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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	Pen Tsao Chemical & Pharmaceutical Industry Co., Ltd.
Corporate address of manufacturer	27B CKK Commercial Centre, 289 Hennessy Road, Wanchai, Hong Kong SAR, China
Inspected site	
Address of inspected manufacturing site if different from that given above	No. 2. Tieli Road, Wusong Shanghai 200940, China
Unit / block / workshop number	MPRP and FTU
Manufacturing license number	Shanghai 20110069
Inspection details	
Dates of inspection	16 -19 November 2015
Type of inspection	Routine inspection
Introduction	
Brief summary of the manufacturing activities	Production and quality control of APIs
General information about the company and site	Pen Tsao Chemical & Pharmaceutical Industry Co., Ltd. is located in Shanghai. It was a manufacturer of fine chemicals, pharmaceutical intermediates and APIs. It was solely owned by Pen Tsao Chemical Industry Ltd. which was registered in Hongkong, SAR,China. At the time of the inspection the site employed approximately 125 employees. Amongst buildings with different functions and other facilities at the site the following were inspected: – MPRP workshop - Multi-Purpose Workshop for intermediates – FTU workshops – Clean area for API finishing – Finished product warehouse

	– Raw material and packaging material warehouses – "Temporary storage area" – QC laboratory There were other intermediates and APIs manufactured at this site at the time of inspection.
History	This was a third WHO inspection with previous inspections by WHO performed in August 2012 and November 2012. This was a routine WHO GMP inspection. The site had been inspected by Japanese PMDA in 2013, but the inspection scope in terms of facilities and products was different to the WHO inspections.
Brief report of inspection activities undertaken	
Scope and limitations	
Areas inspected	The inspection covered the following sections of the WHO GMP for Active Pharmaceutical Ingredients text: • Quality management • Personnel • Buildings and facilities • Process equipment • Documentation and records • Materials management • Production and in-process controls • Packaging and identification labelling of APIs and intermediates • Storage and distribution • Laboratory controls • Validation • Change control • Rejection and reuse of materials • Complaints and recalls • Contract manufacturers (including laboratories)
Restrictions	No
Out of scope	No
WHO product numbers covered by the inspection	Ethionamide (APIMF 105) Prothionamide (APIMF 106)

Abbreviations

AHU	air handling unit
ALCOA	attributable, legible, contemporaneous, original and accurate
API	active pharmaceutical ingredient
APQR	annual product quality review
BDL	below detection limit
BMR	batch manufacturing record

BPR	batch packaging record
CAPA	corrective actions and preventive actions
CC	change control
CFU	colony-forming unit
CoA	certificate of analysis
CpK	process capability index
DQ	design qualification
EM	environmental monitoring
FAT	factory acceptance test
FBD	fluid bed dryer
FMEA	failure modes and effects analysis
FPP	finished pharmaceutical product
FTA	fault tree analysis
FTIR	Fourier transform infrared spectrometer
GC	gas chromatograph
GMP	good manufacturing practice
HACCP	hazard analysis and critical control points
HPLC	high-performance liquid chromatograph
HVAC	heating, ventilation and air conditioning
IR	infrared spectrophotometer
IQ	installation qualification
KF	Karl Fisher
LAF	laminar air flow
LIMS	laboratory information management system
LoD	limit of detection
LOD	loss on drying
MB	microbiology
MBL	microbiology laboratory
MF	master formulae
MR	management review
NMR	nuclear magnetic resonance spectroscopy
NRA	national regulatory agency
OQ	operational qualification
PHA	process hazard analysis
PM	preventive maintenance
PpK	process performance index
PQ	performance qualification
PQR	product quality review
PQS	pharmaceutical quality system
QA	quality assurance
QC	quality control
QCL	quality control laboratory
QRM	quality risk management
RA	risk assessment

RCA	root cause analysis
SOP	standard operating procedure
TAMC	total aerobic microbial count
TFC	total fungi count
TLC	thin layer chromatography
URS	user requirements specifications
UV	ultraviolet-visible spectrophotometer

Part 2	Brief summary of the findings and comments (where applicable)

Brief summary of the findings and comments

1. QUALITY MANAGEMENT

Principles
The quality management system was generally established, documented and implemented.

The site organizational structure was presented and was generally found acceptable. Quality-related activities were defined and documented. The Quality Assurance department was independent from production. The persons authorized to release intermediates and APIs were specified. The General Manager was the qualified Person responsible for product quality.

The inspected two APIs Ethionamide and Prothionamide have been prequalified by WHO PQ programme. The company manufactured a number of grades regarding these two APIs.

