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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	Laurus Labs (Unit 2-FPP)	
Corporate address of manufacturer	Laurus Labs Limited 2nd Floor, Serene Chambers Road No.: 7, Banjara Hills Hyderabad 500034, Telangana, India	
Inspected site		
Name & address of manufacturing site	Laurus Labs Ltd, (Unit-2), Plot No:19, 20 & 21, Western Sector, APSEZ, Atchutapuram Mandal,Visakhapatnam-District, Andhra Pradesh, 531011, India	
Production Block/Unit	MB01	
Desk assessment details		
Date of review	22-29 January 2021	
Products covered by this desk assessment	HP027 Daclatasvir 30mg f.c tablets HP028 Daclatasvir 60mg f.c tablets HA732 Efavirenz/Lamivudine/ Tenofovir Disoproxil Fumarate 400/300/300mg f.c tablets HA679 Tenofovir Disoproxil Fumarate 300mg f.c tablets HA707 Dolutegravir/Lamivudine/Tenofovir Disoproxil Fumarate 50/300/300mg f.c tablets HA709 Darunavir 400mg f.c tablets HA710 Darunavir 600mg f.c tablets HA711 Darunavir 800mg f.c. tablets HA717 Emtricitabine/ Tenofovir Disoproxil Fumarate 200/300mg f.c tablets HA718 Dolutegravir 50mg f.c tablets HA727 Efavirenz/Lamivudine/ Tenofovir Disoproxil Fumarate 600/300/300mg f.c tablets	
Part 2	**Summary of SRA/NRA inspection evidence considered (from most recent to last)**	
JAMPZ - Slovenia	Dates of inspection:	17-20.08.2020
	Type of inspection:	Distant Assessment
	Block/Unit:	MB01
	Type of products/Dosage forms covered:	Primary and secondary packaging of tablets on blister packaging line were reviewed. During the distant

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		assessment batch records and PQR of Tenofovir Disoproxil Fumarate 300mg f.c tablets were reviewed
US FDA, USA	Dates of inspection:	04-08.11.2019
	Type of inspection:	Pre-approval inspection
	Block/Unit:	MB01
	Type of products/Dosage forms covered:	Tablets
BGV-Germany	Dates of inspection:	26-29.11.2018
	Type of inspection:	Product related inspection
	Block/Unit:	MB01
	Type of products/Dosage forms covered:	Capsules and tablets
Part 3	**Summary of the last WHO inspection**	
Date and conclusion of most recent WHO inspection	The most recent WHO Prequalification inspection took place during 13-17 March 2017. This was the first WHO prequalification inspection. The site was deemed GMP compliant	
Brief description of manufacturing activities	At the time of inspection, there were two manufacturing blocks (MB) in the facility; MB01 FPP manufacturing for oral solid dosage forms (tablets and capsules) and MB02 for API manufacturing.	
General information about the company and manufacturing site	Laurus Labs Limited was incorporated as Laurus Labs Private Limited. The company is a pharmaceutical services organization headquartered in Hyderabad, Telangana, India. Laurus Labs Limited offers medicinal chemistry services, API and FPP development and analytical services. At the time of inspection, there were two manufacturing blocks (MB) in the facility; MB01 drug products manufacturing for oral solid dosage forms (tablets and capsules) and MB02 for drug substances manufacturing. Drug MB01 consisted of three floors. Ground floor: Raw Material Warehouse, Manufacturing area, Primary & Secondary Packing area, Change rooms, Secondary, Packaging material warehouse and Finished Goods and warehouse. First floor; Quality Control, Quality Assurance and technical area for housing AHU's. Second floor: Stability chambers, Microbiology Lab (under construction at the time of inspection	
Focus of the last WHO inspection	The inspection focused on MB01 where FPPs were manufactured, especially on Tenofovir Disoproxil Fumarate f.c. tabs.	
Areas inspected	Pharmaceutical quality system Production Quality control Personnel Utilities Materials	

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Out of scope and restrictions (last WHO inspection)	Drug substance manufacturing block (MB-02) Drug product facility currently under expansion Microbiology laboratory under construction
WHO products covered by the last WHO inspection	HA679 Tenofovir Disoproxil (fumarate) (TDF) Tablet, Film-coated 300mg
Additional products covered by this desk assessment:	HP027 Daclatasvir 30mg f.c tablets HP028 Daclatasvir 60mg f.c tablets HA732 Efavirenz/Lamivudine/ Tenofovir Disoproxil Fumarate 400/300/300mg f.c tablets HA707 Dolutegravir/Lamivudine/Tenofovir Disoproxil Fumarate 50/300/300mg f.c tablets HA709 Darunavir 400mg f.c tablets HA710 Darunavir 600mg f.c tablets HA711 Darunavir 800mg f.c. tablets HA717 Emtricitabine/ Tenofovir Disoproxil Fumarate 200/300mg f.c tablets HA718 Dolutegravir 50mg f.c tablets HA727 Efavirenz/Lamivudine/ Tenofovir Disoproxil Fumarate 600/300/300mg f.c tablets
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

