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

Part 1	**General information**
Company information	
Name of Manufacturer	Otsuka Pharmaceutical Co., Ltd., Tokushima Itano Factory
Corporate address of manufacturer	Otsuka Pharmaceutical Co., Ltd 2 – 9 Tsukasa-machi, Kanda, Chiyoda-ku Tokyo 101-8635, Japan +81332952958
Inspected site	
Name & address of manufacturing site	Otsuka Pharmaceutical Co., Ltd., Tokushima Itano Factory 13 Minami, Shishitoki, Matsutani, Itano-cho, Itano-gun, Tokushima, 779-0195, Japan D-U-N-S: 694877866 Latitude: 34° 1473 Longitude: 134° 4379
Production Block/Unit	Solid Dosage Form Manufacturing Line 2
Desk assessment details	
Start and end dates of review	29 – 30 June 2020 01 – 03 July 2020
Products covered by this desk assessment	Delamanid Tablet, Film-coated 50mg
List of documents submitted	1. GMP compliance report, Department of Health and Welfare, Tokushima Prefecture, dates of inspection 5 – 6 December 2017 2. Improvement plan in response to the GMP inspection findings, dates of inspection 5 – 6 December 2017. 3. Notification of results of Compliance Inspection of Pharmaceuticals, Incorporated Administrative Agency Pharmaceuticals and Medical Devices Agency, dates of inspection 12 – 14 June 2018. 4. Response to inquire about GMP Compliance Report, dates of inspection 12 – 14 June 2018. 5. Improvement plan for observations during the GMP inspection, dates of inspection 12 – 14 June 2018 GMP inspection result report, Pharmaceutical Affairs Department, Health and Welfare Division, Tokushima Prefecture, dates of inspection 16 – 19 October 2018 6. Response to inquiry about GMP compliance, dates of inspection 12 – 14 June 2018 7. Notification of results of compliance inspection of Pharmaceuticals, date of inspection 23 February 2018 8. FDA US EIR, dates of inspection 11 – 15 February 2019 9. FDA US inspection Form 483 response, dates of inspection 11 – 15 February 2019

	10. GMP compliance inspection report, date of inspection 26 December 2019 11. Improvement plan for observations during the GMP inspection, dates of inspection 26 December 2019 12. Delamanid 50 mg tablets Annual Product Quality Review 13. List of products manufactured at Itano factory 14. SMF 15. Manufacturing license No 36AZ006003 16. Table specifying which parts of the manufacturing process were covered by the SRA inspection 17. List of regulatory authorities' inspections – last 5 years 18. Delamanid 50 mg tablets batch manufacturing and packaging records 19. Delamanid 50 mg tablets master batch manufacturing and packaging records 20. Analytical raw data Batch No XX & ZZ 21. Declarations – self inspection, recalls, out of stock situation and warning letters	
Part 2	**Summary of SRA/NRA inspection evidence considered and comments**	
Pharmaceutical Affairs Division Department of Health and Welfare Tokushima Prefecture	Dates of inspection:	5 – 6 December 2017
	Type of inspection:	GMP compliance inspection
	Block/Unit:	Not specified
	Type of products/Dosage forms covered:	Tablets
Incorporates Administrative Agency Pharmaceuticals and Medical Devices Agency	Dates of inspection:	12 – 14 June 2018
	Type of inspection:	Pre-approval compliance on-site inspection for Tablets
	Block/Unit:	Not specified
	Type of products/Dosage forms covered:	Tablets
Pharmaceutical Affairs Division Department of Health and Welfare Tokushima Prefecture	Dates of inspection:	16 – 19 October 2018
	Type of inspection:	GMP compliance inspection
	Block/Unit:	Solid Dosage Form Manufacturing Line 2
	Type of products/Dosage forms covered:	• Delamanid 50 mg Tablets/Deltyba, 50 mg, film-coated tablet and well as twenty-one (21) Drug Products - tablets • Ophthalmic Suspension • API (Storage only)
US Food and Drug Administration	Dates of inspection:	11 – 15 February 2019
	Type of inspection:	Evaluate firm's cGMP compliance
	Block/Unit:	Manufacturing line (tablets for USA market)
	Type of products/Dosage forms covered:	TCM – Tablets, Prompt Release

Pharmaceutical Affairs Division Department of Health and Welfare Tokushima Prefecture	Dates of inspection:	26 December 2019
	Type of inspection:	GMP compliance status of the Delamanid Spray-dried (SD) Powder for pharmaceuticals for export, on-site compliance inspection
	Block/Unit:	Not specified
	Type of products/Dosage forms covered:	Delamanid Spray-dried (SD) Powder
Part 3	**Summary of the last WHO inspection**	
Date and conclusion of most recent WHO inspection	The site has not been inspected by WHO	
Abbreviations	**Meaning**	
BPR	Batch production record	
CAPA	Corrective and preventive action	
GMP	Good manufacturing practices	
PQR	Product quality review	
SMF	Site master file	
CC	Change control	
EIR	Establishment inspection report	
VAI	Voluntary actions indicated	

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

a) List of all regulatory inspections performed in the last 5 years and their outcomes:

