World Health Organization

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Prequalification Team Inspection services
WHO INSPECTION REPORT

Desk Assessment of Active Pharmaceutical Ingredient Manufacturer

Part 1	**General information**
Company information	
Name of Manufacturer	Second Pharma Co., Ltd.
Corporate address of manufacturer	No.33 Weiwu Road HangZhou Gulf Fine Chemical Zone, Shangyu City, Zhejiang Province, 312369 China.
Inspected site	
Name & address of manufacturing site	Second Pharma Co. Ltd No.33 Weiwu Road HangZhou Gulf Fine Chemical Zone, Shangyu City, Zhejiang Province, 312369 China.
Production Block/Unit	Workshop 101
Desk assessment details	
Date of review	26 July 2019
APIs covered by this desk assessment	WHOAPI-168- Isoniazid
List of documents submitted	a) Site master file, document number XSK-SMF-EN-00 effective date 31.03.2019 b) License number ZJ20040253 issued on 3.04.2018, by the Zhejiang Food and Drug Administration and valid till 02.04.2023. c) A list of all the APIs or other products (intermediates, dosage forms, etc.) manufactured on-site. The list included International Nonproprietary Names(INN) and CAS. d) List of regulatory inspections conducted in the last five years e) Inspection reports for inspections conducted within the last 3 years along with CAPAs and proof of CAPAs implementation related to the inspection report observations/deficiencies or any warning letter or equivalent regulatory action. f) PQR for Isoniazid for the year 2018. g) Complete batch manufacturing and packaging record including the analytical part for isoniazid batch number 020190322. h) Blank master batch manufacturing and packaging records for isoniazid. i) A statement on the recalls for products manufactured at the site. j) A confirmation made by the Quality director that a self-inspection and external audit for Isoniazid has been performed in the past three years.

	k) A statement that no warning letter and other equivalent regulatory action was issued by any Authority for all the products manufactured at Second Pharma Co., Ltd since the factory was established in 2003. l) A statement reaffirming the availability of isoniazid in the coming year and mentioning that there was no out of stock in the last 3 years.	
Any documents missing?	All required documents were duly submitted.	
Part 2	**Summary of SRA/NRA inspection evidence considered (from most recent to last) and comments**	
USFDA	Dates of inspection:	13.03.2017 to 17.03.2017
	Type of inspection:	cGMP surveillance inspection.
	Block/Unit:	Workshop 101
	Type of products/Dosage forms covered:	APIs by chemical synthesis
Part 3	**Summary of the last WHO inspection**	
Date and conclusion of most recent WHO inspection	10 to 13 November 2015	
Brief summary of manufacturing activities	Warehousing, production, packaging and QC release for Isoniazid API	
General information abou the company and manufacturing site	Second Pharma Co Ltd. was established in 2003. It is located at Hangzhou Gulf Fine Chemical Zone, Shangyu City, Zhejiang Province of China. The 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. According to the site master file document number. XSK-SMF-EN-00 effective date 31.03.2019, the facility employs a total of 639 employees 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 production lines (synthesis, purification and finishing) for Isoniazid API. The company manufactured more than 100 tons of Isoniazid annually. Isoniazid was manufactured in the production block 101 (formally 101B). There were two manufacturing processes for Isoniazid API: 1. MF-IND-002 WHO process 2. MF-IND-003 Process with use of recovered mother liquor. The Isoniazid API was produced as different grades including: CP, EP/ BP, USP, WHO.	

Focus of the last WHO inspection	Production and quality control of isoniazid API
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)
Out of scope and restrictions (last WHO inspection)	The last WHO inspection was restricted to the production and quality control of isoniazid and did not include other APIs.
WHO products covered by the last WHO inspection	WHOAPI-168- Isoniazid
Additional products to be covered by this desk assessment:	No information available to suggest additional products to be covered by this assessment.
Abbreviations	**Meaning**
AHU	Air handling unit
API	Active pharmaceutical ingredient
BMR	Batch manufacturing record
BPR	Batch production record
CAPA	Corrective and preventive action
CC	Change control
FPP	Finished pharmaceutical product
GMP	Good manufacturing practices
NC	Non-conformity
NRA	National regulatory agency
PQR	Product quality review
PQS	Pharmaceutical quality system
QA	Quality assurance
QC	Quality control
QCL	Quality control laboratory
QMS	Quality management system

QRM	Quality risk management
RA	Risk assessment
RCA	Root cause analysis
SMF	Site master file
SOP	Standard operating procedure

Part 4	**Summary of the assessment of supporting documentation**

a) Manufacturing authorization and GMP certificate granted by the local authority:
License number ZJ20040253 issued on 3.04.2018, by the Zhejiang Food and Drug Administration and valid till 02.04.2023 was submitted.

b) Site master file:
Site master file, document number XSK-SMF-EN-00 effective date 31.03.2019 was reviewed and found adequate in content and in line with the WHO guidance on site master files for manufacturers.

c) List of all regulatory inspections performed in the last 3 years and their outcomes:
A list of regulatory inspections performed in the last 3 years and their outcomes was provided. The site was inspected by the USFDA as the most recent and only SRA inspection from the 13.03.2017 to 17.03.2017. Although the USFDA inspection did not cover the WHO PQ API, it covered the same workshop, 101 and the findings from the inspection provide an overview of the firm's quality management systems.

d) List of all the products and dosage forms manufactured on-site:
A list of products manufactured at the site was provided. No beta-lactams, cephalosporins, cytotoxic or hormones are manufactured at this site. Moreover, there was a dedicated section for manufacture of isoniazid API. Overall, there are no foreseen concerns for cross-contamination**.**

e) Most recent product quality review(s) (PQR)(s) of the concerned WHO product(s):
Isoniazid APQR for the year 2018 was reviewed. This covered the period January 2018 to December 2018 with a total of 334 batches manufactured. 23 were tail batches, 20 reprocessed batches, 45 from the mother liquor process(MF-IND-003), and 246 batches were according to the normal process (MF-IND-002). A review of suppliers of critical starting materials was performed. It was observed that all critical materials were from qualified suppliers. Trend analysis was provided for the critical quality attributes of all critical starting materials. A review of critical process parameters was also provided. The review also included a review of all the API specifications. Final API critical quality attributes were trended and where applicable, process capability calculated. A review was also conducted for OOS and OOT results, deviations, change controls, registration/regulatory issues, reprocess and rework, recalls, complaints, returns, recalls and adverse reactions, qualification of equipment, and validation of processes, methods and cleaning, self-inspections and external audit for isoniazid, recommendation from last report.

