World Health Organization

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Prequalification Team Inspection services
WHO PUBLIC INSPECTION REPORT
(WHOPIR)
Desk Assessment of Finished Pharmaceutical Product (FPP) Manufacturer

Part 1	**General information**	
Company information		
Name of Manufacturer	**Dong-A ST (Cheonan City)**	
Corporate address of manufacturer	64, Cheonho-daero, Dongdaemun-gu, Seoul, 02587, Republic of Korea	
Inspected site		
Name & address of manufacturing site	Dong-A ST Co Ltd, 2F SectionB, 3F, 4F SectionB, 200-23. Baekseokgongdan 1-ro, Seobuk-gu, Cheonan-si, Chungcheongnam-do, 31093, Republic of Korea	
Production Block/Unit	NA	
Desk assessment details		
Date of review	26 August 2020	
Products covered by this desk assessment	TB236 Cycloserine Capsules, hard 250mg, Prequalified TB364 Clofazimine Capsules, soft 100mg, Under assessment	
	Summary of SRA/NRA inspection evidence considered (from most recent to last)	
The Korean authority MFDS, Korea	Dates of inspection:	28-31 May 2019
	Type of inspection:	Routine GMP inspection
	Block/Unit:	NA
	Type of products/Dosage forms covered:	Solid dosage form and injections
The Korean authority MFDS, Korea	Dates of inspection:	13-17 June 2016
	Type of inspection:	Routine GMP inspection
	Block/Unit:	NA
	Type of products/Dosage forms covered:	The investigation of manufacturing and quality control standards of pharmaceuticals (content solidifying system, injectors, special agent)

Part 3	**Summary of the last WHO inspection**
Date and conclusion of most recent WHO inspection	14-17 November 2016 Compliant
Brief description of manufacturing activities	Oral solid dosage forms (OSD): tablets, capsules, powders were manufactured There were 97 products listed on the listing for OSD products (11 capsules, 1 dry syrup bulk, other products were tablets – coated and uncoated) Injectables: vials (freeze-dried, liquid), ampoules (freeze-dried, liquid), cytotoxic and non-cytotoxic products are produced at the injection manufacturing area.
General information about the company and manufacturing site	1st floor: PW system and packaging material warehouse. 2nd floor: raw material warehouse and packaging material warehouse. 3rd floor: OSD manufacturing area, finished product warehouse and AHU. 4th floor: injections manufacturing area, QA office and QC laboratory, AHU.
Focus of the last WHO inspection	TB236 Cycloserine 250 mg capsules
Areas inspected	OSD manufacturing area on the 3rd floor of the main building Production schedule: There were only tablets on the production schedule at the days of the inspection.
Out of scope and restrictions (last WHO inspection)	NA
WHO products covered by the last WHO inspection	TB236 Cycloserine 250 mg capsules
Additional products covered by this desk assessment:	TB364 Clofazimine Capsules, soft 100mg - under 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
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
SOP	Standard operating procedure

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

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

- 1290 (Previous 15)
- License date: 13 Dec 1954
- Issue date: 28 April 2020 (Certificate No 2020-G1-1073)

b) Site master file (SMF):

The site master file (SMF-CF-SD-001 (Ver. 17) for Cheon-An Plant dated 19.02.2020 was provided. The SMF provided general information about the manufacturing site.

c) List of regulatory inspections performed in the last 3 years and their outcome:

Date	Regulatory Authorities		Related Items	Result
2016 Jun	MFDS, Korea	GMP Inspection	Oral Solid, Injection Cytotoxic Injection	Complied
2016 Jun	INVIMA, Colombia	GMP Inspection	Zydena	Complied
2016 Nov	WHO	GMP Inspection	Closerin Capsule 250mg	Complied
2019 May	MFDS, Korea	GMP Inspection	Oral Solid, Injection Cytotoxic Injection	Complied
2019 Oct	ANVISA, Brazil	GMP Inspection	Zydena	Complied

d) List of all the products and dosage forms manufactured on-site:

The manufacturer has provided a list of all the products and dosage forms produced on the site. It was noted that the site produces more than 100 products of different dosage forms and therapeutic areas.

e) Most recent product quality review(s) (PQR)(s) of the concerned WHO product(s):

The PQR of Cycloserine 250mg capsule for the review period Jan 2018 and Dec 2018 was reviewed. It was noted that a total of 217 (107+3+107) batches were produced during the review period and exported to various countries and markets. The PQR was finalized on 5th April 2019.

The PQR of Clofazimine 100mg soft capsule for the review period of Aug 2017 and Dec 2018 was reviewed. This product is currently under WHO PQ assessment. During this period, 2 lots were produced. The PQR was finalized on 25th March 2019.