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Part 4	Summary of the assessment of supporting documentation

a) Manufacturing authorization and GMP certificate granted by the local authority:
The facility is licensed to manufacture APIs, intermediates, excipients and FPPs

b) Site master file (SMF):
The company provided the latest version of SMF effective on 18.12.2020 and valid until 17.12.2025. A revision history is available and was also provided. There are two facilities on site. FPPs are manufactured in MB01 and excipients/intermediates/APIs are manufactured in MB02. The SMF is applicable both for MB01 and MB02. The Quality Assurance team is independent from production, covers both MB01 and MB02 and reports via Vice President QA to Executive Director Quality. Based on the wording of the SMF there is one quality system in place applicable to both MB01 and MB02. The SMF is complimented with several Annexes including Annex 1 which contains the site's manufacturing licenses and authorized products

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

No.	Authority	Date	Outcome
1	CDSCO - India	18.03.2018	Compliant
2	JAZMP - Slovenia	29.08.2018	Compliant
3	BGV- Germany	29.11.2018	Compliant
4	US FDA - USA	08.11.2019	Compliant
5	JAZMP - Slovenia	20.08.2020	Distant Assessment - Compliant

d) List of all the products and dosage forms manufactured on-site:
The company provided as Annex 2b of the SMF a list of 46 products in different strengths
A list of excipients, intermediates and APIs manufactured in MB02 was also provided.

e) Most recent product quality review(s) (PQR)(s) of the concerned WHO product(s):
In 2020 out of the 8 WHO products only Tenofovir Disoproxil Fumarate 300mg f.c tablets was manufactured.
22 batches Tenofovir Disoproxil Fumarate 300mg f.c tablets were manufactured during the review period (January – December 2019).
8 batches of Tenofovir API were used in the manufacture of the FPP during the given period. No anomalies were identified for these API batches. Alternate supplier sites for Tenofovir Disoproxil Fumarate, Croscarmellose Sodium, Microcrystalline Cellulose and Lactose Monohydrate were introduced.
No process or cleaning validation were performed during the review period. No recalls were conducted. Stability studies support the shelf-life of the product. No OOS and OOT were registered. 4 deviations were identified. Two of the deviations relate to product yield and a newly installed powder level sensor was identified as the root cause. The company revised the yield specifications to address this issue.

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f) Batch manufacturing and packaging record(s), including the analytical part, for the most recently released batch of relevant product(s):
The following batch records were reviewed:
Emtricitabine/ Tenofovir Disoproxil Fumarate 200/300mg f.c tablets AETT100417
Efavirenz/Lamivudine/ Tenofovir Disoproxil Fumarate 400/300/300mg f.c tablets AELT200118
Dolutegravir/Lamivudine/Tenofovir Disoproxil Fumarate 50/300/300mg f.c tablets ADLT100117
Darunavir 800mg f.c tablets ADRT100117A
It is noted that some of these batches date back to 2017.

g) Master batch manufacturing and packaging record(s) of the product(s) of interest:
Master BMRs and BPRs for all products were provided and did not give rise to any observations

h) Recalls in the past three years related to products with quality defects:
No recalls have been conducted in the last three years

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:
According to the company self-inspection is carried out every 4 months as per Internal Audits/ Self-Inspection SOP. Internal audits cover all quality systems including products manufactured during the given period.

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:
No warning letter or equivalent action has been issued for the site

k) Out-of-stock situations:
No out-of-stock situations have occurred in the last three years and no such situation is foreseen for the near future

l) Additional documents submitted:
Personnel and material movement in the warehouse
Personnel and material movement in MB01

Part 5	**Conclusion – Desk assessment outcome**

Based on the previous WHO inspection 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 ***Laurus Labs Ltd, (Unit-2) - MB01***, located at ***Plot No:19, 20 & 21, Western Sector, APSEZ, Atchutapuram Mandal, Visakhapatnam-District, Andhra Pradesh, 531011, India*** is considered to be operating at an acceptable level of compliance with WHO GMP guidelines.

This compliance status shall be valid until **January 2022** or when another inspection is conducted by WHO or by a stringent regulatory authority. It remains the prerogative of WHO to carry out an inspection any time prior to that.

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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/

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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/

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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

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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

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