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Prequalification Unit Inspection services
WHO PUBLIC INSPECTION REPORT
(WHOPIR)
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	SPARC, Tandalja, Vadadora, Gujarat, India, 290020	
Inspected site		
Name & address of manufacturing site	Sun Pharmaceutical Industries Limited *(Vagra)* Plot No. Z-15, Dahej SEZ Ltd., Taluka-Vagra, Bharuch, Gujarat, 392130, India	
Desk assessment details		
Date of review	05 -13 August 2021	
APIs covered by this desk assessment	• WHO API 354 (Dolutegravir Sodium) • APIMF 354 (Dolutegravir Sodium)	
List of documents submitted	The following documentation was provided for review: a. GMP inspection history b. Most recent inspection report (EIR), CAPA, final decision c. Copy of manufacturing license and GMP certificate d. Site Master File e. List of APIs manufactured on-site f. Most recent PQR g. Most recent BMRs and analytical data h. Master BMR and BPR i. Product recall declaration j. Confirmation on self-inspection k. Media fill declaration l. Declaration on regulatory action m. Out of stock confirmation	
Part 2	**Summary of SRA/NRA inspection evidence considered (from most recent to last)**	
USFDA	Dates of inspection:	06-10.01.2020
	Type of inspection:	Pre-approval inspection
	Block/Unit/Workshop:	N/A
	Type of APIs covered:	Valsartan Metformin HCl

Part 3	**Summary of the last WHO inspection**
Date and conclusion of most recent WHO inspection	A desk assessment of the site was carried out during 17 December 2018 - 5 March 2019. The site was found to be in compliance with WHO GMP
Brief description of manufacturing activities	The site is licensed to manufacture APIs and their intermediates. No β-lactam antibiotics, hormones and cytotoxic substances are manufactured on-site.
General information about the company and manufacturing site	Sun Pharmaceutical Industries Ltd. is a public limited company established in 1983 and managed by a Board of Directors. It manufactures and markets a wide range of pharmaceutical formulations and APIs. The company has established several manufacturing sites around the world. Corporate Headquarters are located in Mumbai, India. The Dahej (CRM-Vagra) site was established in April 2014 and is located approximately 140Km from Vadodara city airport. The campus consists of separate production, quality control and warehouse buildings and a solvent farm.
Focus of the last WHO inspection	The previous desk assessment focused on GMP compliance and Dolutegravir Sodium
Areas inspected	Inspection report USFDA, CAPA plan, PQR and BMR of Dolutegravir Sodium, HVAC and water system, recalls, returns and non-compliance
Out of scope and restrictions (last WHO inspection)	N/A
WHO APIs covered by the last WHO inspection	• WHO API 354 (Dolutegravir Sodium) • APIMF 354 (Dolutegravir Sodium)
Abbreviations	**Meaning**
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:
The company provided copies of a valid manufacturing license and GMP certificate issued by Food & Drug Control Administration, Gujarat.

b) Site master file (SMF):
The latest version of the SMF was provided and did not give rise to any comments.

c) List of all the APIs or other products (intermediates, dosage forms) manufactured on-site:
A list of 16 APIs manufactured on-site was provided. The list of APIs is annexed to the SMF.

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

Authority	Inspection Date	GMP Status
USFDA, USA	06-10.01.2020	Compliant
Food & Drug Control Administration, Gujarat and CDSCO, India	06-07.08.2018 & 15.11.2018	Compliant
USFDA, USA	28.05-06.06.2017	Compliant
LAGeSo (State Office for Health and Social Services Berlin, Germany), Germany	11-12.01.2017	Compliant
Food & Drug Control Administration, Gujarat and CDSCO, India	13-14.06.2016	Compliant

e) Most recent product quality review(s) (PQR)(s) of the concerned WHO API(s):
The company provided the 2021 PQR of Dolutegravir Sodium (batches manufactured during January-December 2020). The API is manufactured in 4 stages and the company conducted a review of each stage. OOS/OOT, deviations were reviewed. Root causes were identified in the majority of cases and CAPA were implemented. Critical process parameters and quality attributes were monitored, trended and found to be within the established limits. Reviews of raw and packaging materials and relevant suppliers were conducted. No significant changes were registered, and all suppliers were found to be qualified during the review period. A review of production yields for each stage was performed. Review of batches in stability studies confirmed the shelf-life of the product. No recalls were registered during the review period.

f) Batch manufacturing and packaging record(s), including the analytical part, for the most recently released batch of relevant API(s):
BMRs and analytical reports for each manufacturing stage were provided and did not give rise to any significant observations.

g) Master batch manufacturing and packaging record(s) of the API(s) of interest:
Master BMRs and BPRs were provided and did not give rise to any comments.

h) Recalls in the past three years related to APIs with quality defects:
The company provided a written confirmation stating that no recall has taken place in the last three 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:
The company confirmed that there is a self-inspection system and programme based on a written procedure. Self-inspection is performed annually by qualified auditors and covers all operations and activities on-site.

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):
No warning letter or equivalent regulatory action has been taken against the site in the last three years.

k) Out-of-stock situations:
The company confirmed that no shortage in supply of Dolutegravir Sodium has been experienced.

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 ***Sun Pharmaceutical Industries Limited (Vagra)*** located at ***Plot No. Z-15, Dahej SEZ Ltd., Taluka-Vagra, Bharuch, Gujarat, 392130, 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 **August 2022** or when another inspection is conducted by WHO or by a stringent regulatory authority.

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. 1025), 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