World Health Organization

20, AVENUE APPIA – CH-1211 GENEVA 27 – SWITZERLAND – TEL CENTRAL +41 22 791 2111 – FAX CENTRAL +41 22 791 3111 – WWW.WHO.INT

Prequalification Unit Inspection services
WHO PUBLIC INSPECTION REPORT

Desk Assessment of Active Pharmaceutical Ingredient (API) Manufacturer

Part 1	**General information**
Company information	
Name of Manufacturer	Sun Pharmaceutical Industries Limited
Corporate address of manufacturer	Sun Pharmaceutical Industries Limited Sun House, 201 B/1, Western Express Highway, Goregaon (East), Mumbai, 400063, , Maharashtra, India
Inspected site	
Name & address of manufacturing site	Sun Pharmaceutical Industries Limited Ltd Village Toansa, P.O. Dist. S.B.S. Nagar (Nawanshahar), Punjab, 144 533 India GPS: Latitude (N):31°00.000` Longitude (E): 76°26.000` D-U-N-S: 65041632
Module	MP-12
Manufacturing license number	Form No 26 No 1313-OSP and Form 26 No 1245-B No. Drugs (6) Pb.2018/998, dated 22-1-2018 – renewal of Manufacturing Drugs Licenses
Desk assessment details	
Start and end dates of review	1 – 4 February 2021
APIs covered by this desk assessment	Tenofovir disoproxil fumarate
List of documents submitted	1. Competent authority of Germany GMP certificate DE_BY_04_GMP-2020_0066, issued 29 May 2020 2. GMP inspection report and close out inspection report EMA, dates of inspection 14 – 18 October 2019 3. Response to the EMA inspection report, signed 6 January 2020 4. COFEPRIS Mexico inspection report (not reviewed) 5. Response to COFEPRIS Mexico inspection report and CAPA implementation status (not reviewed) 6. COFEPRIS Mexico approval & GMP certificate 7. Food & Drugs Administration, Punjab manufacturing authorization No. Drugs (6) Pb.2018/998, dated 22-1-2018 – renewal of Manufacturing Drugs Licenses: • Form No 26 No 1313-OSP and Form 26 No 1245-B 8. Food & Drugs Administration, Punjab GMP certificate No. Drugs (6) Pb. 2019/1602, dated 9-4-19 9. SMF-TON-10 and Appendices + drawings 10. PQR No 3-APR-20-089: Tenofovir disoproxil fumarate, review period: Mar 2019 – Feb 202 and Annexures

	11. BMRs: • Drying, dehydration, milling & sifting, packaging, sealing & labelling 12. Analytical raw data 13. Master BMR: • Drying • Preparation • Milling sifting, packaging, sealing & Labelling 14. Risk assessment: Nitrosamines 15. List of APIs manufactured on site 16. List of regulatory authorities' inspections 17. Declarations: recalls, warning letters, out-of-stock situations, self-inspection, upcoming inspections and solvent recovery	
Any documents missing?	None	
Part 2	**Summary of SRA/NRA inspection evidence considered (from most recent to last) and comments**	
Government of Upper Bavaria, Germany, Finish Medicines Agency, National Institute of Pharmacy and Nutrition, Hungary on behalf of EMA	Dates of inspection:	14 – 18 October 2019
	Type of inspection:	GMP inspection
	Block/Unit/Workshop:	Buildings: MP-1, stream 2&4, MP-6, stream 2, MP-10, stream1
	APIs covered:	1. Midazolam 2. Tamsulosin Hydrochloride 3. Repaglinide 4. Nevirapine Anhydrous
Part 3	**Summary of the last WHO inspection**	
Date and conclusion of most recent WHO inspection	WHO on-site inspection (initial inspection) was performed 11 – 14 June 2013. The site was found to be compliant, however in view of the fact that US FDA raised data integrity issues, inspection closing letter was not sent out and respective API was suspended Following desk assessments were performed: • 12 August 2016 • 8 – 9 September 2019 Outcome of 8 – 9 September desk assessment: 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 **Sun Pharmaceutical IndustriesLimited, API manufacturing site Toansa , India** is considered to be operating at an acceptable level of compliance with WHO GMP guidelines for APIs. This compliance status shall be valid until 10 November 2020 or when another inspection is conducted by WHO or by a stringent regulatory authority.	
Brief summary of manufacturing activities	Production and control of APIs	

General information about the company and manufacturing site	History of Toansa API Plant, previously named as Ranbaxy Laboratories Ltd: Ranbaxy Laboratories Limited, was incorporated in the year 1960 and AFI manufacturing at Toansa started in the year 1987. Ranbaxy merged with Sun Pharmaceutical Industries Ltd. on 25-Mar-2015. Sun Pharmaceutical Industries Limited was incorporated in the year 1983. The acquisition of Ranbaxy started with Sun Pharmaceuticals Industries Ltd in year 2014 and completed in the March 2015. Sun Pharmaceutical Industries Limited has 45 (API & Finished Dosage Forms) manufacturing sites located on 5 continents. Sites are located at: • India • US • Brazil • Canada • Hungary • Israel • Bangladesh. Mexico • Romania • Ireland • Morocco • Nigeria • South Africa • Malaysia
Focus of the last WHO on-site inspection and desk assessment	Tenofovir Disoproxil Fumarate (APIMF 058)
Areas inspected	Desk assessment of SRA inspection report
Out of scope and restrictions (last WHO inspection)	APIs out of scope of WHO PQ
WHO API covered by the last WHO inspection	Tenofovir Disoproxil Fumarate (APIMF 058)
Additional products to be covered by this desk assessment:	None
Abbreviations	**Meaning**
BMR	Batch manufacturing record
CAPA	Corrective and preventive action
GMP	Good manufacturing practices
PQR	Product quality review
SOP	Standard operating procedure

