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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	Pen Tsao Chemical Industry Ltd. 27 B CKK Commercial Centre, 289 Hennessy Road Hong Kong
Inspected site	
Address of inspected manufacturing site if different from that given above	No. 2. Tieli Road, Wusong, Shanghai 200940, China GPS: 31° 21' 59.47" N, 121° 28' 21.77" E
Unit / block / workshop number	MPRP & FTU
Manufacturing license number	HU20160083
Inspection details	
Dates of inspection	4 – 7 July 2017
Type of inspection	Routine inspection
Introduction	
Brief summary of the manufacturing activities	Production and quality control of APIs and intermediates
General information about the company and site	Pen Tsao Chemical & Pharmaceutical Industry Co., Ltd. is located in Shanghai and is solely owned by Pen Tsao Chemical Industry Ltd., a company registered in Hong Kong. At the time of the inspection the site employed approximately 129 employees. The company produces different kinds of produces including anti-TB and anti-leprosy APIs. The company also manufactures a range of intermediates.

History	Previous inspections by WHO had been conducted in 2012 and 2015. The site had been regularly inspected by the local CFDA and had also been inspected by Japanese PMDA in 2013.
Brief report of inspection activities undertaken	
Scope and limitations	
Areas inspected	Amongst buildings with different functions and other facilities at the site the inspection included the following areas: – MPRP workshop - multi-purpose workshop for intermediates and APIs – FTU workshops – clean area for API finishing – Finished product warehouse – Raw material and packaging material warehouses – QC laboratory – FTU-V workshop - partially completed new workshop dedicated to Clofazimine manufacture (see restrictions below) 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	Although the inspection was originally planned to included Ethionamide, Prothionamide and Clofazimine APIs, during the inspection it became apparent that it was not going to be possible to establish GMP compliance for the manufacture of Clofazimine API and another inspection would be required for this API. The new facility was at the stage where major equipment had been installed awaiting pipework connections etc., and was expected to be completed before the end of this year. For the above reasons, the outcome of this inspection can be considered as relevant to Ethionamide and Prothionamide APIs only.
Out of scope	Areas, activities and procedures not relevant to the manufacture of Ethionamide or Prothionamide APIs
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 reviewed and was generally acceptable. Quality-related activities were defined and documented. The Quality Assurance function was independent from production. The persons authorized to release intermediates and APIs were specified.

Product quality review (PQR)
The SOP for PQR was reviewed. The SOP specified that all API variations must be reviewed annually. Responsibilities for PQR were well described. Data was required to be analyzed by various means, including control charts or Cpk, depending on the type of data. The SOP had been changed after the last WHO inspection and appeared to be satisfactory.

The 2016 PQRs for Ethionamide and for Prothionamide were reviewed and were generally acceptable.

Quality Risk Management
Quality risk management and risk assessment was handled and performed according to a Quality risk management procedure. Non-compliances observed during the inspection regarding risk assessment of introduction of new products to the multi-purpose API workshop were addressed by the manufacturer to a satisfactory level.

Release of intermediates and APIs
APIs manufactured at the site were released before distribution by the QA manager according to a SOP on Product Release. Responsibilities for the various steps in the release process were described and there were specific checklists to be used for each product code.

The QA Manager was responsible for final review and release. In the event of this person's absence, the delegation of two other QA personnel had been approved by the QP and QA Manager.

2. Personnel

There appeared to be an adequate number of personnel qualified to perform and supervise the manufacture of intermediates and APIs. Responsibilities were described in various documents, including job descriptions and in SOPs. The sample of documents reviewed generally appeared to be satisfactorily.

The training SOP was reviewed. Personnel hygiene was generally considered to be acceptable. The requirements for entry into the Grade D cleanrooms were documented, including by pictures on change room walls. Staff observed in these areas wore appropriate protective clothing.

