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Prequalification Unit Inspection Services
WHO PUBLIC INSPECTION REPORT
(WHOPIR)
Active Pharmaceutical Ingredient Manufacturer

Part 1	**General information**
Manufacturers details	
Name of manufacturer	Pen Tsao Chemical & Pharmaceutical Industry Co., Ltd. (PTCI SH)
Corporate address of manufacturer	Pen Tsao Chemical Industry Ltd (PTCI HK) 27 B CKK Commercial Centre, 289 Hennessy Road, Wanchai Hong Kong SAR, China
Name & Address of inspected manufacturing site if different from that given above	Pen Tsao Chemical & Pharmaceutical Industry Co., Ltd. (PTCI SH) No 2, Tieli Road, Baoshan, Shanghai, 200940, PR China
Synthetic Unit /Block/ Workshop	MPRP – multipurpose reaction plant FTU I & III & V
Inspection details	
Dates of inspection	11 – 14 March, 2024
Type of inspection	Routine
Introduction	
Brief description of the manufacturing activities	Production and quality control of intermediates and APIs
General information about the company and site	Pen Tsao Chemical & Pharmaceutical Industry Co., Ltd. is located in the Baoshan district of Shanghai and is wholly owned subsidiary of Pen Tsao Chemical Industry Ltd., a Hong Kong registered company.
History	Previous WHO GMP onsite inspection was performed in February 2021. The site was inspected by PMDA in 2023 and was regularly inspected by the local authority Shanghai NMPA.
WHO products covered by the inspection	• APIMF105 Ethionamide • APIMF106 Prothionamide • APIMF324 Clofazimine
Brief report of inspection activities undertaken – Scope and limitations	
Areas inspected	• Quality management • Personnel • Buildings and facilities • Process equipment

	• Documentation and records • Materials management • Production and in-process controls • Packaging and identification labelling of APIs and intermediates • Storage and distribution • Laboratory controls • Validation • Change control • Rejection and reuse of materials • Complaints and returns • Contract manufacturers (including laboratories) **Site areas visit:** • Production workshops • Warehouses • Quality laboratory • HVAC system • Water system
Restrictions	The scope of the inspection was restricted to the API in the WHO PQ programme.
Out of scope	Facilities used for other API production were out of the inspection scope.
Abbreviations	**Meaning**
AHU	Air handling unit
ALCOA	Attributable, legible, contemporaneous, original and accurate
API	Active pharmaceutical ingredient
APR	Annual product review
BER	Batch Analysis Record
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 air flow
LIMS	Laboratory information management system
MB	Microbiology
MBL	Microbiology laboratory
MR	Management review
NC	Nonconformity
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
QP	Qualified person
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
WFI	Water for injection

Part 2	**Summary of the findings and comments (where applicable)**

1. Quality management

A system for managing quality that involved participation of management and appropriate manufacturing personnel was in place. Quality-related activities were defined and documented. The Quality department was independent of the production department. Persons authorized to release intermediates and APIs were specified. Quality-related activities were recorded at the time they were performed. Deviations from established procedures were documented and explained. Regular internal audits were performed in accordance with an approved schedule. The effectiveness of CAPAs were monitored. Regular reviews of the quality of pharmaceutical products were conducted. Quality risk management procedure was in place.

2. Personnel

An organization chart was available. The key personnel of the various department had pharmaceutical qualification and were experienced in pharmaceutical manufacturing. At the time of the current inspection, the site employed approximately 101 employees.

Job description

Job descriptions of QC department manager and QA staffs, as well as the QP were checked and found acceptable.

Training

An adequate number of qualified, trained and experienced personnel was available. All employees were subject to regular training according to the company's training procedure and annual training plan.

Hygiene

The SOP "Staff health policy" was checked. For new personnel, medical examinations were foreseen before joining the company and repeated yearly. Direct contact was avoided between the operator's hands and starting materials, primary packaging materials and intermediate or bulk product. Smoking, eating, drinking, and keeping personal medicines was forbidden in production areas. Personnel with an infectious disease or who have open lesions on the exposed surface of the body were not allowed to work with open product.

3. Buildings and facilities

Design and construction

The production blocks used for the manufacture of Ethionamide and Prothionamide were multi-functional and not dedicated to these APIs. The final stages of Clofazimine production were performed in a dedicated workshop.

