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Prequalification Team Inspection services
WHO PUBLIC INSPECTION REPORT
(WHOPIR)
Desk Assessment of Active Pharmaceutical Ingredient (API) Manufacturer

Part 1	General information
Company information	
Name of Manufacturer	Mylan Laboratories Limited (Unit-10)
Corporate address of manufacturer	M/s. Mylan Laboratories Limited Plot No 564/A/22, Road No 92, Jubilee Hills, Hyderabad-500096 Telangana, India
Inspected site	
Name & address of manufacturing site	Mylan Laboratories Limited (Unit-10), Plot No. 86, Ramky Pharma City (India) Ltd, JN Pharma City, Parawada Mandal, Visakhapatnam, Andhra Pradesh, 531019, India
Synthetic Unit/Block/ Workshop	• MB-4 BAY-2 Pharma area (API) • MB-4 BAY-2 Intermediate area • MB-3 Intermediate area • MB-2 Intermediate area • MB-4 BAY-1 Pharma area • MB-4 BAY-3 Pharma area • MB-1 Intermediate area • MB-3 BAY-1 & BAY – 2 Pharma areas
Desk assessment details	
APIs covered by this desk assessment	• Abacavir hemisulfate • Tenofovir disoproxil fumarate • Efavirenz
List of documents submitted	1. ANVISA Certificate 2. MFDS audit response and certificate 3. USFDA EIR 4. Manufacturing License copy of Abacavir Sulfate, Efavirenz and Tenofovir Disoproxil Fumarate 5. GMP certificate copy of Abacavir Sulfate, Efavirenz and Tenofovir Disoproxil Fumarate 6. Site Master File & Annexures 7. List of APIs with proprietary names and INN 8. PQRs for: a. Abacavir Sulfate APQR Summary report b. Abacavir Sulfate APQR Annexures c. Efavirenz APQR Summary report d. Efavirenz APQR Annexures e. Tenofovir Disoproxil Fumarate APQR Summary report f. Tenofovir Disoproxil Fumarate APQR Annexures g. Annual review of Manufacturing Supporting Systems

	h. Annual review of packaging materials 9. Completed Manufacturing Batch Production Records and Analytical Data for: a) Abacavir sulfate: 1. Executed MBPR 2. In-process Results 3. Analytical data b) Efavirenz: 1. Executed MBPR 2. In-process Results 3. Analytical data c) Tenofovir Disoproxil Fumarate: 1. Executed MBPR 2. In-process results 3. Analytical data 11. Abacavir Sulfate Master Batch Production Record 12. Efavirenz Master Batch Production Record 13. Tenofovir Disoproxil Fumarate Master Batch Production Record 14. Declaration for Recalls 15. Declaration for self-inspection 16. Declaration for Warning letters 17. Declaration for Out of stock	
Part 2	**Summary of SRA/NRA inspection evidence considered (from most recent to last) and comments**	
US FDA	Dates of inspection:	29.10.2018 to 02.11.2018
	Type of inspection:	Routine inspection
	Block/Unit/Workshop:	MB1; MB2; MB3; MB4; and MB4 Bays 2 and 3
	APIs covered:	• Tenofovir Disproxil Fumarate • Abacavir Sulfate USP

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 3	Summary of the assessment of supporting documentation

a) Manufacturing authorization and GMP certificate granted by the local authority:
Form 26 No 34/VP/AP/2012/8/R, granted on the 22-08-2012 has been renewed from 22-08-2017 to 21-08-2022.

b) Site master file (SMF):
Submitted – acceptable, prepared according to the WHO TRS No. 961, Annex 14

c) List of all the APIs or other products (intermediates) manufactured on-site:

No.	Product Name	Proprietary Name	INN
1	Tenofovir Disoproxil Fumarate	VIREAD	Tenofovir Disoproxil Fumarate
2	Citalopram Hydrobromide	CELEXA	Citalopram Hydrobrornide
3	Efavirenz	SUSTIVA	Efavirenz
4	Tenofovir Disoproxil Maleate	--	Tenofovir Disoproxil Maleate
5	Abacavir Sulfate	ZIAGEN	Abacavir Sulfate
6	Elvitegravir	VITEKTA	Elvitegravir
7	Tenofovir Alafenamide Fumarate	VEMLIDY	Tenofovi r Alafenamide Fumarate
8	Tenofovir Disoproxil Orotate	--	Tenofovir Disoproxil Orotate
9	Carvedilol	COREG	Carvedilol
10	Carvedilol Phosphate	COREG CR	Carvedilol Phosphate
11	Escitalopram Oxalate	LEXAPRO	Escitalopram Oxalate
12	Mafenide Acetate	SULFAMYLON	Mafenide Acetate
13	Esomeprazole Magnesium Trihydrate	NEXIUM	Esomeprazole Magnesium Trihydrate
14	Sucroferric oxyhydroxide	VELPHORO	Sucroferricoxyhydroxide
15	Dolutegravir Sodium	TIVICAY	Dolutegravir Sodium

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

Date of Inspection	Name of the Regulatory Agency	Name of the Country	Status
10.12.2014 to 11.12.2014	CDSCO & DCA	India	Approved
07.09.2015 to 11.09.2015	USFDA	USA	Approved
30.09.2015	WHO (Desk Review)	Geneva	Approved
16.12.2015 to 17.12.2015	AGES	Austria	Approved
24.10.2016 to 26.10.2016	MFDS	Korea	Approved
18.05.2017 to 19.05.2017	CDSCO & DCA	India	Approved

Date of Inspection	Name of the Regulatory Agency	Name of the Country	Status
17.07.2017 to 21.07.2017	ANVISA	Brazil	Approved
29.10.2018 to 02.11.2018	USFDA	USA	Approved

e) Most recent product quality reviews (PQRs) of the concerned WHO APIs:
Submitted and reviewed for:

1) Abacavir Sulfate APQR
   a) Summary report
   b) Annexures
2) Efavirenz APQR
   a) Summary report
   b) Annexures
3) Tenofovir Disoproxil Fumarate
   a) APQR Summary report
   b) Annexures
4) Annual review of Manufacturing Supporting Systems
5) Annual review of packaging materials

f) Batch manufacturing and packaging records, including the analytical part, for the most recently released batch of relevant APIs:
Submitted and reviewed for:

1) Abacavir sulfate:
   a) Executed MBPR
   b) In-process Results
   c) Analytical data
2) Efavirenz:
   a) Executed MBPR
   b) In-process Results
   c) Analytical data
3) Tenofovir Disoproxil Fumarate:
   a) Executed MBPR
   b) In-process results
   c) Analytical data

g) Master batch manufacturing and packaging records of the APIs of interest:
Submitted and reviewed for:

1) Abacavir Sulfate Master Batch Production Record
2) Efavirenz Master Batch Production Record
3) Tenofovir Disoproxil Fumarate Master Batch Production Record

h) Recalls in the past three years related to APIs with quality defects:
Submitted: Declared - no recalls

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:
Submitted

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):
Submitted: Declared - no warning letters

k) Out-of-stock situations:
Submitted: Declared -no out-of-stock

l) Additional documents submitted:
N/A

Part 4	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 ***Mylan Laboratories Limited (Unit-10)*** located at ***Plot No. 86, Ramky Pharma City (India) Ltd, JN Pharma City, Parawada Mandal, Visakhapatnam, Andhra Pradesh, 531019, 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 5	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 ***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 GMP Guidelines or WHO TRS No. 986, Annex 2***
   http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_986/en/

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. 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/

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 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 TRS No. 961, 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 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. WHO Recommendations for quality requirements when plant – derived artemisin is used as a starting material in the prosecution 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