World Health Organization

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Prequalification Team Inspection services
WHO PUBLIC INSPECTION REPORT
(WHOPIR)
Desk Assessment of Active Pharmaceutical Ingredient (API) Manufacturer

Part 1	**General information**
Company information	
Name of Manufacturer	ST Pharm Co., Ltd. (Sihwa Site)
Corporate address of manufacturer	231 Hyeomnyeok-ro, Siheung-si, Gyeonggi-do, 15086, Republic of Korea Telephone Number: 82-31-488-1399 Fax Number: 82-31-498-3001 Email Address: jyyun@stpharm.co.kr 24 hrs Telephone Number: 82-10-2420-5276
Inspected site	
Name & address of manufacturing site	ST Pharm Co., Ltd. - Sihwa Site 231 Hyeomnyeok-ro, Siheung-si, Gyeonggi-do, 15086, Republic of Korea DUNS No. of Sihwa Site: 557795512
Synthetic Unit/Block/Workshop	Plant 5 (Cycloserine, Clofazimine, Terizidone) Plant 6 (Sofosbuvir)
Desk assessment details	
Date of review	18 September 2019 to 07 November 2019
APIs covered by this desk assessment	Terizidone (TB346) Cycloserine (APIMF118, WHOAPI-118) Clofazimine (APIMF331, WHOAPI-331, TB364) Sofosbuvir (HP024)
List of documents submitted	• Certificate of translation for ST Pharm of Sihwa site • List of regulatory inspections performed at the site during the last 5 years. • PMDA inspection report. • US FDA inspection report, 483 table, proof of CAPA. • GMP Certificate, Certificate No. 2018-D1-1360 issued on the 11/06/2018 by Ministry of Food and Drug Safety valid until 05/09/2020. • Manufacturing license, Certificate No. 2018-D1-1359(License No.1301) issued on the 11/06/2018 by Ministry of Food and Drug Safety. • Pharmaceutical Product Certificate, number 2019-D1-0663 issued on the 12/03/2019 (Cycloserine), 2019-D1-0673 issued on the 14/03/2019 (Clofazimie), and 2019-D1-0675 issued on the 14/03/2019 (Terizidone) by Ministry of Food and Drug Safety. • Site master file, effective date 23/05/2018 • List of all the products manufactured on-site • The APQR reports for Cycloserine, Clofazimine, Terizidone and Sofosbuvir.

	• Completed BMRs for Cycloserine, Clofazimine, Terizidone and Sofosbuvir. • Blank BMR for Cycloserine, Clofazimine, Terizidone and Sofosbuvir. • Recall statement: No any recall related to APIs, Cycloserine, Terizidone, Clofazimine and Sofosbuvir have occurred in the past 3 years. • GMP Declaration Letter: API manufactured, and QC tested in full compliance with the GMP. Self-inspections were performed. • A warning letter statement: No any warning letter related to APIs, Cycloserine, Terizidone, Clofazimine and Sofosbuvir has issued by any authority. • A statement: No out-of-stock situation related to APIs, Cycloserine, Terizidone and Clofazimine has occurred in the past 3 years.	
Part 2	**Summary of SRA/NRA inspection evidence considered (from most recent to last)**	
US Food and Drug Administration (US FDA)	Dates of inspection:	5-8 November 2018
	Type of inspection:	Routine Inspection
	Block/Unit/Workshop:	Plant 6
	Type of APIs covered:	Sofosbuvir (one of the WHO APIs)
Pharmaceuticals and Medical Devices Agency (PMDA)	Dates of inspection:	4-7 September 2018
	Type of inspection:	Routine Inspection
	Block/Unit/Workshop:	Plant 5 (Cycloserine) and Plant 6 (Sofosbuvir)
	Type of APIs covered:	Cycloserine and Sofosbuvir (Both were belongs to WHO APIs)
Part 3	**Summary of the last WHO inspection**	
Date and conclusion of most recent WHO inspection	WHO has not yet performed an onsite inspection. Last desk assessment was conducted by PQT from 21- 28 February 2017.	
Brief description of manufacturing activities	According to the SMF, this site's major activity is cGMP compliant custom manufacturing of small molecule especially APIs and their intermediates as well as oligo nucleotides. It does not conduct any other manufacturing activities including toxic and hazardous materials.	
General information about the company and manufacturing site	According to the SMF, there are five (5) commercial scale plants (Plant 1, Plant 2, Plant 3, Plant 5, Plant 6), two (2) pilot scale plants for manufacturing pharmaceutical and its total size is 166,550 m^2.	