Ethionamide (APIMF 105):
Grade: USP, IP, EP and EPW

Prothionamide (APIMF 106):
Grade: IP, CP, BPD, BPDW, BP

Product quality review (PQR)
The SOP for PQR was reviewed. Product PQRs reviewed included Ethionamide PQR 2014 and Prothionamide PQR 2013. They were found generally acceptable. Both PQRs indicated that processes were consistently able to produce API's that met specifications.

Quality Risk Management
Quality risk management and risk assessment was handled and performed according to quality risk management procedure. The quality risk regarding the introduction of new products was reviewed and discussed during the inspection.

Release of intermediates and APIs
The intermediates and APIs manufactured at the site were released before distribution by the QA manager according to a product release procedure.

2. PERSONNEL

Personnel qualifications

There was adequate number of personnel qualified to perform and supervise the manufacture of intermediates and APIs. Key personnel responsibilities were specified in a written document. Job descriptions were reviewed including Qualified Person/General Manager, Vice General Manger, QA manager, QC manager, and production managers. The QC manager was newly recruited at the time of the inspection.

Training

Training was conducted according to a SOP on training procedure. Training programme and records were maintained. Some training records was reviewed and discussed.

Personnel hygiene

Sanitation on the site was considered to be acceptable in general. The requirements for entry into the Grade D cleanrooms were documented, including by photographs on change room walls. Staff observed in these areas wore appropriate protective clothing.

3 BUILDINGS AND FACILITIES

Design and construction

In general buildings and facilities used in the manufacture of intermediates and APIs were located, designed and constructed to facilitate appropriate cleaning and maintenance. The manufacturing facilities were multi-functional and not dedicated to the inspected APIs.

The workshops and the facilities inspected including workshops of MPRP and FTU were maintained to be acceptable.

Intermediates were manufactured in the block MPRP which was Multi-Purpose Workshop. The main production activities included dilution, reaction, phase separation, concentration (distillation), centrifugation, crystallization.

There was a Clean Room Class D Area with four separate Units (FTU). The production activities included concentration, crystallization, centrifugation, drying, and packaging.

Utilities

Adequate ventilation, air filtration and exhaust systems were provided. The HVAC system provided filtered air to the Grade D cleanrooms. The air from FTU was directly exhausted and was not recycled.

Water

Purified water system consisted of one RO followed by mix bed column. The source water was supplied by the local municipality.

Purified water was used in the final purification of ETA and PTA APIs. The testing and monitoring of the purified water were reviewed and discussed during the inspection.

Containment

The APIs in the inspection scope were produced in non-dedicated facilities. There were no other highly sensitizing materials either produced or handled at this site, nor were there any other APIs of high pharmacological activity, such as steroids or cytotoxic as claimed by the company management.

Lighting

Lighting was considered to be adequate in all areas visited during the inspection.

4 PROCESS EQUIPMENT

Design and construction

The process equipment was multi-purpose. The equipment had unique identification number. The equipment used to manufacture APIs was generally of an acceptable standard and of suitable design and construction for the allocated processes. Additional new type of equipment was introduced into the production since last WHO inspection.

Equipment maintenance and cleaning

Equipment was maintained according to written SOP and an annual schedule of required maintenance was available. Documented cleaning procedures for equipment were reviewed. Equipment use records were maintained and recorded.

Calibration

All measuring equipment examined was labelled with a calibration sticker. All were being used within their calibration dates.

Computerized systems

No computerized systems were used in the production of APIs. There was a software used in the warehouse for material receiving and dispensing purpose.

5 DOCUMENTATION AND RECORDS

Documentation system and specifications

Documents were controlled according to several written SOPs. Documents were reviewed every three years if there was no change made.

According to a SOP, API batch records were required to be retained for a specified the time period, and electronic data were required to be back up regularly. Records required to be maintained were also available and were generally satisfactory.

Equipment cleaning and use record

Records of equipment cleaning and use were kept in an equipment log book. Equipment status labels and product logs of equipment use were available in place.

Records of raw materials, intermediates, API labelling and packaging materials

Manual systems were used for records of raw materials, intermediates, API labels and packaging materials. The sample of records of material receipt, quarantine, release and status labelling were satisfactory.

Master production instructions (master production and control records)
An approved master batch production and packaging record was available for API and was controlled by QA.

Batch production records (batch production and control records)
Batch production records were prepared for APIs inspected according to the master BMR. The batch numbers were generated according to a SOP.

Laboratory control records
Laboratory control records, including data derived from tests conducted, were inspected. Records for the sampling and testing of Ethionamide batches and purified water were reviewed and discussed.

