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Prequalification Team Inspection services
WHO PUBLIC INSPECTION REPORT
Active Pharmaceutical Ingredients

Part 1	**General information**
Manufacturers details	
Name of manufacturer	**Changzhou Yabang - QH Pharmachem Co., Ltd** No.18, Jinlong Road, Chunjiang Town, Xinbei District, Changzhou City, Jiangsu Province, P. R. China North latitude: 31.9744N East longitude: 119.9663E
Corporate address of manufacturer	As above
Name & address of inspected manufacturing site if different from that given above	As above
Buildings	J and V
Workshops	Plant 1 Plant 3: Line I and Line II
Dates of inspection	20 - 23 May 2019
Type of inspection	Routine
Introduction	
Brief description of the manufacturing activities	The company manufactures APIs and API intermediates for human and veterinary use.
General information about the company and site	Changzhou Yabang - QH Pharmachem Co., Ltd was established in 2004. Most of its manufacturing facilities were constructed in 2004 and 2005, but workshop 3 was designed and constructed in 2007-2010. The site has four chemical workshops, several warehouse buildings, one utility building, one QC/R&D building and two administration buildings. It is located 28 kilometers from the business center of Changzhou city. The city is about 200 kilometers away from Shanghai city. The company already obtained a GMP certificate and certification on ISO 14001 Environmental Protection Management System and OHSAS 18001 Occupational Health and Safety Management System.

History	

Authority	Dates of inspection
Jiangsu Province Food and Drug Administration	March 2014
EDQM	April 2015
Ministry of Agriculture of P. R. China	June 2015
Jiangsu Province Food and Drug Administration	February 2016
World Health Organization	July 2016
U.S. Food and Drug Administration	November 2016

Areas inspected	See Part 2 below
Restrictions	N/A
Out of scope	APIs out of scope of prequalification
WHO products numbers covered by the inspection	API for Anthelmintic medicine

Abbreviations	**Meaning**
AC	Air conditioner
ADE	Acceptable daily exposure
ADR	Adverse drug reaction
AHU	Air handling unit
ALCOA	Attributable, legible, contemporaneous, original and accurate
API	Active pharmaceutical ingredient
APQR	Annual product quality review
AQL	Acceptance quality limit
ATTC	American Type Culture Collection
BMR	Batch manufacturing record
BPR	Batch production record
CAPA	Corrective action preventive action
CC	Change control
CCEA	Complete, consistent, enduring, available
CDS	Chromatography data systems
CFU	Colony-forming unit
CIP	Cleaning in place
CoA	Certificate of analysis
Cpk	Process capability
DQ	Design qualification
EDI	Electro-deionization
EM	Environmental monitoring
EP	European Pharmacopoeia
FMEA	Failure modes and effects analysis
FPP	Finished pharmaceutical product
FTA	Fault tree analysis
GMP	Good manufacturing practices
GPT	Growth promotion test
HEPA	High efficiency particulate air

HPLC	High-performance liquid chromatography (or high-performance liquid chromatography equipment)
HVAC	Heating, ventilation and air conditioning
IPC	In-process control
IQ	Installation qualification
IT	Information technology
KPI	Key performance indicator
LAF	Laminar air flow
LIMS	Laboratory information management system
LIR	Laboratory investigation report
LoD	Limit of detection
LOD	Loss on drying
MACO	Maximum allowable carry over
MB	Microbiology
MBL	Microbiology laboratory
MF	Master formulae
MR	Management review
MSDS	Material safety data sheet
NC	Non-conformity
NCA	National control authority
NCL	National control laboratory
NOEL	No observed effect level
NRA	National regulatory agency
OOS	Out of specification
OOT	Out of trend
OQ	Operational qualification
P&ID	Piping and instrumentation diagram
PDE	Permitted daily exposure
PHA	Process hazard analysis
PLC	Programmable logic controller
PM	Preventive maintenance
PPE	Personal protective equipment
PQ	Performance qualification
PQR	Product quality review
PQS	Pharmaceutical quality system
PW	Purified water
QA	Quality assurance
QC	Quality control
QCL	Quality control laboratory
QP	Qualified Person
QMR	Quality management review
QMS	Quality management system
QRM	Quality risk management
R&D	Research and development
RA	Risk assessment
RCA	Root cause analysis
RH	Relative humidity
RO	Reverse osmosis

RPN	Risk priority number
SMF	Site master file
SOP	Standard operating procedure
T	Temperature
URS	User requirements specification
UV	Ultraviolet-visible spectrophotometer
WFI	Water for injection

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

1. Quality system

Principle

Production and control operations were specified in written form and GMP requirements were essentially being met. Product and processes were monitored, and the results were reviewed as part of the approval process of batch release. Regular monitoring and reviews of the quality of pharmaceutical products were being conducted according to documented schedules and procedures.

Management review (MR)

SOP "Quality management review (QMR)" and QMR minutes from April 2019 were briefly discussed. According to the SOP, the QMR should be performed every 3 months. QMR standard agenda was specified and according to the QMR report followed. KPIs were specified.

