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Prequalification Team Inspection services
WHO PUBLIC INSPECTION REPORT
(WHOPIR)
Active Pharmaceutical Ingredient Manufacturer

Part 1	**General information**
Manufacturers details	
Name of manufacturer	Jiangsu Chengxin Pharmaceutical Co Ltd. (CX Pharma)
Corporate address of manufacturer	No. 338, Shanghai Road, Binjiang Pharm-Chem Industry Park, Qidong, Jiangsu, 226221, P.R. China
Inspected site	
Name & 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
Synthetic unit /Block/ Workshop	Workshop-1 (WS-1)
Inspection details	
Dates of inspection	21-24 October 2019
Type of inspection	Routine GMP inspection
Introduction	
Brief description of the manufacturing activities	Jiangsu Chengxin Pharmaceutical Co. Ltd is a manufacturer of APIs, API Intermediates and Starting Materials, Enzyme synthesized product (cosmetic ingredients, food additives) and 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. Based on the presentation delivered at the opening meeting, there were 201 full-time employees at the time of inspection. The main API produced at the site was Praziquantel along with several other APIs. It was confirmed by the company that there were no highly potent, toxic or hazardous substances such as antibiotics, hormones or cytostatics manufactured on-site.
History	This was the second WHO PQ inspection of Jiangsu Chengxin Pharmaceutical Co Ltd, China. The site was first time inspected by WHO Pre-qualification Team (PQT) in January 2018. In addition, the manufacturing site has been inspected by the local Chinese regulatory authorities.

Brief report of inspection activities undertaken – Scope and limitations	
Areas inspected	The inspection focused on the production and control of the aPI, Praziquantel. The scope of the inspection covered the sections of the WHO good manufacturing practices for active pharmaceutical ingredients (APIs), 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 are manufactured in the same workshop as the grade subjected to WHO PQ.
Out of scope	Other starting materials/APIs not relevant to the manufacture of Praziquantel API.
WHO APIs covered by the inspection	Both micronized and non-micronized Praziquantel. Micronisation and non-micronisation are part of the manufacturing processes declared in the PQ dossier. APIMF338 (Praziquantel)
Abbreviations	**Meaning**
AHU	Air handling unit
ALCOA	Attributable, legible, contemporaneous, original and accurate
API	Active pharmaceutical ingredient
APR	Annual product review
BMR	Batch manufacturing record
BPR	Batch production record
CC	Change control
CIP	Cleaning in place
CoA	Certificate of analysis
CpK	Process capability
DQ	Design qualification
EDI	Electronic deionization
EM	Environmental monitoring
FMEA	Failure modes and effects analysis
FPP	Finished pharmaceutical product
FTA	Fault tree analysis
GMP	Good manufacturing practices
HEPA	High-efficiency particulate air
HPLC	High-performance liquid chromatography (or high-performance liquid chromatography equipment)
HVAC	Heating, ventilation and air conditioning
IQ	Installation qualification
KF	Karl Fisher
LAF	Laminar airflow
LIMS	Laboratory information management system
MB	Microbiology

MBL	Microbiology laboratory
MR	Management review
NC	Non-conformity
NRA	National regulatory agency
OQ	Operational qualification
PHA	Process hazard analysis
PLC	Programmable logic controller
PM	Preventive maintenance
PQ	Performance qualification
PQR	Product quality review
PQS	Pharmaceutical quality system
PW	Purified water
QA	Quality assurance
QC	Quality control
QCL	Quality control laboratory
QMS	Quality management system
QRM	Quality risk management
RA	Risk assessment
RCA	Root cause analysis
RO	Reverse osmosis
SMF	Site master file
SOP	Standard operating procedure
URS	User requirements specifications
UV	Ultraviolet-visible spectrophotometer

Part 2	**Summary of the findings and comments**

1. Quality management

A formal framework for quality management had been established, with systems and procedures covering quality elements such as organization structure and responsibilities of key manufacturing personnel, QA, QC, GMP, PQR and QRM and self-inspection**.** The Quality Department, divided into QA and QC, is independent of the Production Department. Management responsibilities were specified in written job-descriptions. Product quality and manufacturing processes were monitored, and these results were considered during batch release.

Product quality review (PQR)

PQR was performed according to a written procedure to demonstrate the reliability of manufacturing processes and consistency of product quality. Management system procedure for annual product review described that PQR was performed on a calendar year basis. In addition to the use of control charts, process capability (CpK) was also performed using the Minitab.

Several batches of non-micronized and micronized Praziquantel of WHO Grade had been manufactured since October 2018. The batch size varied for non-micronized and micronized Praziquantel. Praziquantel was also manufactured for other international markets.