Batch production record review
Batch production records were prepared for the APIs inspected and included information relating to the production and control of each batch in general.

6 MATERIALS MANAGEMENT

General controls
There were written procedures describing the receipt, labelling, quarantine, storage, and handling of materials, as well as the procedures for sampling, testing and approval or rejection of materials.

Vendor qualification
A SOP for Supplier Evaluation and Audit Procedure was reviewed and found acceptable.

Receipt and quarantine
Materials were examined upon receipt and placed in quarantine until tested and released.

Sampling and testing of incoming production materials
Production materials were sampled in a designated sampling area according to a sampling plan and tested by QC before release. The containers sampled were identified.

Storage
Various warehouses for the storage of specified materials were available. Temperature and humidity requirements were specified and monitored. The records reviewed indicated compliance with the specifications. Pest control stations were evident at various points within and outside the warehouses.

All the warehouses visited were clean and tidy with materials well organized and appropriately labelled.

Re-evaluation
Material labels included a re-test date. Released materials examined were within their re-test dates.

7 PRODUCTION AND IN-PROCESS CONTROLS

Production operations

Raw materials were weighed using suitable equipment. The processing status of major equipment was indicated by means of attached tags. Examination of the flow of the manufacturing process and relevant equipment was in line with the BMR and the process described in the submitted dossier generally.

Expected yields at key stages were specified in the BMR and actual yields were required to be within the limits specified. Some of production operations such as synthesis and drying were conducted during the inspection.

In-process sampling and controls

In-process controls were performed and considered to be acceptable.

Blending batches of intermediates or APIs

Validation protocol and report for Ethionamide blending process were reviewed. The validated blending range was specified. The validation studies were considered to be acceptable.

8 PACKAGING AND IDENTIFICATION LABELLING OF APIs AND INTERMEDIATES

General

Packaging and labelling operations were conducted as per standard operating procedures in controlled areas. The packaging remained the same as the last inspection.

Label issuance and control

This was not covered by this inspection.

Packaging and labelling operations

Packaging and labelling materials were managed according to a SOP for reception, identification, and release. Packaging and labelling operations were not carried out during the inspection.

9 STORAGE AND DISTRIBUTION

Warehousing procedures

The solid, liquid and flammable liquid raw materials were stored separately in warehouses. The environmental conditions in the raw material warehouses were not controlled.

The finished API products were stored in the finished product warehouse. The warehouse temperature was controlled within the specified condition.

Distribution procedures

APIs were released for distribution after being released by the quality assurance department. The product release management procedure was reviewed and no observation was made.

10 LABORATORY CONTROLS

General controls

The QC laboratories were responsible for physical and chemical testing of starting materials, packaging materials, intermediates, products (API's) and microbiology testing of environmental monitoring samples.

The quality control unit was equipped with GC, HPLC, UV-VIS spectrophotometer, pH meter, analytical balances, KF titrator etc. No networked software was used in the analytical instrument. The testing procedure and the data were reviewed and discussed regarding the data security and traceability.

The microbiology testing of the APIs and the purified water were performed by a contract laboratory.

Testing of intermediates and APIs

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

Stability monitoring of APIs

Stability study was conducted under $30^0C \pm 2^0C$, RH 65% ± 5%. The accelerated stability study was under $40^0C \pm 2^0C$, RH 75% ± 5%. Stability study was performed according to a SOP on management procedure of stability monitoring.

Reserve/retention samples

Appropriately identified retention samples of each batch of were retained for one year beyond the expiry date. The retention sample was stored in the same packaging system in which the API was stored.

Handling of out of specification (OOS) results

A procedure for handling of out of specification material and a procedure for handling of out of specification product were reviewed and discussed during the inspection.

11 VALIDATION

Validation policy

The company's overall validation policy was described in a SOP on validation and qualification management procedure. Revalidation/requalification was performed every 5 years if there were no changes.

Process validation programme

Critical process parameters were controlled and monitored during process validation studies.

Documents for process validation related to the inspected products were reviewed and considered acceptable. The process validation of EPA performed in 2015 was trigged by the batch size increase.

Cleaning validation

The cleaning validation status remained unchanged since last inspection.

Validation of analytical methods

The analytical method remained the same as the last inspection.

12 CHANGE CONTROL (CC)

A change control procedure described requirements for handling any change. Changes regarding PTA manufacturing process, product shelf life extension and adding a new distillation equipment were reviewed.

A deviation control procedure and deviation register were available for inspection. A deviation regarding packaging of a PTA batch was reviewed and considered acceptable.

