WHO PUBLIC INSPECTION REPORT (WHOPIR) API Manufacturer

Part 1: General information

Name of Manufacturer	Second Pharma Co. Ltd
Unit number	NA
Production Block	101 (Isoniazid workshop)
Physical address	HangZhou Gulf Fine Chemical Zone, Shang Yu City, Zhejiang Province, 312369 CHINA
Contact person and email address.	Mr Guo Yongzheng guoyongzheng@zjxsk.com
Dates of inspection	10 to 13 November 2015
Type of inspection	Routine inspection
Active Pharmaceutical Ingredient(s) included in the inspection	Isoniazid (APIMF 168)
Summary of the activities performed by the manufacturer	Production and quality control of APIs

Part 2: Summary

General information about the company and site

Second Pharma Co Ltd. was established in 2003. It is located at Hangzhou Gulf fine Chemical Zone, Shang Yu City, Zhejiang Province of China. The whole site occupies an area of approximately 133,400 m^2 with a built up area of 66,700 m^2 including 3 workshops for APIs manufacturing. Approximately 400 staff was employed at the site at the time of the inspection. The site operates in 3 shifts.

Second Pharma Co Ltd. manufactures a range of APIs, but no beta lactams, steroids or hormones. The main products manufactured on the site include Valsartan, Amlodipine Besylate, Bendazol (Dibazole), Isoniazid, Nicotinamide, Sulfamethazine, Terazosin HCL and Levetiracetam. The API facilities included dedicated blocks (synthesis, purification and finishing) for Isoniazid API.

No computer system was used in the material management, QC and production.
Isoniazid was manufactured in the production block 101 (formally 101B).

There were two manufacturing processes for Isoniazid APIs. The Isoniazid API was produced as the different grades including: CP, EP/ BP, USP, WHO etc.

History of WHO and/or regulatory agency inspections

This was a third WHO inspection with previous inspections by WHO performed on 14 to 16 March 2012 and 11 to 14 December 2012.

The site had been inspected by US FDA in 2009, 2012 and 2015, but the inspection scope in terms of facilities and products was different to the WHO inspections.

Focus of the inspection

The inspection focused on the production and control of Isoniazid API. The inspection covered all the sections of WHO good manufacturing practices for active pharmaceutical ingredients, including premises, equipment, documentation, materials, validation, sanitation and hygiene, production, quality control and utilities.

Inspected Areas

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)

PART 3: INSPECTION OUTCOME

3.1 QUALITY MANAGEMENT

The quality management system was generally established, documented and implemented. The site organizational structure was reviewed and was 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.

Quality Risk Management

QRM was conducted according to a SOP. Risk assessment report regarding the process parameter was reviewed. Non-compliances observed during the inspection that was listed in the full report regarding quality risk management were addressed by the manufacturer to a satisfactory level.

Product quality review (PQR)

PQRs were conducted on an annual basis according to Annual Product Review SOP. The 2013 and 2014 PQRs for Isoniazid API were reviewed. The required elements had been considered and documented.

Deviation management

The Deviation Procedure and Deviation Register were reviewed. Some deviation records related to Isoniazid were spot checked. The procedure was followed properly.

Batch numbering system:

Batch numbering procedure referenced a SOP was reviewed and was found acceptable in general. The system allowed differentiating the finished APIs obtained from the two manufacturing processes.
Product code of Isoniazid:02
02150401 to 02150407 normal batch
02150408 tailing blended batch
02150409 batch using recovered mother liquor
02150410 reprocessing batch
Batch number +R: reworked batch
Batch number +M: micronised batch

The general OOS procedure SOP, 2015 OOS log book and OOS records were reviewed.

Self-audits

The SOP for self-audits was reviewed. Self-audits were performed at least every 12 months. 2015 self- audit protocol was planned to be performed in the October 2015.

3.2 PERSONNEL

Personnel qualifications

There was adequate number of personnel suitably qualified by education and training to perform and supervise the manufacture of APIs. The personnel met during the inspection were experienced and appeared to be knowledgeable about GMP.

An organization chart was available. Key personnel responsibilities were specified in job descriptions.

Training

Training was conducted according to a SOP. Annual training plan for 2015 and training record of a staff in Registration department was reviewed.

Personnel Hygiene

The requirements for entry into the Grade D cleanrooms were well documented, including by approved photographs on change room walls. Staff observed in these areas wore appropriate protective clothing.

3.3 BUILDINGS AND FACILITIES

Design and construction

In general, the building and facilities used to produce Isoniazid appears to be adequate for the operation. The maintenance and housekeeping of the production area and warehouse are basically acceptable.

Utilities

Four Air Handling Units for four different cleaning areas were installed in the same room on the 3rd floor of west side of Workshop 101. Among these AHUs, one dedicated AHU was equipped to the cleaning area for Isoniazid.

Water

There were two purified water system on the site. Purified Water System 1 which had two loops A and B for workshop 101 was inspected. The second water system supplied the purified water to loop 202 E.

