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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	Jiangsu Chengxin Pharmaceutical Co. LTD.
Corporate address of manufacturer	No. 338, Shanghai Road, Binjiang Pharm-Chem Industry Park, Qidong, Jiangsu, 226221, P.R. China
Inspected site	
Address of inspected manufacturing site if different from that given above	No. 338, Shanghai Road, Binjiang Pharm-Chem Industry Park, Qidong, Jiangsu, 226221, P.R. China
Unit / block / workshop number	WS 1
Manufacturing license number	SU20160250
Inspection details	
Dates of inspection	22 to 24 January 2018
Type of inspection	First inspection
Introduction	
Brief summary of the manufacturing activities	APIs API Intermediates & Starting Materials Enzyme synthesized product (cosmetic ingredient, food additives) Fine Chemicals
General information about the company and site	Jiangsu Chengxin Pharmaceutical Co., Ltd. located at No. 338 Shanghai Road, Binjiang Pharm-Chem Industry Park, Qidong, Jiangsu, P.R. China is a privately-owned company founded in 2010. The site inspected covered an area of 60,000 m2. There were approximately 256 full time employees at the time of inspection. The main API produced at the site was Praziquantel along with several other APIs. No toxic or hazardous substances such as antibiotics, hormones or cytostatics are manufactured on site.
History	This was the first WHO inspection of the site. Apart from the site being inspected by the Chinese provincial drug regulatory authority, to date, no National Medicines Regulatory Authority had inspected the site
Brief report of inspection activities undertaken	
Scope and limitations	

Areas inspected	The inspection focused on the production and control of Praziquantel API. The inspection covered the sections of WHO good manufacturing practices for active pharmaceutical ingredients including premises, equipment, documentation, materials, validation, sanitation and hygiene, production, quality control and utilities.
Restrictions	Note: the company manufactures several grades of Praziquantel and these may be manufactured in the same workshop as the grade subjected to prequalification. Different grades may be manufactured using differing sources of starting material and processing conditions.
Out of scope	It was noted that the company provides micronized Praziquantel to some markets which includes CEP material. Micronization is not a process declared in the PQ dossier and thus not reviewed during the inspection. Other SMs/APIs not relevant to the manufacture of Praziquantel API.
WHO product numbers covered by the inspection	Praziquantel (APIMF338)

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 key quality elements being in place. Operations were specified in written form and critical GMP requirements were essentially being met. The procedures that were reviewed and discussed during the inspection were generally of a satisfactory standard; however in some cases improvements were sought and implemented as part of CAPA to this inspection. 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 and several quality metrics were being conducted according to documented schedules and procedures. The Quality Department was divided into QA and QC, which was separate to the production department.

Product quality review (PQR)

PQR was performed according to written procedure, MSP-QA-0007 version 04 with the stated objectives of demonstrating the stability, reproducibility and reliability of processes and products. This procedure required the PQR to be performed annually using data collected from all manufacturing batches of APIs and to be completed annually before end of March. The SOP specified the review of IPC test results and API test results, summary of validation work done, OOS batches, deviations, changes, stability monitoring, returns, complaints and recalls, and adequacy of CAPAs. The SOP did describe how regulatory compliance/commitment should be reviewed, however this aspect was deficient and was subsequently satisfactorily dealt with in CAPA.

Quality risk management

Quality risk was managed according to MSP-QR-0001. The system was found to be relatively immature and needs further work. Whilst there was evidence of risk assessments in certain cases, the consistency and extent of assessments and management plans need further improvement. The main tool used in the company was FMEA. The FMEA risk reduce template was not attached to and the calculation was not described fully in relevant SOPs.

2. Personnel

Personnel qualifications

There were an adequate number of personnel who were suitably qualified through qualifications, experience and training. Responsibilities were described, including in position descriptions for all personnel.

Personnel hygiene

Personnel were required to wear protective clothing suitable for the type and stage of manufacturing. Suitable sanitation and change room facilities were provided. Smoking and eating was not permitted in manufacturing areas.

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 provided appropriate space for the placement of equipment.

Workshop 1 (WS1) was used for the four steps synthesis, drying and packaging of WHO grade Praziquantel API. Final crystallization took place in a controlled and classified area and centrifuging, drying and packaging in Grade D clean area.

Water system

There was one PW station on site. PW meet CP and EP standard. PW was used in equipment cleaning and final purification step. Controls appeared satisfactory.

4. Process equipment

Design and construction

Equipment used in the manufacture of Praziquantel appeared to be of appropriate design and size for its intended use. In general cleaning and maintenance appeared satisfactory. Manufacture and material transfer took place in closed systems wherever possible.

Computerized systems

Computerized systems were not used for material or production control.

A computerized system was used in QC lab for HPLC and GC networking. Basic data integrity controls were in place.

5. Documentation and records

Documentation system and specifications

Documents were managed according to a written procedure. Activities were documented in SOPs and other appropriate documents such as batch manufacturing records (BMRs). These were all approved and version controlled. All records and other documentation requested during the inspection were readily available. Several of the SOPs inspected were found to be a little too brief and high level to be fully effective and improvements requested. The company was recommended to address this observation in a systematic manner when reviewing and updating its procedures.

Master production instructions (master production and control records)

Approved master production instructions were available for review.

Batch production records (batch production and control records)

After copying master batch records, these were signed, dated and independently checked by quality assurance prior to use.

Batch production record review

The productions records for a batch of Praziquantel manufactured in 2017 and the associated records for the intermediates used in this batch were reviewed and discussed. Batch number allocation was reviewed. Praziquantel with or without micronization were differentiated by product code.