	Competent Authority	Date	Products and Scope	Result	Type of Inspection
1	EMA	Mar. 16, 2015	DELTYBA 50-mg tablets	Complies	On-site
2	Tokushima (JPN)	Jul. 09, 10, 2015	Mucosta Ophthalmic Suspension UD 2%	Complies	On-site
3	Tokushima (JPN)	Nov. 24, 27, 2015	Tablets	Complies	On-site
4	Turkey	Nov. 30 Dec. 04, 2015	DELTYBA 50-mg tablets	Complies	On-site
5	Tokushima (JPN)	Mar. 22, 2016	DELTYBA 50-mg tablets	Complies	On-site
6	PMDA (JPN)	Apr. 01, 2016	Tablets	Complies	Desk-top
7	FDA (US)	Jul. 18-22, 2016	Tablets	Complies	On-site
8	PMDA (JPN)	Aug. 01, 2016	Granules	Complies	Desk-top
9	Tokushima (JPN)	Dec. 16, 19,20, 2016	Tablets	Complies	On-site
10	TGA (Australia)	17-Feb-2017	GMP Clearance	Complies	Desk-top

11	Tokushima (JPN)	Dec. 05, 06, 2017	Tablets	Complies	On-site
12	PMDA (JPN)	June 12-14, 2018	Tablets	Complies	On-site
13	PMDA (JPN)	Jun. 24, 2018	Routine GMP inspection	Complies	Desk-top
14	Tokushi ma	Oct. 16-19, 2018	Inspection prior to Renewal Manufacturing License /	Complies	On-site
15	CFDA (China)	Jan. 21-24, 2019	DELTYBA 50-mg tablets	Complies	On-site
16	FDA (US)	Feb. 11-15, 2019	Tablets	Complies	On-site
17	ANVISA (Brazil)	Jun. 10-14, 2019	DELTYBA 50-mg tablets	Complies	On-site
18	Tokushim a (JPN)	Dec. 26, 2019	Delamanid Spray Dried Powder	Complies	On-site
19	FSI «SIDG	Feb. 17-18, 2020	DELTYBA 50-mg tablets	Complies	On-site

b) Manufacturing authorization granted by national authorities:
License: MIA11724

c) Site master file:
SMF submitted and reviewed. SMF written according to the WHO TRS No. 961, Annex 14

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

N	Therapeutically groups	Product
1	Anti-tubercular	Delamanid / Deltyba Tablets
2	Anti-gastric ulcer	Tablets
3	Hyperlipidemia agent	Tablets
4	Carnitine Deficiency	Tablets
5	Antipsychotic	Tablets
6	Vasopressin Antagonist	Tablets, Granules
7	Alcoholism	Tablets
8	Dry Eye	Ophthalmic Suspension

e) Most recent product quality review (PQR) of the concerned WHO product:
Delamanid 50 mg tablets 2019 Annual Product Quality Review submitted and reviewed.

f) Batch manufacturing and packaging records, including the analytical part, for the most recently released batch of relevant product:
Submitted and reviewed:
- Delamanid 50 mg tablets Batch No XX
- Analytical raw data Batch No XX & XX
- Test procedures and acceptance criteria for intermediates Delamanid 50 mg tablets process tests

g) Master batch manufacturing and packaging records of the product of interest:
Submitted and reviewed:
- Delamanid 50 mg tablets

h) If any of the products are sterile, the completed batch records for the most recent media fill validation that is relevant to the product(s) of interest and report on its outcome:
N/A

i) Recalls in the past three years related to products with quality defects:
Not reported – declaration submitted.

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

k) 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:
Not reported – declaration submitted.

k) Out-of-stock situations:
Not reported – declaration submitted.

l) Additional documents submitted:
N/A

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 ***Otsuka Pharmaceutical Co., Ltd., Tokushima Itano Factory,*** located at ***13 Minami, Shishitoki, Matsutani, Itano-cho, Itano-gun, Tokushima, 779-0195, Japan*** is considered to be operating at an acceptable level of compliance with WHO GMP guidelines.

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 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 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 TRS No. 957, Annex 2***
   http://www.who.int/medicines/publications/44threport/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.
   Short name: WHO TRS 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.
   Short name: WHO TRS No. 929, Annex 4
   http://whqlibdoc.who.int/trs/WHO_TRS_929_eng.pdf?ua=1

5. 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 TRS No. 1010, Annex 8**
   http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_1010/en/

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.
   Short name: WHO TRS 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.
   Short name: WHO TRS 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 3.
Short name: WHO TRS No. 957, Annex 3
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.
Short name: WHO TRS 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.
Short name: WHO TRS 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. ***Short name: WHO TRS 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. ***Short name: WHO TRS 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.
Short name: WHO TRS 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. ***Short name: WHO TRS 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. ***Short name: WHO TRS 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. ***Short name: WHO TRS 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.
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

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. ***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

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. ***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

20. 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 guidance or ***WHO TRS No. 996, Annex 5***
http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex05.pdf

21. 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 Multisource guidance or ***WHO TRS No. 996, Annex 10***
http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex10.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. Production of water for injection by means other than distillation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fourth Report. Geneva, World Health Organization, 2020 (WHO Technical Report Series, No. 1025), Annex 3.
Short name: WHO TRS No. 1025, Annex 3
https://www.who.int/publications-detail/978-92-4-000182-4

24. Good chromatography practice. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fourth Report. Geneva, World Health Organization, 2020 (WHO Technical Report Series, No. 1025), Annex 4.
Short name: WHO TRS No. 1025, Annex 4
https://www.who.int/publications-detail/978-92-4-000182-4

25. Points to consider for manufacturers and inspectors: environmental aspects of manufacturing for the prevention of antimicrobial resistance. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fourth Report. Geneva, World Health Organization, 2020 (WHO Technical Report Series, No. 1025), Annex 6.
Short name: WHO TRS No. 1025, Annex 6
https://www.who.int/publications-detail/978-92-4-000182-4

26. 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