Loop B went through the cleaning area used for Isoniazid. On Loop B, there was a small Loop D to provide cold PW (≤10°C) to wash the API cakes after centrifugation. In April 2014, 3 new use points of Loop D were added. The change control was raised and DQ/IQ/OQ/PQ was completed in May 2014. The design of Purified Water System 1 was reviewed and discussed.

Procedures for purified water quality monitoring and for cleaning and distribution of purified water were available and reviewed. 2014 Annual review report on Purified Water System 1 was reviewed. No deviation was found. The microbial limit testing results of all points of use were less than 10 cfu/ml. The alert limit and action limit were established.

Lighting

Lighting in all areas visited was appeared to be adequate.

Sanitation and maintenance
All manufacturing areas visited appeared to be maintained and clean at an acceptable level.

Containment
As claimed by the company, there were no penicillin, cephalosporin or other highly sensitizing materials or APIs of high pharmacological activity (such as steroids or cytotoxic) produced or handled at the site.

3.4 PROCESS EQUIPMENT

Design and construction
Equipment used for the APIs within the scope of the inspection was generally of an acceptable standard and suitable for intended use. The equipment used for Isoniazid manufacturing was dedicated.

Equipment maintenance and cleaning
Equipment was maintained and cleaned according to written procedure. In May 2013, the Substitution Reactor (3F-13-05-0362) was replaced by a new one due to the leakage of jacket. The size and style of this new Reactor is same as the previous one. DQ/IQ/OQ of the new Reactor was finished in May 2013.

Calibration
Measuring equipment was labelled with a calibration tag when necessary. All of those reviewed indicated that the calibration was within the expiry date. However, it was observed that the level bubble on the balance FM-D010 used in the grade D area was missing.

Computerized systems
No computerized system is applied for Isoniazid production.

3.5 DOCUMENTATION AND RECORDS

Documentation system and specifications
SOPs for Document Control of Document and Printing, distribution, Filling and Filing of the Record were reviewed. The control of documentation has been improved since last inspection. BMRs and Working Sheets for testing were copied and issued by QA department with record. Logbooks were pre-printed and numbered without loose paper.

Equipment cleaning and use record
A SOP on Crystallisation and Centrifugation of Isoniazid and filters cleaning record were reviewed. The cleaning record of equipment was available generally.

Records of raw materials, intermediates, API labelling and packaging materials
All records reviewed relating to materials, including intermediates and APIs were generally acceptable.

Master production instructions (master production and control records)
Isoniazid Production Instruction was reviewed. The version was updated, reviewed and approved according to the SOP of control of documentation. The critical steps and their parameters were consistent with the dossier APIMF168.

Batch production records (batch production and control records)
The current version of BPR for Isoniazid and BMRs of two Isoniazid batches were reviewed. The information included in BPR was traceable.

Batch production record review
The in-process QC records and the completed QC records reviewed were completed and were generally acceptable.

3.6 MATERIALS MANAGEMENT

General controls
Suppliers of materials were required to be approved according to a SOP. Critical suppliers were required to be re-audited once every 2 years and non-critical was 3-4 years. The supplier will be disqualified if there was two times OOS of the material. 2015 audit plan was reviewed. An audit report for the supplier of a key starting material for Isoniazid was reviewed.

Receipt and quarantine
Starting materials were received and quarantined according to SOP.

Sampling and testing of incoming production materials
Sampling of starting materials was performed by QC personnel according to a documented sampling plan. Sampling areas were available in the warehouses.

3.7 PRODUCTION AND IN-PROCESS CONTROLS

Production operations
The final crystallization, drying and packaging of Isoniazid API took place in dedicated and self-contained facilities. The initial process was performed with dedicated equipment in a non-dedicated block.

Processing took place according to the instructions in the BMR. The steps reviewed indicated that the BMR had been kept up to date.

Manufacturing process
Before September 4, 2013, three different processes were used for Isoniazid to different markets. In 2013, the process was improved. There were two manufacturing process used in production of Isoniazid. The process changes were reviewed. Three batches of Isoniazid were produced for validation purpose. Long term and accelerated stability study for the validation batches were performed. Updated dossier to above process change was submitted to WHO and was approved in September 2013.

Time limits
Stability study on holding time for wet Isoniazid API before drying was performed in 2013. The appearance and related impurities were evaluated after for storage of wet Isoniazid.

In-process sampling and controls

The IPC laboratory was located on the first floor of QC lab. IPC was done by QC staff in three shifts.

Blending batches of intermediates or APIs

Control procedure of Fractions from Single Batches and logbooks for tailing Isoniazid were reviewed. BPR of Isoniazid blended batch was spot checked. The practice and control of blending batches of Isoniazid was good and record was traceable and completed.

3.8 PACKAGING AND IDENTIFICATION LABELLING OF APIs AND INTERMEDIATES

The packaging operations of final API's were designed in order to minimize the risk of contact with the environment and personnel. Non-compliances observed during the inspection that was listed in the full report regarding the material management were addressed by the manufacturer to a satisfactory level.

3.9 STORAGE AND DISTRIBUTION

The company had appropriate and separate storage warehouses and areas for starting materials, packaging materials, intermediates, and finished APIs. Appropriate manual records for stock and distribution were maintained.