Product Quality Review (PQR)

SOP "Product quality review and report" was briefly discussed. PQRs per product type were required to be performed. The review period was specified as a calendar year, namely January - December. The review was to be completed in the first quarter of the following year - PQR should be performed by end of March. The company stated that all batches were included in the review, irrespective of whether product was distributed to the domestic or export market or if manufactured in Plant 1 or 3. If no commercial production occurred during review period, a PQR was required to be performed.

Process capability was evaluated by Cpk.

The annual PQR for 2018 for XX manufactured in Plant 1 and Plant 3 was discussed.

Quality Risk Management

SOP "Quality risk management procedure" was briefly discussed. The completed RA register was presented to inspectors. SOP specified circumstances for periodic RA review. According to the SOP, review of performed RAs should be carried out quarterly and depended on classification of risk.

Deviations

SOP "Deviation management procedure", its flow chart and register were briefly discussed. were classified as:

- Critical
- Non-critical

Preliminary classification was done by department and confirmed/approved by QA. Deviations related to the manufacturing processes were recorded in the relevant BMR/BPR. QC related deviations were recorded in the analytical worksheets. A number of deviation investigation records were briefly discussed.

Corrective actions and preventive actions (CAPA)
SOP "Corrective actions and preventive actions", its flow chart and registers for 2018 and 2019 were briefly discussed. The SOP was applicable but not limited to:

- Deviations
- Abnormal results
- Complaints
- PQR
- Self-inspection
- External audits

CAPAs were classified according to 3 levels and CAPAs were trended every 3 months and trends were compiled annually. It was discussed that trending by levels should be included in trends and management review as well as specified in registers.

A number of CAPA records were briefly discussed, CAPAs records also contained CAPA follow up actions and effectiveness checks.

Change control (CC)
SOP "Change control procedure" and its flow chart was briefly discussed. A number of CCs records were briefly discussed

Complaints
SOP "Customer complaint", its flow chart and register from 2017 were briefly discussed. Handling of customer complaints was the QA department responsibility. According to the SOP, complaints should be trended annually. Investigation of complaint should be finalized within 30 working days, if not possible "interim investigation report" should be prepared and sent to the customer. Complaints were categorized as:

- Label
- Packaging
- Product quality
- Others

A number of complaint investigation records were briefly discussed.

Recalls
SOP "Product recall" and its flow chart were briefly discussed. Decision about a recall should be made by the Qualified Person (Vice General Manager, Quality). Recall committee, consisting of top management, was responsible for handling recalls. Recalls were classified as:

- Class I: Notification within 24 hours.
- Class II: Notification within 48 hours.
- Class III: Notification within 72 hours.

Effectiveness of the recall procedure was checked by performing mock recall every 2 years. Mock recalls were performed for domestic and export market. According to the company there were no actual recalls.

Documentation
SOP "Good documentation management" was briefly discussed. SOP was applicable to all paper-based documents.

Personnel

The following documents were briefly discussed:

- SOP "Training procedure".
- Training plan for 2019 and training follow-up register.
- SOP "Analysts technical training". Job specific training should be carried out annually. Practical performance of analysts was observed by the supervisor and results compared with already tested sample. Acceptance criteria were specified.
- Analyst training record for XX.
- Production supervisor and operator training records. Training effectiveness was evaluated using multiple choice questions and open questions.
- Qualification and training of internal auditors was explained in SOP. Lead auditor training records were briefly discussed.

2. Production system

Production operations followed defined procedures. Significant deviations from the initial protocol were recorded and investigated, root causes were determined and CAPAs were implemented where necessary. Checks on yields and reconciliation of quantities were carried out. Access to production premises was restricted to authorized personnel.

3. Facilities and equipment system

In general production premises were located, designed, constructed, adapted and maintained to suit the operations to be carried out. Premises were cleaned and disinfected according to written procedures; records were maintained. In general production premises visited were seen to be maintained in good order. Production areas were equipped with automatic alarming gas detectors (flammable and explosive) and the required equipment was grounded. Inspectors visited Plant 3 synthesis area; centrifugation and Plant 3 Line 1 clean rooms.

Validation and qualification

A number of equipment qualification protocols and reports were briefly discussed.

SOP "Process validation" was briefly discussed.

Cleaning validation

SOP "Cleaning validation program" was briefly discussed and cleaning validation was required under the following conditions:

- New product introduced
- New cleaning procedure introduced
- New equipment introduced

For each piece of equipment, the most difficult to clean was determined.

SOP "Cleaning validation procedure", its flow chart and SOP "Acceptance criteria used for cleaning validation" were briefly discussed. The SOPs were based on APIC "Guidance on aspects of cleaning validation in active pharmaceutical ingredient plants".