13 REJECTION AND RE-USE OF MATERIALS

A product return/recall procedure and an operation procedure for product reprocessing, reworking and destroying were reviewed and considered acceptable.

14 COMPLAINTS AND RECALLS

According to product quality review inspected, there had been no complaints or recalls of the APIs in the inspection scope. A mock recall was performed according to a SOP.

15 CONTRACT MANUFACTURERS (INCLUDING LABORATORIES)

According to the company, the only manufacturing/quality control activity "contracted out" was the microbiology testing of APIs, and purified water.

PART 3

Conclusion

Based on the areas inspected, the people met and the documents reviewed, and considering the findings of the inspection, including the deficiencies listed in the Inspection Report, as well as corrective actions taken and planned, Ethionamide (APIMF 105) and Prothionamide (APIMF 106) manufactured at Pen Tsao Chemical Industry Limited located at No. 2. Tieli Road, Wusong Shanghai, China were considered to be manufactured in compliance with WHO GMP for Active Pharmaceutical Ingredients.

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

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

PART 4

List of GMP guidelines referenced in the inspection report

1. WHO good manufacturing practices for active pharmaceutical ingredients. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957), Annex 2.
http://www.who.int/medicines/publications/44threport/en/

2. WHO good manufacturing practices for pharmaceutical products: main principles. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-eight Report Geneva, World Health Organization, 2014 (WHO Technical Report Series, No. 986), Annex 2.
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_986/en/

3. WHO Good Manufacturing Practices: water for pharmaceutical use. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fourth-six Report. Geneva, World Health Organization, 2012 (WHO Technical Report Series, No. 970), Annex 2
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_970/en/

4. WHO guidelines for sampling of pharmaceutical products and related materials. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-ninth Report. Geneva, World Health Organization, 2005 (WHO Technical Report Series, No. 929), Annex 4
http://whqlibdoc.who.int/trs/WHO_TRS_929_eng.pdf?ua=1

5. WHO guidelines on good manufacturing practices for heating, ventilation and air-conditioning systems for non-sterile pharmaceutical dosage forms. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 5
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

6. Supplementary guidelines on good manufacturing practices: validation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fortieth Report. Geneva, World Health Organization, 2006 (WHO Technical Report Series, No. 937), Annex 4
http://whqlibdoc.who.int/trs/WHO_TRS_937_eng.pdf?ua=1

7. WHO Good Practices for Pharmaceutical Quality Control Laboratories. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957, Annex 1
http://www.who.int/medicines/publications/44threport/en/

8. WHO Good Practices for Pharmaceutical Products Containing Hazardous Substances. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957), Annex 2
http://www.who.int/medicines/publications/44threport/en/

9. WHO good manufacturing practices for sterile pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 6
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

10. WHO guidelines on transfer of technology in pharmaceutical manufacturing WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 7
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

11. Model guidance for the storage and transport of time-and temperature-sensitive pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 9
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

12. General guidelines for the establishment maintenance and distribution of chemical reference substances. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-First Report Geneva, World Health Organization 2007 (WHO Technical Report Series, No.943) Annex 3
http://whqlibdoc.who.int/trs/WHO_TRS_943_eng.pdf?ua=1

13. WHO good practices for pharmaceutical microbiology laboratories. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 2
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

14. WHO guidelines on quality risk management. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Seventh Report Geneva, World Health Organization, 2013 (WHO Technical Report Series, No. 981), Annex 2
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_981/en/

15. WHO guidelines on variation to a prequalified product. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Seventh Report Geneva, World Health Organization, 2013 (WHO Technical Report Series, No. 981), Annex 3
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_981/en/

16. WHO guidelines for drafting a site master file. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 14
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

17. WHO Guidelines on good manufacturing practices: validation, Appendix 7: non-sterile process validation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 3
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

18. WHO General guidance on hold-time studies WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 4
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

19. WHO Technical supplements to Model Guidance for storage and transport of time – and temperature – sensitive pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 5
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

20. WHO Recommendations for quality requirements when plant – derived artemisin is used as a starting material in the prosecution of antimalarial active pharmaceutical ingredients. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 6
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

21. WHO good manufacturing practices for biological products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifties Report Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 3
http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex03.pdf

22. Guidance on good data and record management practices. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifties Report Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 5
http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex05.pdf

23. WHO general guidance on variations to multisource pharmaceutical products. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifties Report* Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 10
http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex10.pdf

24. WHO good manufacturing practices for biological products. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifties Report* Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 3
http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex03.pdf