Corrective and preventive action (CAPA)
Management system procedure for CAPA was revised twice since the last WHO PQ inspection. An effectiveness check of the CAPA had been incorporated.

Quality risk management (QRM)
Management system procedure for quality risk assessment was revised after the last WHO PQ inspection. The FMEA tool was used for risk analysis. The procedure was not adequately drafted as to which tool to be used for which risk analysis.

Management review (MR)
Management system procedure for QMS review was discussed. The MR was conducted once every three months and chaired by the General Manager. These management review meetings were attended by the department heads. The General Manager, in turn, provided feedback to the Chairman/owner of the company using formal communication as well as informal platforms.

Handling of deviations
Management system procedure for deviation handling was available and discussed.

2. Personnel

There were adequate number of competent personnel with appropriate qualifications, experience and training. Their responsibilities were described in job and position descriptions. A breakdown of the staff from the different departments are shown in the table below.

Department	Number of staffs
QA	6
QC	18
Production	84
Engineering	17
Warehouse	5
R & D	21
Supply Chain	2
Administration, HR, EHS & Finance	48
Total	201

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 were not permitted in manufacturing areas.

3. Buildings and facilities

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 good space for the placement of equipment.

Workshop 1 (WS-1) was used for a 4-step synthesis, followed by drying and packaging of Praziquantel API. Final crystallization took place in a controlled and classified area, and centrifuging, drying and packaging was conducted in a Grade D clean area.

WS-1 was located in a building with four floors. There were two Praziquantel production lines located in the 3rd and 4th floors of WS-1. Four crystallization tanks were installed in the clean area of WS-1. Micronisation process was performed according to customers' requirement.

4. Process equipment

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 transfers took place in closed systems, wherever possible.

Computerized systems were not used for material or production control. The computerized system was used in the QC lab for HPLC and GC networking.

The procedure for general preventive maintenance requirements for equipment was discussed. An annual maintenance program was developed by the maintenance department and approved by QA. The last schedule was prepared on 28 December 2018, wherein it was specified that equipment were classified A, B and C, with their frequency of preventive maintenance stipulated. Reactors classified as Grade A were more frequently maintained compared to Grade B Reactors (i.e. monthly versus quarterly).

Metrological management procedure was discussed. The procedure described frequency for calibration of pressure gauges, temperature sensors and other pieces of equipment. The calibration schedule dated 2 January 2019 for all equipment and instruments was in place. The schedule described the frequency for calibration of production and laboratory equipment. It was noted that laboratory equipment was calibrated by third party/suppliers whereas most of the production equipment are calibrated by an in-house maintenance department.

5. Documentation and records

Documents were managed according to a written procedure. Manufacturing activities were documented in batch manufacturing records (BMRs) and other appropriate SOPs. These SOPs and documents were all approved, and version controlled. All records and other documentation requested during the inspection were readily available.

Management system procedure for evaluation and releasing of produced products was in place. The quality director was responsible for batch release, and in his absence, the QA manager was responsible. The procedure was supported by a checklist which included a review of changes, deviations, environmental conditions, yield, OOS and data integrity aspects.

6. Materials management

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.

On receipt, materials were checked for damage and against the approved supplier list.

Materials were sampled by QC following a documented sampling procedure and tested by QC before release.

Materials were stored in designated warehouses that were generally well organized, clean and tidy. Where storage conditions were specified, temperature and humidity were monitored, and records maintained.

7. Production and in-process controls

Production of Praziquantel took place in the 3rd and 4th floors. Micronisation and blending operations were carried out when needed.

All the above production areas were inspected and generally found to be of a suitable standard, clean and logically organized to suit their intended purpose.

In-process sampling was performed at defined stages during processing. It was confirmed that in-process testing was carried out in common quality control (QC) laboratory.

The inspectors visited WS-1 and the following points were noted:

- WS-1 was spread over 4 floors of the building
- The synthesis was performed on the 3rd and 4th floor of the building
- Centrifugation, wet milling and drying were performed on the 1st floor
- Recrystallization was performed on the 1st floor (in a cleanroom)

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.

9. Storage and distribution

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.

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

10. Laboratory controls

There was an independent quality department comprising of quality assurance and quality control. The director quality was the overall in-charge of quality operations.

The procedures, specifications and methods of analysis were in place for the product in question.

- Specification of non-micronized Praziquantel was in place. There were some changes made since the last revision, such as the formatting and validation of the Excel spreadsheet used for calculation of assay, related substances and residual solvents.)
- Specification of micronized Praziquantel was in place.