3. Buildings and facilities

In general the buildings and facilities used in the manufacture of intermediates and APIs were considered suitable for their intended use. They were located, designed, and constructed to facilitate appropriate cleaning and maintenance. The manufacturing facilities used to manufacture Ethionamide and Prothionamide were multi-functional and not dedicated to these APIs. Adequate ventilation, air filtration and exhaust systems were provided. The HVAC system provided filtered air to the Grade D cleanrooms (FTU).

Purified water was used in the final purification of Ethionamide and Prothionamide APIs. Purified water was produced by RO and a mixed bed ion exchange column with distribution through a stainless steel loop to usage points. The source water was supplied by the local municipality. The system appeared to be well maintained and the results of regular monitoring showed that it was under satisfactory control.
Lighting in the areas visited during the inspection was considered adequate.

4. Process equipment

Process equipment in the MPRP and FTU workshops used to manufacture Ethionamide and Prothionamide was multi-purpose. The equipment was uniquely identified and status labels were used to indicate the status of each piece of equipment. The equipment used to manufacture APIs was generally of a satisfactory standard and of suitable design and construction for the allocated processes.

Equipment was required to be maintained according to written procedures and an annual schedule for preventive maintenance was available. Examples of preventive maintenance procedures and records for selected equipment (e.g. PW water system filters and a centrifuge) were reviewed and found satisfactory.

Measuring equipment was labelled with its calibration status and all reviewed were within their calibration due dates.

5. Documentation and records

Documents were required to be managed according to an SOP. This procedure was generally considered satisfactory. Documents were required to be reviewed every three years, but were not re-issued if no change was required. Some records of the review process were examined and were found satisfactory.

Cleaning procedures and records of equipment cleaning and use were maintained.

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

An approved master batch production and packaging record was available for each API and was controlled by QA. Batch production records were prepared from the master BMR for the APIs inspected. Batch numbers were generated according to an SOP and records of this were maintained.

A sample of completed batch production records for Ethionamide and Prothionamide were reviewed and generally found acceptable.

6. Materials management

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.

Materials were required to code numbers according to an SOP. Document for the list of material codes was present, but this document was not complete or properly approved.

Material suppliers were required to be approved according to a SOP on Supplier Evaluation and Audit. As an example of the process, the evaluation of the supplier of one material was reviewed and found satisfactory. The supplier of this material was included in the list of approved suppliers available in the warehouse. Non-compliances observed during the inspection that was listed in the full report regarding the identification of the actual manufacturer of the material were addressed by the manufacturer to a satisfactory level.

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

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 inspected were clean and tidy with materials well generally organized and appropriately labelled.
Material labels included a re-test date. Released materials examined were within their re-test dates.

7. Production and in-process controls

Examination of the flow of the manufacturing process and relevant equipment was in line with the BMRs examined during the inspection to MPRV. Raw materials were weighed using suitable equipment. The processing status of major equipment was indicated by means of attached batch tags.

Expected yields at key stages were specified in the BMR and actual yields were required to be within the limits specified. In-process controls were performed by the QC laboratory and the records reviewed were considered to be acceptable.

Although a multipurpose facility, precautions to minimize the likelihood of cross contamination had been taken. For example, centrifuge bags were dedicated to specific APIs and were appropriately labelled accordingly.

The final stages of production, e.g. purification and drying, were conducted in a Grade D environment.

Deviations were required to be handled according to an SOP. Deviations were risk classified as critical and minor by QA. The deviation register for 2017 was reviewed and a sample of reported deviations reviewed. The SOP required a 3 monthly QA review of deviations for trends and this had been recorded. The system for handling deviations was considered to be satisfactory.

8. Packaging and identification labelling of APIs and intermediates

Packaging and labelling operations were conducted as per standard operating procedures in controlled areas. There was no activity in this area during the inspection.

Packaging and labelling materials were managed through the SOP for reception, identification, and release of materials. Finished APIs were required to be labelled according SOP on Label Management Procedure. Finished API labels were printed in-house and checked by QA before application to containers.