Laboratory control records

Laboratory testing records were kept and available. These are discussed under section 11.

6. Materials management

General controls

Procedures for the receipt, quarantine, storage, handling, sampling, testing and approval or rejection of materials were inspected and generally found satisfactory. The company had mainly manual controls and systems in place. In some cases several documents were needed to construct an entire history of the movement of a lot and records could be improved to make the system easier to operate.

Receipt and quarantine

On receipt, materials were checked for damage and against the approved supplier list. Non-compliances observed during the inspection, listed in the full report regarding material code management were addressed by the manufacturer to a satisfactory level.

Sampling and testing of incoming production materials

Materials were sampled by QC following documented sampling procedures and tested by QC before release. The tank farm for solvents delivered by trucks was inspected. The procedures for sampling and testing of incoming solvents were found to be satisfactory and the hoses for connecting truck and tank were dedicated.

Storage

Materials were stored in designated warehouses that were generally well organized, clean and tidy. Where storage conditions were specified, temperature and humidity was monitored and records maintained. Non-compliances observed during the inspection that was listed in the full report regarding temperature monitoring were addressed by the manufacturer to a satisfactory level.

Finished APIs were stored in a warehouse provided with environmental control. Records indicated that the specified conditions had been maintained.

Re-evaluation

The approved label applied after release included a retest date. All materials examined were within this date. An improvement was made regarding label content and the COA for finished APIs.

7. Production and in-process controls

All of the above production areas were inspected and generally found to be of suitable standard, clean and logically organized to suit their intended purpose. This quantity is well within the operational capacity of the plant.

In-process sampling and controls

In-process sampling was performed at defined stages during processing. In-process samples were test in WS1.

Blending batches of intermediates or APIs

Blending of API batch was permitted. Blending process validation was performed.

Contamination control

API purification, crystallization and drying were performed with dedicated equipment in the clean area of WS1.

8. Packaging and identification labelling of APIs and intermediates

Packaging materials and labels were subjected to quality control before release. Packaging and labelling were not in operation at the time of inspection. The packaging and labelling operations were described in batch packaging instructions. Line clearance 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. A manual bin card system was used to control stock and although the release CoA was available, the release label on the API was discussed.

Distribution procedures

APIs and intermediates were released for distribution following release by the Quality Unit.

10. Laboratory controls

Sample receiving and distribution

Sample receiving procedure and corresponding register were available for inspection. They were reviewed and discussed.

Testing of intermediates and APIs

QC testing was conducted as specified in the relevant specification and according to documented test methods.

Reference standards management procedure was in place. Secondary reference standards were prepared against the primary reference standards.

Reserve/retention samples

There was a designated temperature controlled area for storage of retention samples inside of warehouse. Access to this area was restricted. A sample of each batch of API manufactured was kept. Retention samples were stored in a system that were comprised of the same materials as those used for the final API.

Handling of out of specification (OOS) results

OOS/OOT was managed according to an SOP. The procedure, OOS flow chart and following OOS were reviewed had several issues were noted and corrected in CAPA.

Stability monitoring of APIs

A range of stability chambers were available. Stability monitoring programme and sample were checked. Observations made have been satisfactorily addressed in CAPA.

Data management

The company currently is operating only partially networked HPLC and GC equipment. Basic data integrity controls were in place. System administration was outside of the QA/QC group. It was noted that systems are backed up to two portable hard drives but these were said to be stored in the same location.

11. Validation

Validation and qualification was described in a Validation Master Plan (VMP) and management system procedure for verification and validation. Process validation was required to be either prospective or concurrent.

Validation documentation

Validation protocols for Praziquantel API had been established to define how validation would be conducted. A validation report had been prepared with results compared to acceptance criteria with a documented conclusion.

Process validation protocols and associated validation reports for Praziquantel (PVR 2023) were reviewed and generally found acceptable. Validation of blending protocol and report for the manufacture of Praziquantel were also reviewed.

PV for a new process to produce Praziquantel was on going at the time of inspection. The PV protocol was reviewed and found generally acceptable.

Qualification

Qualification of key equipment was a prerequisite for process validation. Qualification protocols and reports were available for key equipment. These were cross-referenced in the process validation documentation.

Cleaning validation:

SOP, protocol and cleaning validation report for Praziquantel were available for review. Analytical method validation for residue material in cleaning validation was briefly reviewed and discussed.

12. Change control

Change Control was managed according to an SOP and classified into major and other. Several CCs were reviewed.

13. Rejection and re-use of materials

Reprocessing and Reworking

Reprocessing and reworking were managed according to SOPs. They were reviewed and discussed.

Recovery of materials and solvents

Solvents and mother liquor were recovered in the various stages of the production of Praziquantel for use in the production. Recovered solvents were stored in separate storage tanks. Relevant procedures for use of solvent recovery were reviewed and discussed.

14. Complaints and recalls

The company has procedures to manage complaints and recalls. The company periodically tests its procedures but the testing performed annually has only being to the first customer level, and essentially only to domestic customers.

15. Contract manufacturers (including laboratories)

There was no contract manufacturing of Praziquantel API or key starting materials. 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 observations listed in the Inspection Report, ***Jiangsu Chengxin Pharmaceutical Co. LTD. located at No. 338, Shanghai Road, Binjiang Pharm-Chem Industry Park, Qidong, Jiangsu, 226221, P.R. China*** was considered to be operating at an acceptable level of compliance with WHO good manufacturing practices for pharmaceutical products.

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

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

PART 4

List of GMP guidelines referenced in the inspection report

1. WHO good manufacturing practices for 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. Forty-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