly legible. The version used for this batch was checked for those changes that had been implemented after CAPAs as a result of the previous WHO inspection. No comments were made.

Laboratory control records
Laboratory control records, including a sample receiving and distribution register, and test records, were available for inspection.

Batch production record review (BMR)
The first page of the BMR format is a Finished Product Review and Release sheet. On it a record is made of the steps in releasing the product. Product release was acceptable. The final batch release is done by the QA Manager on the basis of reviews of batch records, QC results and checks on electronic data that was signed off by QA staff.

6. Materials management

General controls
The supplier approval system was considered satisfactory. An approved list of approved suppliers was available.
Receipt and quarantine
Materials were required to be checked on receipt, including for damage, and verified against a list of approved suppliers which is drawn up per product. Bulk liquids were received in drum or in truck. Solid raw materials were placed in quarantine by cordoning off and labelling the storage location.

Sampling and testing of incoming production materials
Production materials were sampled by QC according to a SOP in a designated sampling area and according to a defined sampling plan. The containers sampled were appropriately marked. After testing by QC, materials were released by applying a label to each container. The records viewed were satisfactory.

Storage
Materials were stored in designated areas of the warehouse, depending on the type of material. Warehouse for finished API was monitored and controlled.

7. Production and in-process controls

Production operations
The production of PQT API took place in several steps with two different processes for USP and Chinese Pharmacopoeia (CP) grades. Processing was conducted according to the instructions in the BMR. A PQT BMR was reviewed.

Time limits
Time limits for processing steps were included in the BMR in general.

In-process sampling and controls
Requirements for in-process sampling were described in the BMRs and acceptance criteria included.

Blending batches of intermediates or APIs
The final batch size of PQT was blended by three sub-batches according to the production instruction. The testing and release for sub-batch before blending was reviewed and discussed during the inspection.

Contamination control
Contamination risk was reviewed. Non-compliances observed during the inspection that was listed in the full report regarding contamination risk was addressed by the manufacturer to a satisfactory level.

8. Packaging and identification labelling of APIs and intermediates

Packaging and labelling operations were not in operation during the inspection and not reviewed during this inspection.

9. Storage and distribution

A tour was made of the warehouse for starting materials. The status of containers is indicated by a colored belt: green is released and yellow is quarantine.

Warehousing procedures
Finished APIs were stored in a designated warehouse and held in quarantine until released by the Authorized Person (AP). A manual bin card system was used to control stock. The inventory and release register of PQT 2016 was checked and found acceptable.

Distribution procedures
APIs and intermediates were released for distribution after they had been released by the Quality Unit.

10. Laboratory controls

General controls
The QC laboratory was briefly visited. In the lab, all HPLCs could be accessed by each of every terminal which are connected to a central server. Access rights were described in a document. The data in the list correspond with the tables in Empower software. Administrator level is granted to one person only. Manual integration was controlled with procedure. An example of an audit trail for one of the HPLCs was checked. No comments were made.

The equipment was well maintained. Columns are stored in an orderly fashion in drawers under the HPLCs. For each product one or more dedicated columns are used. In the respective column logbooks the test runs are logged.

Sample receiving and distribution
Sample receiving and distribution procedure and register for raw materials and finished APIs were reviewed and found acceptable.

Handling of out of specification (OOS) results
The OOS handling procedure and register 2015 and 2016 were available for review and discussed during inspection. Some deficiencies were raised.

Stability monitoring of APIs
A range of stability chambers were available. PQT stability batches were studied under the condition of 30° C 65% RH and 40° C 75%RH. At least one batch of API per year was required to be placed on on-going stability study.

Reserve/retention samples
The reserve samples were kept in a dedicated room . The retention samples were packaged in same/similar material composition to the market drums. Observation was made regarding the temperature monitoring in the room.

11. Validation

Process Validation
The process validation protocols and associated validation reports for PQT drying process were reviewed. It was triggered by a new equipment. Validation records for the validation batches were reviewed and generally found acceptable..

An SOP for batch numbering system was reviewed and discussed.

Qualification
The equipment qualification report of a dryer in clean area was reviewed. The qualification was done on the basis of an IQ, OQ and the subsequent process validation during the production of the first three batches in October/November 2016. No comments were made.

Cleaning validation
Cleaning validation was performed according to an SOP. Various methods for calculating maximum carry over were used. The protocol and report for PQT cleaning validation were reviewed and discussed.

Computerized system validation
In 2015 a validation was done of the Empower 3 software. This consisted of IQ and OQ. The system as a whole was accepted on the basis of the Change Control report. Preparations have started to re-validate the software and the associated system in 2018.

12. Change control (CC)

A Change Control SOP was reviewed. Changes were classified into Significant, Major and Other. A change control regarding the installation of the double cone drier/blender and some other examples were reviewed. Non-compliances observed during the inspection that was listed in the full report regarding change control management were addressed by the manufacturer to a satisfactory level.

13. Rejection and re-use of materials

Reprocessing/reworking
There is a company procedure on reprocessing/reworking. Reprocessing is allowed provided validation was done and stability data were available for the reprocessed material. Whenever reprocessing is done, an “R” is added to the batch number. Besides the general SOP there are product specific procedures, e.g. for WHO grade PQT.

Recovery of materials and solvents

The company stated that solvent and material recovery had not been used and applied for WHO grade PQT API.

14. Complaints and recalls

Complaints were handled according to an SOP and complaints classified as either serious, major or minor, with definitions of each. Annual log books of quality related complaints were maintained and those for 2014, 2015 and 2016 were checked. There was no complaint related to Praziquantel.

The recall procedure was reviewed and discussed. Non-compliance observed during the inspection that was listed in the full report regarding recall was addressed by the manufacturer to a satisfactory level.

15. Contract manufacturers (including laboratories)

Contracts for the testing of packaging materials were reviewed. No comments were made.

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 Minsheng Group Shaoxing Pharmaceutical Co., Ltd. located at 315 Tanggong Road, Paojiang Industrial Zone Shaoxing, Zhejiang Province, China, 312071 was 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