9. Storage and distribution

The separate warehouses for solid, liquid and flammable liquid raw materials were visited during the inspection. None of the materials viewed were labelled with particular storage requirements and the environmental conditions in the raw material warehouses were not controlled. However they were monitored, with temperature and humidity recorded for information.

Finished APIs were stored in the finished product warehouse. The environmental requirements for finished API storage were specified as 10-28ºC and RH 30-70%, and were controlled by air-conditioning. The results of regular monitoring were satisfactory.

A locked solid wall room within a soft wall outside structure was available for storing rejected materials.

APIs were released for distribution after being released by the Quality Assurance department. Distribution procedures were not reviewed.

10. Laboratory controls

The QC laboratory was responsible for physical and chemical testing of starting materials, packaging materials, intermediates and finished APIs.

Since the last inspection, HPLC and GC instrument had been networked using suitable system. The server was in a different building and was equipped with a separate UPS. Two SOPs relevant to the management and control of the system were reviewed on Computer System Management and Regulation, and Management of Agilent OpenLab Data Store System. Non-compliances observed during the inspection that was listed in the full report regarding computerized system management and validation were addressed by the manufacturer to a satisfactory level.

Microbiological testing was done by a contract laboratory with samples collected by QC personnel. Sample collection and management was required to be done according to SOP. Guidance on sample collection was provided and the procedure required a driver to be waiting to take the samples to the contract lab immediately. The 2016 microbiological test results for purified water and Ethionamide API were selected for review and found satisfactory.

Ongoing stability studies were required to be conducted according to SOP. Suitable stability chambers were available.

Retention samples of each batch of API were required to be retained for one year beyond the expiry date. Retention samples were stored in the same packaging system in which the API was stored.

The out of specification handling procedure was reviewed during the inspection.

11. Validation

Validation and qualification was required to be performed according to a SOP on Validation and Qualification Management. The process validation SOP was applicable to both validation and re-validation and reasons for re-validation were described. The SOP covered prospective, concurrent and retrospective validation, with guidance on the use of these approaches.

For each API, the status of validation activities was required to be reviewed during the annual PQR. The 2016 PQR for Ethionamide listed a number of validations that had been done during 2016 and as an example the protocol and reports were reviewed. Conclusions had been recorded and the validation study was considered to be satisfactory.

Cleaning validation was required to be performed according to SOP. Cleaning validation regarding shared equipment was reviewed. Non-compliances observed during the inspection that was listed in the full report regarding cleaning validation were addressed by the manufacturer to a satisfactory level.

A computerized system had been introduced in the QC lab since last inspection. The computerized system validation was reviewed.

12. Change control

The change control (CC) SOP and change control register for 2017 were available and checked. Several CCs, including Ethionamide batch size change were reviewed.

13. Rejection and re-use of materials

The Operation Procedure for reprocessing, reworking and destroying SOP had not been changed since the last inspection and was considered acceptable. A reprocessing record was reviewed.

14. Complaints and recalls

Complaints were required to be handled according to an SOP which was reviewed and found to be satisfactory. According to the 2016 PQRs for Ethionamide and Prothionamide there were no complaints for these APIs during 2016. The complaints register for 2017 was examined and there were also no complaints for these APIs for 2017 to date.

15. Contract manufacturers (including laboratories)

Microbiological testing was contract out to an external laboratory. According to SOP, the laboratory was required to be assessed and approved, and contract agreement for the services required signed by both parties. The contract agreement was also reviewed and found satisfactory. The contract laboratory had been audited in March 2016 and the report was reviewed.

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 and Prothionamide manufactured at
Pen Tsao Chemical & Pharmaceutical Industry Co., Ltd. located at No. 2. Tieli Road, Wusong, Shanghai 200940, China
was 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-eighth Report Geneva, World Health Organization, 2014 (WHO Technical Report Series, No. 986), Annex 2.
   http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_986/en/

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
   http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_970/en/

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

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

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

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

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

9. WHO good manufacturing practices for sterile pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 6

http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

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

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

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

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

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

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

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

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

18. WHO General guidance on hold-time studies WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 4

http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

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

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

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

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

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

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