QC laboratories

Laboratory area and operations were separate from production areas.

Purified Water (PW) system

The water system was visited. PW generation scheme was documented. System was in continuous circulation via UV. Flow rate, conductivity and temperature were checked on-line. The physical-chemical and microbiological analysis followed the SOP "Process water management regulations".

HVAC system

HVAC units served the area of FTU I-IV was briefly visited and found to be generally satisfactory.

Environmental monitoring (EM)

EM covered clean rooms and secondary change rooms. Total microbial counts and airborne particles were monitored.

Nitrogen system

Nitrogen used in production was supplied in cylinder from external suppliers.

4. Process equipment

Design and construction

Equipment used in the manufacture of Ethionamide, Prothionamide and Clofazimine was in general of appropriate design and size for its intended use.

Equipment maintenance

The SOP "Equipment maintenance management regulation" was checked. Records of equipment maintenance, cleaning and use were maintained. They were found generally acceptable. Equipment maintenance plan in 2024 was available and reviewed.

Calibration

The SOP "Measuring instrument verification & calibration regulation" was checked. The procedure defined that Technical department was responsible for all equipment calibration. The equipment list and calibration schedule were available. Spot checks showed that schedules were followed. The calibration status of selected equipment in production was checked and found to be valid.

5. Documentation and records

Documents related to the manufacture of intermediates or APIs were prepared, reviewed, approved and distributed according to written procedures. The issuance, revision, superseding and withdrawal of all documents was controlled and revision histories maintained.

An established procedure for retention of documents was in place. Document retention periods were specified. Records of major equipment use, cleaning, sanitization and maintenance showed the date, time, product and batch number of each batch processed in the equipment, and the person who performed the cleaning and maintenance. Laboratory control records included complete data derived from all tests conducted to ensure compliance with established specifications and standards.

6.Materials management

A manual system was used for material management.

Supplier management

The SOP "Supplier evaluation and audit procedure" was checked. All critical materials purchased from suppliers were listed in the company's Approved Supplier List. The procedure stated that only suppliers, that have the relevant qualification documentation and have subsequently sustainably provided qualified material would be accepted and maintained as an Approved Supplier. If necessary, a member of QA team is required to perform site audits to the suppliers of critical materials. New supplier and approved Suppliers are required to be reassessed periodically according to the SOP.

Warehouses

Several warehouses were briefly visited. Different dedicated warehouse areas for a range of starting materials had been established. Generally, the warehouses were adequately maintained. The materials status control and management were acceptable.

The company had a separate tent warehouse facility used for the storage of materials for recycling and sale to other chemical manufacturers. The rejected materials store was also located in the tent warehouse. The access control and the rejected material logbook was checked.

7. Production and in-process controls

Production blocks MPRP production area for Prothionamide and Ethionamide and FTU-V for Final purification, crystallization, drying and packaging of Clofazimine were visited. Adequate status labels on the major equipment indicated the status of the synthetic processes being performed.

Blending batches of intermediates or APIs

The SOP "Regulation for blending batches of API products" was checked. Blending was allowed for tailings of batches and small batches, which complied with specification.

Contamination control

Final Clofazimine API drying, and packaging were performed using dedicated equipment in the clean area of plants.

8. Packaging and identification labelling of APIs and intermediates

Packaging materials and labels were subjected to quality control before release. Packaging and labelling were in operation at the time of inspection. The packaging and labelling operations were described in batch packaging instructions. Line clearance was checked and showed that it was done before and after labelling/packaging procedures.

10. Storage and distribution

Warehousing procedures

API products were stored in the finished product warehouse and held until released by the authorized person. The environmental condition for finished API storage was monitored and recorded for temperature and RH. The monitoring results were satisfactory.

A manual bin card system was used to control stock. The release procedure and labelling of the API were inspected and discussed.

Distribution procedures

APIs were released for distribution following release by the Quality department. They were found generally acceptable.

11. Laboratory controls

The physical and chemical testing of starting materials, packaging materials, intermediates and finished APIs was conducted in the QC laboratory. Procedures were in place describing sampling, testing, approval, or rejection of materials and recording and storage of laboratory data. Specifications and sampling plans were available.