Abbreviations	Meaning
BMR	Batch manufacturing record
BPR	Batch production record
CAPA	Corrective and preventive action
CC	Change control
GMP	Good manufacturing practices
SMF	Site master file
NC	Non conformity
SRA	Stringent regulatory authority
NRA	National regulatory agency
APQR	Annual Product quality review
PQS	Pharmaceutical quality system
QA	Quality assurance
QC	Quality control
IPC	In-process control
QCL	Quality control laboratory
QMS	Quality management system
QRM	Quality risk management
RA	Risk assessment
RCA	Root cause analysis
SOP	Standard operating procedure

Part 4	Summary of the assessment of supporting documentation

a) Manufacturing authorization and GMP certificate granted by the local authority:

Manufacturing license, Certificate No.:2018-D1-1359 (License No.: 1301)

- Issued:11/06/2018 by Ministry of Food and Drug Safety

GMP Certificate, No. 2018-D1-1360

- Issued: 11/06/2018 by Ministry of Food and Drug Safety
- Expiry: 05/09/2020

Pharmaceutical Product Certificate, No. 2019-D1-0663

- Issued: 12/03/2019 by Ministry of Food and Drug Safety

Pharmaceutical Product Certificate, No. 2019-D1-0673, 2019-D1-0675

- Issued: 14/03/2019 by Ministry of Food and Drug Safety

b) Site master file (SMF):

Site master file, effective date 23/05/2018. Annexures of printouts of water treatment and air handling systems, including pipeline and instrumentation drawings was reviewed and found acceptable and in line with the WHO TRS No. 961, Annex 14.

c) List of all the APIs or other products (intermediates, dosage forms) manufactured on-site:
List: Sofosbuvir, Atorvastatin Calcium Trihydrate, Terizidone, Irbesartan, Losartan Potassium, Valsartan, Clopidogrel Bisulfate, Formoterol fumarate Dihydrate, Entecavir Monohydrate, Rosuvastatin Calcium, Voriconazole, Montelukast Sodium, Atorvastatin Calcium (anhydrous), Lacosamide, Gadobutrol Monohydrate, Evogliptin Tartrate, Zidovudine, Clofazimine, Calcobutrol, Cycloserine.
No beta-lactam or cytotoxic products are manufactured at the site.

d) List of all regulatory inspections performed in the last 3 years and their outcomes:
MFDS, US FDA and PMDA: GMP compliant.

e) Most recent product quality review(s) (PQR)(s) of the concerned WHO API(s):
The APQR report for Cycloserine (Issued on 29/3/2019) shows that there were 66 batches (including 2 reprocess batches) of Cycloserine were manufactured from 1/1/2018 to 31/12/2018. Process capability assessment was conducted for 66 batches of products (2) manufactured in 2018 and the process capability indexes of the main test items, Assay, Condensation product(UV), Specific rotation, pH, LOD, Residue on ignition, were checked. The indexes were sufficient.

The APQR report for Clofazimine (Issued on 29/3/2019) shows that there were 3 batches of Clofazimine were manufactured until 2018. The product was approved by MFDS in 2018.

The APQR report for Terizidone (Issued on 29/3/2019) shows that there were 20 batches (including 1 reprocess batch) of Terizidone manufactured from 1/1/2018 to 31/12/2018. The production result and quality management system of TER were evaluated, and no quality issue with potential adverse effect on product's quality occurred. The 20 batches manufactured in 2018 met the acceptance criteria.

The APQR report for Sofosbuvir (Issued on 31/10/2018) shows that there were 12 batches of Sofosbuvir were manufactured from 1/1/2018 to 30/9/2018. The production result and quality management system of sofosbuvir were evaluated, and no quality issue with potential adverse effect on product's quality occurred. It was concluded that the API manufactured from ST Pharm has been in compliance with reproducibility.

f) Batch manufacturing and packaging record(s), including the analytical part, for the most recently released batch of relevant API(s):
- Cycloserine Manufacturing Batch Records and QC analysis data (Executed).
- Clofazimine Manufacturing General Batch Records, IPC analysis Data and QC analysis data (Executed).
- Clofazimine QC Milling Batch Records, IPC analysis Data and QC analysis data (Executed).
- Terizidone Manufacturing Batch Records, IPC analysis Data and QC analysis data (Executed).
- Sofosbuvir Manufacturing Batch Records, IPC analysis Data and QC analysis data (Executed).

g) Master batch manufacturing and packaging record(s) of the API(s) of interest:
Blank master batch manufacturing records of the above listed PQ products were submitted.

h) Recalls in the past three years related to APIs with quality defects:
Recall statements stating that no any recall related to APIs, Cycloserine, Terizidone, Clofazimine and Sofosbuvir has occurred in the past 3 years.

i) Confirmation by the senior quality assurance representative that a full self-inspection or external audit dedicated to the API(s) has been performed and all matters dealt with:
A GMP Declaration Letter: API manufactured, and QC tested in full compliance with the GMP. Self-inspections were performed.

j) Copy of any warning letter, or equivalent regulatory action, issued by any authority for their market, to which the site provides or has applied to provide the API(s):
A warning letter statement: No any warning letter related to APIs, Cycloserine, Terizidone, Clofazimine and Sofosbuvir has issued by any authority.

k) Out-of-stock situations:
A statement confirming that no out-of-stock situation related to APIs, Cycloserine, Terizidone, Clofazimine and Sofosbuvir has occurred in the past 3 years.

l) Additional documents submitted:
None.

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. The site **ST Pharm Co., Ltd**. located at ***231 Hyeomnyeok-ro, Siheung-si, Gyeonggi-do, 15086, Republic of Korea*** is considered to be operating at an acceptable level of compliance with WHO GMP guidelines for APIs.

This WHOPIR will remain valid until 8/11/2021 (3 years from the last US FDA GMP inspection), 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 or 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*. Fourty-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