The most recent PQR of Closerin Capsule 250mg (D-Cycloserine capsule 250mg™) for the review period Jan-Dec 2019 was reviewed. The batch size of the product is 291,000 EA. The PQR included a review of the manufacturing and packaging process, raw and packaging materials, water quality, manufacturing environment, qualification of equipment, quality management system and stability studies. In general, the PQR appeared to be adequate.

The manufacturer has provided the following clarification for the abbreviations and codes used for Cycloserine Capsules:

1. CS FM: Closerin Capsules Final Mixture Process (Export Code)
2. CS_Fill: Closerin Capsules_Capsule Filling Process (Export Code)
3. CSK FM: Closerin Capsules Final Mixture Process (Domestic Code)
4. CSK_Fill: Closerin Capsules_Capsule Filling Process (Domestic Code)

To note: CS FM and CS_Fill are codes for each stage of CS production for overseas export including the WHO market. As an example. in 2018 CS PQR, WHO-PQ CS was manufactured such that the manufacturing processes are indicated as CS FM and CS_Fill. The packaging process of WHO-PQ CS is indicated as FCSP100-WO which is code for WHO CS FPP. The difference between CS and CSK is whether they are for export or domestic release. There is no difference in the manufacturing process between CS FM and CSK FM or between CS_Fill and CSK_Fill.

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

The batch manufacturing report of Cycloserine 250mg (Code: CS) for batch number CSP2002325 (start date 13/02/2020 and end date 27/02/2020) was reviewed. The batch manufacturing report (packaging) of Cycloserine 250mg for batch number CSP2002325 (start date 31/03/2020 and end date 31/03/2020) was reviewed. The test record (start date 01/04/2020) of Cycloserine 250mg for batch number CSP2002325 was reviewed. In general, the submitted records appeared adequate.

The batch manufacturing record of Clofazimine 100mg soft capsule (Code: FLMP_P) for batch number 19##012 was reviewed. The batch was manufactured dated 16/12/2019. The batch manufacturing report (packaging) for batch number FLP2002012 (start date 13/03/2020 and end date 13/03/2020) was reviewed. The test record of Clofazimine 100mg soft capsule for batch number FLP2002012 was reviewed. In general, the submitted records appeared adequate.

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

The Master Batch manufacturing record, batch log sheet and batch log sheet (packaging) of Cycloserine 250mg capsule was provided. Similarly, batch manufacturing record and batch manufacturing record (packaging) of Clofazimine soft capsule 100mg was provided. In general, the submitted records appeared adequate.

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

The manufacturer has confirmed that they have not carried out any quality defect-related recall of the applications TB236 and TB364.

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 letter of the declaration was provided by the manufacturer confirming that self-inspection and regulatory inspections covering products in questions are carried out as per the schedule. Appropriate corrective actions and preventive actions are taken for all matters dealt with these self-inspections and regulatory inspections.

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:

The manufacturer has submitted the notification of administrative disposition issued by the MFDS dated 12 August 2019.

The manufacturer has not been inspected by the USFDA, EMA and other Stringent Regulatory Authorities (SRA), hence there was no regulatory action issued by any of the SRAs (except MFDS, Republic of Korea).

k) Out-of-stock situations:

A letter of the declaration was provided by the manufacturer confirming that there were no out of stock situations that have taken place in the last 3 years for both products. It is also confirmed that the company does not expect there will be out of the stock situation in the future WHO supplies.

l) Additional documents submitted:

The manufacturer has confirmed that the manufacturing facility has been inspected by the National Regulatory Authority of Korea, MFDS in 2019 which included the production areas where the WHO Prequalified and Under Assessment products (TB236 and TB364) are manufactured.

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 ***Dong-A*** located at ***200-23, Baekseokgongdan 1-ro, Seobuk-gu, Cheonan City, Chungcheongnam-do, Republic of Korea*** is considered to be operating at an acceptable level of compliance with WHO GMP guidelines.

This WHOPIR will remain valid for **1 year**, 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 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 ***TRS No. 986, Annex 2***
   http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_986/en/

2. 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 ***WHO TRS No. 957, Annex 2***
   http://apps.who.int/medicinedocs/documents/s20119en/s20119en.pdf

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. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-second Report Geneva, World Health Organization, 2018 (WHO Technical Report Series, No. 1010), Annex 8. ***Short name: WHO HVAC Guidelines*** *or* ***WHO TRS No. 1010, Annex 8***
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_1010/en/

7. 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.
Short name: WHO TRS No. 937, Annex 4
http://whqlibdoc.who.int/trs/WHO_TRS_937_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 GPPQCL guidelines **or** ***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 2.
Short name: WHO TRS No. 957, Annex 2
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 GDRMP guidelines or ***WHO TRS No. 996, Annex 5***
http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex05.pdf

22. 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

23. 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