Laboratory controls were followed and documented at the time of performance. Departures from procedures were documented and explained. OOS results obtained were investigated and documented according to a procedure.

A Microbiological laboratory was not available on the site. Microbiological testing for PW and API products were done by a contract laboratory,

Stability study

Stability studies were performed according to written protocol and addressed in PQRs. The sample register was maintained. Stability chambers were provided, including standby chambers at following condition:

- 25 ± 2 °C, RH 60 ± 5%
- 30 ± 2 °C, RH 65 ± 5%
- 30 ± 2 °C, RH 70 ± 5%
- 40 ± 2 °C, RH 70 ± 5%

Chambers were equipped with sound and text message alarm system.

Certificate of an analysis (CoA)

Templates of the CoA were available specifying test items and specifications. Tests results were entered by QC manager assistant or Laboratory supervisor. CoA was approved by QC manager.

Data management

The SOP "Management and operation of backup and recovery for Agilent OpenLab system" was checked. HPLCs were networked, unlike the IR and UV which were stand-alone equipment. HPLC and GC data restoration followed the SOP "Management of Agilent OpenLab data store system" and the SOP "Laboratory data integrity management procedure".

Sample receiving and distribution

Sample of finished APIs, packaging materials and raw materials were collected by QC personnel. Samples receiving/storage/distribution records were maintained. Samples for analysis were distributed by Laboratory supervisor following the SOP "Sampling management procedure".

OOS management

The SOP "QC laboratory deviations and OOS" was checked. OOS investigations were performed following:

- Phase I Lab investigations
- Phase II full scale investigations

Retention samples

APIs retention samples was managed following the SOP "Retention sample management procedure".

Laboratory equipment calibration

Laboratory equipment/instrument calibrations were performed, and records kept. Equipment/instruments were calibrated according to written procedures and an established schedule. Calibration status of

equipment/instruments was known and verifiable. All laboratory equipment/instruments had usage logbooks. Calibration labels were attached to all equipment/instruments.

12. Validation

Validation and qualification were required to be performed according to written procedure. The validation documentation was checked and discussed. The revalidation was required to be performed according to "Validation and qualification management procedure" and "PV procedure". Annual validation plan for 2024 was available.

Cleaning validation

The SOP "Cleaning validation procedure" and the Cleaning validation documentation for Clofazimine API were checked and discussed.

Analytical method validation

The analytical method validation report for testing Clofazimine API residue in the cleaning validation was spot checked. The LOD and LOQ of UV method appeared meeting the residue limit.

Equipment qualification

The equipment qualification of some instruments was checked. The qualification report including IQ, OQ, and the PQ performed with an actual production batch were documented and found acceptable.

Computerized system validation

Computerized systems were not used for material or production control.

13. Change control (CC)

In general, change control system was established. Potential impact of the proposed change on the quality of the intermediate or API was evaluated. Measures were taken to ensure that documents affected by the changes were revised. Clients and manufacturers of the finished dosage forms were notified of changes from established production and process control procedures that can impact the quality of the API.

The SOP "Change control procedure" and SOP "Change notification procedure" were checked. According to the SOP risk assessment were performed for every change. Changes were classified as:

- Minor
- Major
- Critical

The CC register for 2023 and several major CCs were checked.

Deviations

The SOP "Deviation control procedure" was checked. Deviations were classified as:

- Minor
- Critical
- Repeated

Deviations were recorded in BMR. The 2023 deviation register was in place. Several deviations were checked.

CAPA

The SOP "Corrective and preventive action Procedure" was checked. QA was responsible for follow up and implementation of CAPAs. CAPAs logbook for 2023 was checked. Tools used for root cause analysis (RCA) were explained in the risk assessment procedure.

14. Rejection and re-use of materials

The SOP "Operation for reprocessing, reworking and destroying" was checked. Reprocessing/reworking were reviewed by Quality team and approved by QA manager. It was stated that until the date of inspection no batches were reworked. The register for reprocessing was maintained.

15. Complaints and recalls

Complaints

Quality-related complaints were recorded and investigated according to the "Procedure for handling customer complaint and ADR report". Records of complaints were retained. Complaints were classified as:

- Minor
- Major

If necessary, complaint investigation could lead to the product recall. According to the SOP investigation should be performed to identify if previous batches should be investigated. Timeline for closing complaints was specified. The complaint registered in 2023 was checked.