Out of specifications (OOS)
Management system procedure for OOS/OOT was revised twice after the last WHO PQ inspection. In 2018, a total of 26 OOS were reported by the company. 21 OOS related to WS-1 or Praziquantel, 10 related to raw material, intermediate and recovery of solvents, and residual solvent (methylene chloride) in the finished product. In 2019, a total of 12 OOS were reported by the company.

Elemental impurities
Risk assessment was performed on elemental impurities based on the analysis of three batches. It was confirmed that no control strategy was available and the routine production batches did not need to be tested for elemental impurities. The test for elemental impurities was carried out by the third party. The qualification was based on some paper assessment which included the certificate to demonstrate that ICAS had been accredited to ISO/IEC 17025:2005 by CNAS.

Stability study program
Management system procedure for stability program was in place. The procedure stated that at least one batch should be added for on-going stability monitoring program at 30 degrees C/65% RH and 30 degrees C/75% RH. The stability study on the initial validation batches were completed up to 24 months for non-micronized Praziquantel, and 12 months for micronized. Praziquantel. The procedure appeared to be ambiguous as it stated that the stability study needs to be conducted at 40 degrees C/75% RH for ongoing stability study batches.

Nitrosamine impurities
The risk assessment of the existing manufacturing processes was performed by the company to confirm the absence of nitrosamine impurities in the products made by the company.

Data integrity system
The company has a networked computerized system for all their HPLC and GC equipment. Basic data integrity controls were in place.

11. Validation
Validation and qualification were described in a Validation Master Plan (VMP).

Cleaning validation protocol and cleaning validation report were in place and discussed.

Analytical method validation protocol and AMV report were in place.

Process validation
It has been noted that the company has made two changes in the existing validated process of Praziquantel. The company confirmed that no revalidation was required for these changes.

Air-handling units
The operation and performance qualification of HVAC of the cleanroom for WS-1 was in place and discussed. The HEPA leak test was performed by an outside party whereas the rest of the tests were performed by in-house engineers. The requalification was performed once per year.

12. Change control

Management system procedure for change control was in place. Two changes pertaining to the manufacturing process were discussed.

13. Rejection and re-use of materials

Reprocessing and reworking were managed according to written procedures.

14. Complaints and recalls

Management system procedure for customer complaints was in place and discussed.
Management system procedure for product recall was in place and discussed. A committee (comprising the general manager, marketing manager, production manager) was responsible for the recall of products. A mock recall had been performed for products supplied to the India and Hong Kong markets.

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 – Inspection outcome**

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 GMP Guidelines for APIs.

All the non-compliances observed during the inspection that were listed in the full report 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. ***Short name: WHO GMP for APIs or WHO TRS No. 957, Annex 2***
   http://apps.who.int/medicinedocs/documents/s20119en/s20119en.pdf

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. ***Short name: WHO GMP*** or ***WHO TRS 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.
   Short name: WHO TRS 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.
   Short name: WHO TRS No. 929, Annex 4
   http://whqlibdoc.who.int/trs/WHO_TRS_929_eng.pdf?ua=1

5. Guidelines on heating, ventilation and air-conditioning systems for non-sterile pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-second Report Geneva, World Health Organization, 2018 (WHO Technical Report Series, No. 1010), Annex 8. ***Short name: WHO HVAC Guidelines*** *or* ***WHO TRS No. 1010, Annex 8***
   http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_1010/en/

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.
   Short name: WHO TRS 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.
   Short name: WHO TRS 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.
   Short name: WHO TRS 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.
   Short name: WHO TRS 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.
    Short name: WHO TRS 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. ***Short name: WHO TRS 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. ***Short name: WHO TRS 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.
    Short name: WHO TRS 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. ***Short name: WHO TRS 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. ***Short name: WHO TRS 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. ***Short name: WHO TRS 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. ***Short name: WHO TRS 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. ***Short name: WHO TRS 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. ***Short name: WHO TRS 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 production 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
Short name: WHO TRS No. 992, Annex 6
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

21. 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.
Short name: WHO GDRMP guidance or WHO TRS No. 996, Annex 5
http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex05.pdf

22. 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.
Short name: WHO Multisource guidance or WHO TRS No. 996, Annex 10
http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex10.pdf

23. Stability testing of active pharmaceutical ingredients and finished pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-second Report Geneva, World Health Organization, 2018 (WHO Technical Report Series, No. 1010), Annex 10.
Short name: WHO TRS No. 1010, Annex 10
http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex10.pdf