Part 4	Summary of the assessment of supporting documentation

a) Manufacturing authorization and GMP certificate granted by the local authority:
Form No 26 No 1313-OSP and Form 26 No 1245-B No. Drugs (6) Pb.2018/998, dated 22-1-2018 – renewal of Manufacturing Drugs Licenses, issued by Food & Drugs Administration, Punjab
GMP certificate No. Drugs (6) Pb. 2019/1602, dated 9-4-19, issued by Food & Drugs Administration, Punjab

b) Site master file (SMF):
SMF and Appendices + drawings submitted and reviewed. SMF written according to the WHO TRS No. 961, Annex 14

c) List of all the APIs or other products (intermediates, dosage forms) manufactured on-site:
In total 74 APIs are manufactured at the site. Therapeutic categories:

1. Antineoplastic
2. Antifungal
3. Antimalarial
4. Antipsychotic
5. Cardiovascular
6. Hypercholesterolemia
7. Antihypertension
8. Vasodilators
9. Anticonvulsant
10. Diabetes Mellitus, Type 2
11. Antihistamine
12. Antidementia
13. HIV drugs called nucleoside reverse
14. Antiviral
15. Antiepileptic
16. Gastrointestinal
17. Antihistamine
18. Dermatological
19. Antiepileptic
20. Antibiotic/ Antibacterial
21. Antianxiety/Antipsychotic
22. Hypnotic
23. Antiparkinsonian
24. Antidepressant
25. Antiadrenergic
26. Urological
27. Antiplatelet
28. Hyponatremia
29. Analgesic/Antipyretic
30. Antidiabetic
31. Long acting beta agonist

d) List of all regulatory inspections performed in the last 3 years and their outcomes:

Name of the regulatory authority	Inspection date	Scope of Inspection
CDSCO, India	7-May-2015 to 8-May-2015	GMP Inspection
EMA (HPRA, Ireland, TGA, Australia and Germany)	8-12 Jun 2015	GMP Inspection
PMDA, Japan	3-5 Nov-2015	GMP Inspection (Product: Cilazapril)
CDSCO, India	5-6 May-2016	Renewal of Written Confirmation
State Food and Drugs Administration, S.B.S. Nagar (Nawanshahar), Punjab, India	23-Feb-2017	Renewal of GMP Certificate
State Food and Drugs Administration, S.B.S. Nagar (Nawanshahar), Punjab, India	02-Mar-2017	Approval of Site Plan
CDSCO, India	22-23 May-2017	Revalidation and Grant of new COPPs
Health Canada, Canada	12-16 Jun-2017	GMP Inspection
EMA (HPRA, Ireland, Germany and TGA, Australia)	06-10 Nov-2017	GMP Inspection (Repaglinide, Nevirapine Anhydrous)
State Food and Drugs Administration, S.B.S. Nagar (Nawanshahar), Punjab, India	29-Nov-2017	Renewal/Retention of Drug Manufacturing License
State Food and Drugs Administration, S.B.S. Nagar (Nawanshahar), Punjab, India	24-Sep-2018	GMP Inspection
State Food and Drugs Administration, S.B.S. Nagar (Nawanshahar), Punjab, India	27-Mar-2019	Renewal of GMP certificate
CDSCO, India	02-03 May-2019	Revalidation & Grant of new COPPs and Renewal of Written Confirmation
EMA (Finland, Hungary and Germany)	14-18 Oct-2019	GMP Inspection (Tamsulosin Hydrochloride, Repaglinide, Midazolam, Nevirapine Anhydrous
COFEPRIS, México	18-22 Nov-2019	GMP Inspection (Isotretinoin)
TGA, Australia	01-05 Mar-2020	GMP Inspection

e) Most recent product quality review (PQR) of the concerned WHO API:
Submitted and reviewed:
Tenofovir disoproxil fumarate Module MP-06, MP-10, MP-12), review period: Mar 2019 – Feb 2020 and Annexures

f) Batch manufacturing and packaging records, including the analytical part, for the most recently released batch of relevant API:
Submitted and reviewed:
- Drying
- Dehydration
- Milling sifting, packaging, sealing & labelling
- Analytical raw data

g) Master batch manufacturing and packaging records of the API of interest:
Submitted and checked:
- Drying
- Preparation
- Milling sifting, packaging, sealing & Labelling

h) Recalls in the past three years related to APIs with quality defects:
Declaration submitted: no recalls in past 3 years

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

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:
Declaration submitted: no warning letter, or equivalent regulatory action, issued

k) Out-of-stock situations:
Declaration submitted: no out-of-stock situations

l) Additional documents submitted:
1. Risk assessment**:** Nitrosamine impurities
2. Declarations submitted:
   - No solvent recovery outsourced for Tenofovir disoproxil fumarate
   - No notifications of upcoming inspections by competent authorities

Part 5	**Conclusion – Desk assessment outcome**

Based on the desk assessment and on GMP evidence received and reviewed, it is considered that a desk assessment is acceptable in lieu of a WHO onsite inspection. The ***site Sun Pharmaceutical Industries Limited Ltd, manufacturing module MP-12***, located at ***Village Toansa, P.O. Dist. S.B.S. Nagar (Nawanshahar), Punjab, 144 533, India*** 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 WHO 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 TRS No. 986, Annex 2**
   http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_986/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. 961, 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. WHO Recommendations for quality requirements when plant – derived artemisin is used as a starting material in the production 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

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 guidance 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 Multisource guidance or 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

24. 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. 1015), Annex 3.
Short name: WHO TRS No. 1025, Annex 3
https://www.who.int/publications-detail/978-92-4-000182-4

25. 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

26. 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

27. 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