Utilities HVAC

Two AHUs supplied air to clean rooms. The HEPA filter integrity test was contracted out and performed annually. Pressure differentials between primary and secondary filters was checked daily and filters were replaced either annually or when pressure differentials reached specified pressure limits. Filters change log was presented to inspectors. AHUs visited were seen to be well maintained and in good order, however condensate drain cleaning procedure was not in place.

Utilities Purified water (PW)

PW was generated by reverse osmosis and equipped with electro-deionization (EDI). Conductivity, temperature and water velocity were monitored online at return loop. Inspectors visited PW system located at Plant 3. Water was circulated at ambient temperature.

Laboratory premises

Inspectors visited chemical/physical and microbiology laboratories. Laboratory facilities were of a suitable size, construction and location and were designed to suit the functions and operations to be conducted. Chemical/physical/instrumental laboratories were separated from the microbiological laboratory. Laboratories were seen to be clean and well maintained.

Laboratory equipment

The following SOPs were briefly discussed:

- SOP "QC computer system management procedure"
- SOP "Electronic data management procedure in QC lab".

OOS

SOP "Out of specification" was briefly discussed.

Stability studies

Inspectors visited the stability study room. Adequate number of chambers was provided for stability studies including calibrated stand-by chambers. T and RH was recorded online every 30 minutes and checked daily. Stability chambers were provided with an audible and text message alarm system.

Stability studies were conducted as follows:

- Real time studies were performed at 25 °C ± 2 °C at 60 % ± 5 % and 30 °C ± 2 °C at 75 % ± 5 % for 5 years.
- Accelerated studies were performed at 40 °C ± 2 °C at 75 % ± 5 % for 6 months.

Retention samples

Retention samples of each batch of API was retained for 1 year after the expiry date or after all sales of the batch (3 years), whichever is the longer. The samples were stored in the same packaging system as the API.

QC Microbiology

The Microbiology laboratory was separated from the Chemistry laboratory. Access was restricted to authorized personnel only. The laboratory activities, such as media, equipment preparation, growth promotion testing, positive testing, sample testing and enumeration of microorganisms was segregated. There were appropriate entry and exit procedures, including gowning procedures.

4. Laboratory control system
During the laboratory tour, inspector cross-checked XX API batch No. YY analytical raw data with equipment ID numbers and usage logs, reference standard usage log, no discrepancies were noted.

SOP 2 "Data integration procedure for chromatographic system" was briefly discussed. Manually integration was considered as a deviation. Manual integration was approved by QA manager.

Reference standards were stored in a room along with samples waiting for analysis and leftovers from analysis.

5. Materials system
Inspectors visited the solid materials (starting materials and intermediates) and finished good warehouses. Materials in the warehouses visited were stored in orderly fashion to permit batch segregation and stock rotation. There was no computerised system for stock control - This was controlled manually.

The following documents were briefly discussed:
- SOP "Handling procedure for rejected products". The procedure explained handling of OOS raw materials, intermediates and APIs.
- SOP "Recovered materials handling procedure". SOP was applicable to solvents and mother liquids recovery. However, the company stated that only solvents could be recovered. Maximum allowed recovery cycles were specified in the product master production instruction.
- SOP "Returned product handling procedure" and register.

6. Packaging and labelling system
During inspection packaging and labelling operations were not carried out. It was explained that labels applied to bags and containers were printed and controlled by QA.

Part 3	**Initial 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, ***Changzhou Yabang - QH Pharmachem Co., Ltd,*** located at ***No.18, Jinlong Road, Chunjiang Town, Xinbei District, Changzhou City, Jiangsu Province, P.R.China*** was considered to be operating at an acceptable level of compliance with WHO good manufacturing practices for active pharmaceutical ingredients guidelines.

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. ***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 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 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. 961, 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

24. Production of water for injection by means other than distillation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-forth Report. Geneva, World Health Organization, 2020 (WHO Technical Report Series, No. 1015), Annex 3.
Short name: WHO TRS No. 1025, Annex 3
https://www.who.int/publications-detail/978-92-4-000182-4

25. Good chromatography practice. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-forth Report. Geneva, World Health Organization, 2020 (WHO Technical Report Series, No. 1025), Annex 4.
Short name: WHO TRS No. 1025, Annex 4
https://www.who.int/publications-detail/978-92-4-000182-4

26. Points to consider for manufacturers and inspectors: environmental aspects of manufacturing for the prevention of antimicrobial resistance. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-forth Report. Geneva, World Health Organization, 2020 (WHO Technical Report Series, No. 1025), Annex 6.
Short name: WHO TRS No. 1025, Annex 6
https://www.who.int/publications-detail/978-92-4-000182-4

27. WHO guidance on good practices for desk assessment of compliance with good manufacturing practices, good laboratory practices and good clinical practices for medical products regulatory decisions. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-second Report. Geneva, World Health Organization, 2018 (WHO Technical Report Series, No. 1010), Annex 9.
Short name: WHO TRS 1010, Annex 9
https://www.who.int/medicines/areas/quality_safety/quality_assurance/TRS1010annex9.pdf?ua=1