APIs were stored in Finished Product Warehouse. The temperature and relative humidity were monitored continuously and automatically.

APIs were only released for distribution to third parties after they have been released by the quality assurance unit.

3.10 LABORATORY CONTROLS

General controls

The QC lab was moved from the third floor of Administration Building to a new QC lab located on the first and second floor of the same building from May to October, 2013.

The company had an organized and suitably equipped QC laboratory. Equipment included HPLC, GC and other testing instruments. Agilent HPLCs were networked by a software while Ultimate HPLC were stand alone. Furthermore, inspector was informed that the regulatory submission required data were generated by the registration department including the product testing and method validation. Non-compliances observed during the inspection that was listed in the full report regarding the management in the separate laboratory which generated data for dossier submission were addressed by the manufacturer to a satisfactory level.

Testing of intermediates and APIs

Samples for testing are registered and issued to the analysts by group leaders of Chemical Lab, Microbiological Lab and IPC Lab separately. The size of samples issued to the analysts was sufficient to finish twice of full tests.

A SOP on QC Electronic Data Management was reviewed. Data processing systems of IR, HPLC in QC laboratory were inspected. In microbiological Lab, Testing samples inside the incubator were checked. Non-compliances observed during the inspection that was listed in the full report regarding data management and API testing were addressed by the manufacturer to a satisfactory level.

Validation of analytical procedures

The analytical method for related substance validation performed in 2011 and briefly reviewed.

Stability monitoring of APIs

Long-term Stability Study Protocol of Isoniazid, Accelerated Stability Study Protocol of Isoniazid and study reports were reviewed. Stability studies were performed properly according to the protocols.

Reserve/retention samples

Retention Sample Room was located on the 2nd floor of QC Lab. The temperature and relative humidity in this room were monitored and recorded manually twice every day, not continuously. Specified quantity of Isoniazid per batch was stored as retention samples till one year after the expiry date. The appearance of retention samples was checked once every year.

3.11 VALIDATION

Validation policy

Management of Qualification/Validation SOP, Validation Master Plan for year 2013 and 2015 were reviewed. The qualifications and validations were organized and performed accordingly.

Validation documentation

Protocol and report were drafted, reviewed and approved for each qualification or validation.

Qualification

DQ/IQ/Protocol and Report of Substitution Reactor used for Isoniazid were reviewed. A reactor's OQ Report as well as IQ/OQ/PQ report of a Pressure Filter was reviewed during the inspection.

Approaches to process validation

Prospective and concurrent approaches were applied to process validation.

Process validation programme

Process Validation SOP, Process Validation Protocol and Report of Isoniazid were reviewed. Three batches of Isoniazid were validated for updated process. Process Validation Protocol and Report of Isoniazid triggered by adding a new vendor of the key starting material were reviewed too.

Cleaning validation

Supplement Cleaning Validation Protocol of Equipment used for Isoniazid in Workshop 101 was reviewed. Holding time before and after cleaning was added in the protocol. The supplement cleaning validation is scheduled to be performed in 2016.

3.12 CHANGE CONTROL

Change Control **(CC)** Procedure and register were reviewed. Some critical and major Isoniazid related change control records were spot checked. The procedure was well followed. Related process validations and testing method validation were completed. Supplementary documents related to process, specification and test method were submitted to WHO for approval before initiating the changes.

3.13 REJECTION AND RE-USE OF MATERIALS

Rejection

Rejected APIs could be reprocessed according to the written procedure.

Reprocessing

A SOP on Reprocessing and Reworking for Products was reviewed. For the reprocessed batch of APIs by the process not validated before, long-term study was required to be performed. Before this SOP was effective, long-term study was not required even if new expiry date was given to the reprocessed batch.

Reworking

Rework was not allowed in production of APIs.

Recovery of materials and solvents

There were two manufacturing process used to produce Isoniazid API. The second process as mentioned above used the recycling of mother liquor. The company claimed that no recovery solvent and materials was used in production of WHO grade Isoniazid.

Returns

A SOP on Returned Product and register were reviewed. The record for one batch of returned Isoniazid (non-WHO grade) due to failure on particle size was spot checked. The investigation to the transportation company and the customer was done before assessment on the returned product. Sampling and testing of the returned product were also the part of assessment. Finally, this returned batch was re-crystallised and its quality was assessed before release.

3.14 COMPLAINTS AND RECALLS

A SOP on Customer Complaint and register were reviewed. The investigation and records for one complaint relating to quality deficiency found in returned Isoniazid were checked. The procedure was followed properly. The root cause was found after investigation. The filters used before crystallisations were changed to improve the effectiveness of filtration.

3.15 CONTRACT MANUFACTURERS (INCLUDING LABORATORIES)

No manufacturing and testing activity is outsourced for the inspected API Isoniazid.

Part 4: Conclusion

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, as well as the corrective actions taken and planned, Isoniazid (APIMF 168) manufactured at Second Pharma Co. Ltd located at Hangzhou Gulf Fine Chemical Zone, Shangyu City, Zhejiang, 312369 P.R. 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.