Recalls

The SOP "Product return/recall procedure" was checked. Recalls were classified as:

- Class I
- Class II
- Class III

According to the SOP, a mock recall should be performed periodically.

16. Contract manufacturers (including laboratories)

Manufacturing activities were not contracted out. Several external contract laboratories were used. The testing service agreement with contract laboratories were available and checked. The GMP responsibilities of the contract giver and contract acceptor were defined. The contract permitted the contract giver to audit the contract acceptor's facilities.

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, ***Pen Tsao Chemical & Pharmaceutical Industry Co., Ltd. (PTCI SH), manufacturing blocks MPRP, FTU I & III & V,*** located at ***No 2, Tieli Road, Baoshan, Shanghai, 200940 P.R. China*** was considered to be operating at an acceptable level of compliance with WHO GMP guidelines.

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 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.
   Short name: WHO TRS No. 986, Annex 2

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.
   Short name: WHO TRS No. 957, Annex 2

3. WHO Good Manufacturing Practices: water for pharmaceutical use. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-Fifth Report. Geneva, World Health Organization, 2021 (WHO Technical Report Series, No. 1033), Annex 3.
   Short name: WHO TRS No. 1033, Annex 3

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

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

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

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

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 3.
   Short name: WHO TRS No. 957, Annex 3

9. WHO good manufacturing practices for sterile pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-Sixth Report Geneva, World Health Organization, 2022 (WHO Technical Report Series, No. 1044), Annex 2.
   Short name: WHO TRS No. 1044, Annex 2

10. WHO guidelines on technology transfer in pharmaceutical manufacturing. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-Sixth Report Geneva, World Health Organization, 2022 (WHO Technical Report Series, No. 1044), Annex 4.
    Short name: WHO TRS No. 1044, Annex 4

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**

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

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

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

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

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

17. Good Manufacturing Practices: Guidelines on validation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-Third Report Geneva, World Health Organization, 2019 (WHO Technical Report Series, No. 1019), Annex 3.
Short name: WHO TRS No. 1019, Annex 3

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

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

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

21. Guideline on data integrity. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-Fifth Report Geneva, World Health Organization, 2021 (WHO Technical Report Series, No. 1033), Annex 4.
Short name: WHO TRS No. 1033, Annex 4

22. 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.
Short name: WHO TRS No. 996, Annex 10

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

24. Guidelines on heating, ventilation and air-conditioning systems for non-sterile pharmaceutical products. Part 2: Interpretation of Guidelines on heating, ventilation and air-conditioning systems for non-sterile pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-Third Report Geneva, World Health Organization, 2018 (WHO Technical Report Series, No. 1019), Annex 2.
Short name: WHO TRS No. 1019, Annex 2

25. Points to consider when including Health-Based Exposure Limits in cleaning validation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-Fifth Report Geneva, World Health Organization, 2021 (WHO Technical Report Series, No. 1033), Annex 2.
Short name: WHO TRS No. 1033, Annex 2

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-Fourth Report Geneva, World Health Organization, 2020 (WHO Technical Report Series, No. 1025), Annex 6.
Short name: WHO TRS No. 1025, Annex 6

27. Production of water for injection by means other than distillation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-Fourth Report. Geneva, World Health Organization, 2020 (WHO Technical Report Series, No. 1025), Annex 3.
Short name: WHO TRS No. 1025, Annex 3

28. Good chromatography practice. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-Fourth Report. Geneva, World Health Organization, 2020 (WHO Technical Report Series, No. 1025), Annex 4.
Short name: WHO TRS No. 1025, Annex 4

29. WHO good practices for research and development facilities of pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-Sixth Report Geneva, World Health Organization, 2022 (WHO Technical Report Series, No. 1044), Annex 6.
Short name: WHO TRS No. 1044, Annex 6

30. WHO good manufacturing practices for investigational products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-Sixth Report Geneva, World Health Organization, 2022 (WHO Technical Report Series, No. 1044), Annex 7.
Short name: WHO TRS No. 1044, Annex 7

31. WHO good manufacturing practices for excipients used in pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-Fourth Report. Geneva, World Health Organization, 2024 (WHO Technical Report Series, No. 1052), Annex 2.
Short name, WHO TRS No. 1052, Annex 2