Ongoing stability data, water systems, HVAC systems and nitrogen systems related to the product were contained and reviewed in separate reports. This was mentioned in the product quality review SOP, document number QA-012-06 effective date 20.12.2018.

The ongoing stability report for isoniazid for 2018, document number APR-IND-ST-2018 was reviewed. Overall, 66 batches were placed under long-term stability conditions while 15 batches were placed under accelerated conditions. Of these, 14 batches of the WHO specifications had been placed on long term stability studies while 3 batches were on accelerated stability studies. The results of the stability indicating parameters were analysed for all the batches. There were no stability failures and the results were acceptable.

The purified water system annual quality review report for 2018, document number PSW-01-2018 provided a discussion of all sampling point results for both chemical and microbial parameters for the purified water used at the site. The results were trended, 2 OOT results were identified and investigated. No OOS results were registered.

Annual review of the isoniazid air-handling system was contained in report number HVAC-03-2018 dated 18.02.2019. The report contained a review of the requalification of the system which was done in 2018, and trending of the various parameters such as differential pressure, humidity, temperature and viable microbial count. The results were within predefined limits.

Annual review report for nitrogen generating system for 2018, document number NMS-01-2018 contained a review and trending of the quality parameters of the nitrogen system, including composition, particulate matter and airborne microorganisms. This was acceptable overall

The APQR conclusion indicated that the manufacturing process for the API was under control and consistently delivered product of acceptable quality.

f) Batch manufacturing and packaging record(s), including the analytical part, for the most recently released batch of relevant product(s):

Executed manufacturing batch records for isoniazid API batch number 020190322, batch size 500kg manufactured on 19.03.2019 was submitted. Records were overall acceptable. Both batch and testing record were reviewed by respective supervisors and approved. The batch was released on 3.04.2019.

g) Master batch manufacturing and packaging record(s) of the product(s) of interest:

Blank master batch manufacturing and packaging record for isoniazid was submitted.

h) Recalls in the past three years related to products with quality defects:

A statement mentioning that no recalls had been conducted in the last three years related to APIs manufactured at the site was provided.

i) Confirmation by the senior quality assurance representative that a full self-inspection or external audit dedicated to the product(s) has been performed and all matters dealt with:

A confirmation made by the Quality director that a self-inspection and external audit for Isoniazid has been performed in the past three years and all matters dealt with was provided.

j) Copy of any warning letter, or equivalent regulatory action, issued by any authority to which the site provides or has applied to provide the product:

A statement that no warning letter and other equivalent regulatory action was issued by any Authority for all the products manufactured at Second Pharma Co., Ltd since the factory was established in 2003 was submitted.

k) Out-of-stock situations:

A statement reaffirming the availability of isoniazid in the coming year and mentioning that there was no out of stock in the last 3 years was submitted.

l) Additional documents submitted:

Not applicable.

Part 5	**Conclusion – Desk assessment outcome**

Based on the previous WHO inspections and on the GMP evidence received and reviewed, it is considered that a desk assessment is acceptable in lieu of a WHO onsite inspection, ***Second Pharma Co., Ltd (Workshop 101)*** located at ***No.33 Weiwu Road*** **HangZhou Gulf Fine Chemical Zone, Shangyu City, Zhejiang Province, 312369 China** is considered to be operating at an acceptable level of compliance with WHO GMP guidelines for APIs.

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

Part 6	**List of guidelines referenced in this inspection report**

1. WHO good manufacturing practices for active pharmaceutical ingredients. *WHO Expert Committee on Specifications for Pharmaceutical Preparations*. Forty-Fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957), Annex 2. ***Short name: WHO GMP for APIs*** or ***TRS No. 957, Annex 2***
http://apps.who.int/medicinedocs/documents/s20119en/s20119en.pdf

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

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

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

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

6. 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, 2019 (WHO Technical Report Series, No. 1019), Annex 2. **Short name: WHO TRS No. 1019, Annex 2**
https://apps.who.int/iris/bitstream/handle/10665/312316/9789241210287-eng.pdf?ua=1

7. 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**
https://apps.who.int/iris/bitstream/handle/10665/312316/9789241210287-eng.pdf?ua=1

8. 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. 957, Annex 1
http://www.who.int/medicines/publications/44threport/en/

9. 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
http://www.who.int/medicines/publications/44threport/en/

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

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

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

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

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

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

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

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

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

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

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

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

22. Stability testing of active pharmaceutical ingredients and finished pharmaceutical products. *WHO Expert Committee on Specifications for Pharmaceutical Preparations*. Fifty-Second Report Geneva, World Health Organization, 2018 (WHO Technical Report Series, No. 1010), Annex 10.
Short name: WHO TRS No. 1010, Annex 10
http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex10.pdf

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.
Short name: WHO TRS No. 996, Annex 10
http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex10.pdf

24. 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
Short name: WHO TRS No. 992, Annex 6
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf