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Prequalification Team Inspection services
WHO PUBLIC INSPECTION REPORT

Desk Assessment of Active Pharmaceutical Ingredient (API) Manufacturer

Part 1	**General information**
Company information	
Name of Manufacturer	Mylan Laboratories Limited, Unit-2
Corporate address of manufacturer	Plot No 564/A/22, Road No 92, Jubilee Hills, Hyderabad-500 096 Telangana, India. Tel: 040-30866666 Fax: 040-30866699.
Inspected site	
Name & address of manufacturing site	Mylan Laboratories Limited, Unit-2. Survey No.10/42, Gaddapotharam, Kazipally Industrial Area, PIN-502319, Sanga Reddy District Telangana, India. Tel: 08458-277248 Fax:08458277211.
Synthetic Unit/Block/Workshop	Unit 2 Manufacturing Blocks (MB-01 to 06)
Desk assessment details	
Date of review	07 October 2019
APIs covered by this desk assessment	See table below

PQT Number	**Active Pharmaceutical Ingredient**
APIMF039	Emtricitabine
APIMF050	Lopinavir
APIMF069	Lamivudine anhydrous
APIMF070	Nevirapine anhydrous
APIMF072	Zidovudine
APIMF310	Dolutegravir sodium
WHOAPI-039	Emtricitabine
WHOAPI-050	Lopinavir
WHOAPI-069	Lamivudine anhydrous
WHOAPI-070	Nevirapine anhydrous
WHOAPI-072	Zidovudine
WHOAPI-310	Dolutegravir sodium.

Note:
In addition to the above, API from Mylan Unit 2 is used in the following FPPs :

	HA117 (Lamivudine), HA128 (Lamivudine), HA268 (Nevirapine anhydrous), HA286 (Lamivudine, zidovudine), HA291 (Lamivudine, Zidovudine), HA298 (Nevirapine), HA323 (Lamivudine, nevirapine), HA392 (Lamivudine, Zidovudine), HA396 (Nevirapine), HA411 (Lopinavir), HA414 (Lamivudine), HA426 (Zidovudine, Lamivudine), HA433 (Lamivudine, zidovudine, nevirapine), HA437 (lamivudine, zidovudine), HA444 (emtricitabine), HA464 (Zidovudine), HA466 (Lamivudine), HA483 (Zidovudine), HA485 (Zidovudine), HA524 (Lamivudine, nevirapine, zidovudine), HA537 (Zidovudine), HA552 (Emtricitabine), HA553 (Emtricitabine), HA555 (Zidovudine), HA557 (Lamivudine, zidovudine), HA567 (Nevirapine), HA568 (Nevirapine),HA569 (Nevirapine), HA570 (Nevirapine), HA572 (Lamivudine, Zidovudine), HA629 (Nevirapine), HA635 (Lamivudine), HA678 (Dolutegravir), HA688 (Lamivudine, Dolutegravir), HA697 (Lopinavir), HA706 (Lamivudine anhydrous), HA721 (Lamivudine)	
List of documents submitted	a) Site master file document number U-2/SMF/001/04 version 4 effective date 21.03.2019. b) Manufacturing license number 66/MD/AP/04/B/CC valid till 14-05-2020 and issued by the Drugs Control Administration of Telangana. c) Full inspection reports and proof of CAPA implementation and final decisions for inspections carried out by the USFDA, over the last three years. d) A list of all the APIs or other products manufactured on site. e) Product quality reviews for six WHO PQ APIs. f) The completed batch manufacturing and packaging record including the analytical part for six WHO PQ APIs. g) Blank master batch manufacturing and packaging records of the APIs of interest. h) Declaration signed by the Head Quality Unit 2, confirming that no recalls were initiated for products manufactured at the site within the last three years. i) Declaration signed by the Head Quality Unit 2, confirming that self-inspections are being performed with regards to the activities related to APIs being manufactured at the site and that the site is in compliance with principles of GMP. j) Declaration signed by the Head Quality Unit 2, confirming that no warning letter or equivalent regulatory action has been issued by any regulatory authority with regards to any API manufactured at Mylan Laboratories Limited Unit 2. k) Declaration signed by the Head Quality Unit 2, confirming that no out of stock situation occurred in the last 3 years or foreseen in the next year for the products manufactured at Mylan Unit 2	
Any documents missing?	All documents required for the desk assessment were duly submitted.	
Part 2	**Summary of SRA/NRA inspection evidence considered (from most recent to last) and comments**	
USFDA	Dates of inspection:	15-19 October 2018.

	Type of inspection:	Pre-approval Inspection.
	Block/Unit/Workshop:	Unit 1 (MB-01 to MB-11) and Unit 2 (not inspected) Note: Unit 2 is 5-7 minutes away by vehicle and each unit is of significant size. There are 17 production blocks in total for both units combined.
	APIs covered:	API by chemical synthesis
	Physical areas inspected:	Production facilities (MB06, MB07, MB08), Materials management systems, quality control laboratories, utilities, and quality management systems.
USFDA	Dates of inspection:	12-16 March 2018.
	Type of inspection:	Post Approval Audit Inspection
	Block/Unit/Workshop:	Unit 1 and Unit 2 Note: Only Unit 1, MB-03, MB02 and cleanrooms were inspected and some of the manufacturing areas used for Lamivudine USP (SVL) in Unit 2
	APIs covered:	APIs by chemical synthesis
	Physical areas inspected:	Quality systems for both units, Unit I: Solid materials warehouse, manufacturing block MB-03, MB-02 and Cleanrooms with a focus on equipment used for efavirenz and ancillary areas.
Part 3	**Summary of the last WHO inspection**	
Date and conclusion of most recent WHO inspection	Mylan Unit 2 was last inspected by the WHO from 18 to 21 April 2016. This was the third inspection of the site by WHO. The inspection was closed with a compliance letter after the submission of CAPA to 3 major and 14 other deficiencies.	
Summary of manufacturing activities	The site is involved in the warehousing, production and quality control of APIs.	
General information about the company and manufacturing site	Mylan Laboratories Limited (India) has its corporate office in Jubilee Hills, Hyderabad and nine API manufacturing sites in India. This site was renamed as Mylan Laboratories Limited, Unit-2 in 2015 (previously Matrix Laboratories Limited, and Astrix Laboratories Limited). The site is located in Survey No:10 and 42, Gaddapotharam, Kazipally Industrial Area, Sanga Reddy District, Telangana, 502319 India. Key intermediates and APIs are manufactured at this site. This site occupies a total land area of 1,15,339 Sq.mt; of which 40,150 Sq.mt was built-up area used as pharmaceutical manufacturing facilities. Penicillin and	

<table>
<tr><td></td><td>Cephalosporin APIs were not manufactured on the site.</td></tr>
<tr><td>Focus of the last WHO inspection</td><td>The last WHO inspection focused on the production and quality control of APIs listed with the PQ programme.</td></tr>
<tr><td>Areas inspected</td><td>Warehousing, production, QMS, quality control and utilities</td></tr>
<tr><td>Out of scope and restrictions (last WHO inspection)</td><td>The last WHO inspection was restricted to the WHO PQ APIs.</td></tr>
<tr><td>WHO APIs covered by the last WHO inspection</td><td>
<table>
<tr><th></th><th>Active Pharmaceutical Ingredient.</th><th>PQT number</th></tr>
<tr><td>1</td><td>Stavudine</td><td>APIMF-068</td></tr>
<tr><td>2</td><td>Didanosine</td><td>APIMF-087</td></tr>
<tr><td>3</td><td>Lamivudine USP</td><td>APIMF-069</td></tr>
<tr><td>4</td><td>Lopinavir</td><td>APIMF-050</td></tr>
<tr><td>5</td><td>Nevirapine USP (Anhydrous)</td><td>APIMF-070</td></tr>
<tr><td>6</td><td>Emtricitabine</td><td>APIMF-039</td></tr>
<tr><td>7</td><td>Zidovudine USP</td><td>APIMF-072</td></tr>
</table>
</td></tr>
<tr><td>Additional products to be covered by this desk assessment:</td><td>
<table>
<tr><td>WHOAPI-310 / APIMF 310</td><td>Dolutegravir sodium (prequalified)</td></tr>
</table>
</td></tr>
<tr><th>Abbreviations</th><th>Meaning</th></tr>
<tr><td>BMR</td><td>Batch manufacturing record</td></tr>
<tr><td>BPR</td><td>Batch production record</td></tr>
<tr><td>CAPA</td><td>Corrective and preventive action</td></tr>
<tr><td>CC</td><td>Change control</td></tr>
<tr><td>GMP</td><td>Good manufacturing practices</td></tr>
<tr><td>NC</td><td>Non-conformity</td></tr>
<tr><td>NRA</td><td>National regulatory agency</td></tr>
<tr><td>PQR</td><td>Product quality review</td></tr>
<tr><td>PQS</td><td>Pharmaceutical quality system</td></tr>
<tr><td>QA</td><td>Quality assurance</td></tr>
<tr><td>QC</td><td>Quality control</td></tr>
<tr><td>QCL</td><td>Quality control laboratory</td></tr>
<tr><td>QMS</td><td>Quality management system</td></tr>
<tr><td>QRM</td><td>Quality risk management</td></tr>
<tr><td>RA</td><td>Risk assessment</td></tr>
<tr><td>RCA</td><td>Root cause analysis</td></tr>
<tr><td>SOP</td><td>Standard operating procedure</td></tr>
</table>

Part 4	Summary of the assessment of supporting documentation

a) Manufacturing authorization and GMP certificate granted by the local authority:
License number 66/MD/AP/04/B/CC valid till 14-05-2020 and issued by the Drugs Control Administration of Telangana was submitted.

b) Site master file (SMF):
Site master file document number U-2/SMF/001/04 version 4 effective date 21.03.2019 was reviewed and found adequate in content and in line with the WHO guidance for site master files.

c) List of all the APIs or other products (intermediates, dosage forms) manufactured on-site:
A list of all APIs manufactured at the site was provided. The list contained 10 APIs. No penicillin or other highly sensitising products were manufactured at this site. There is thus no foreseen risk of cross-contamination from this category of products.

d) List of all regulatory inspections performed in the last 3 years and their outcomes:
A list of regulatory inspections performed in the last 3 years and their outcomes was provided. The site was inspected by the USFDA, most recently in 2018. CAPA reports were submitted and accepted by the USFDA. These inspection reports are overall acceptable and comprehensive in lieu of an onsite inspection.

e) Most recent product quality review(s) (PQR)(s) of the concerned WHO API(s):
PQRs for 6 APIs were submitted. PQR for dolutegravir sodium report number APR/U-2/2018/DOS/00 for the review period January 2018 to December 2018 was reviewed. It was noted that no batches were manufactured during the review period. However, the company performed a review of other parameters such as suppliers, technical agreements, complaints, ongoing stability, change controls, recalls, regulatory variations among others. A trend showing increasing levels of any other impurity during ongoing stability testing for batches manufactured was observed, however these were below the upper specification limit. The company recommended to monitor this in the next review of stability data.

PQR for emtricitabine, report number APR/U-2/2018/EMB/00 for the review period January to December 2018 was briefly reviewed. No batches had been manufactured during the review period. The PQR provided a discussion of change controls (6 reported), OOS (1 reported), complaints, reprocessed batches, returned goods, recalls and validations, (0 reported). 12 ongoing stability studies were reported. Stability test results were within specifications and no trends were observed.

PQR for lamivudine report number APR/U-2/2018/LVM/00 for the review period January to December 2018 was briefly reviewed. 3 batches of LVM-I and 5 batches of LVM-IRP and 4 powder processing batches LVM-BL intermediates and 8 discrete batches of final API were manufactured and released. No OOS, CAPA, recalls, reworks were reported. Statistical analysis was not performed because a minimum of 30 batches was required to perform CPK calculations. Other parameters expected in a product quality review were discussed in sufficient detail.

Separate reviews were performed for the packaging materials, water system, compressed air, nitrogen, and HVAC systems. All parameters were generally within the prescribed limits.

PQR for other APIs was briefly reviewed. It was noted that the company did not in many cases manufacture many of the PQ APIs during the period of review.

f) Batch manufacturing and packaging record(s), including the analytical part, for the most recently released batch of relevant API(s):

Batch manufacturing and testing records for emtricitabine batch number 20076566 batch size 100kg manufactured on 25.06.2017 and released on 05.07.2017, lamivudine batch number 25512485 batch size 480kg, manufactured on 16.02.2018 and released on 22.03.2019 were reviewed. Generally, the APIs appear to have been manufactured according to the manufacturing instructions, in process tests and final analytical test results showed compliance with specifications. No remarkable issues were noted.

A declaration was provided by the applicant that three APIs of dolutegravir sodium, lopinavir and zidovudine had not been manufactured over the last three years.

g) Master batch manufacturing and packaging record(s) of the API(s) of interest:

Blank master batch manufacturing and packaging records of 6 PQ APIs were submitted.

h) Recalls in the past three years related to APIs with quality defects:

Declaration signed by the Head Quality Unit II, confirming that no recalls were initiated for products manufactured at the site within the last three years was submitted.

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:

Declaration signed by the Head Quality Unit II, confirming that self-inspections are being performed with regards to the activities related to APIs being manufactured at the site and that the site is in compliance with principles of GMP was 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):

Declaration signed by the Head Quality Unit II, confirming that no warning letter or equivalent regulatory action has been issued by any regulatory authority with regards to any API manufactured at Mylan Laboratories Limited Unit 1 was submitted.

k) Out-of-stock situations:

Declaration signed by the Head Quality Unit II, confirming that no out of stock situation occurred in the last 3 years or foreseen in the next year for the products manufactured at Mylan Unit I was submitted.

l) Additional documents submitted:

Not applicable.

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. ***Mylan Laboratories Limited unit 2*** located at ***Survey N0.10/42, Gaddapotharam, Kazipally Industrial Area, PIN-502319, Sanga Reddy District Telangana, 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 ***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*. Forty-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. Part 2: Interpretation of Guidelines on heating, ventilation and air-conditioning systems for non-sterile pharmaceutical products. *WHO Expert Committee on Specifications for Pharmaceutical Preparations*. Fifty-Third Report Geneva, World Health Organization, 2019 (WHO Technical Report Series, No. 1019), Annex 2. **Short name: WHO TRS No. 1019, Annex 2**
https://apps.who.int/iris/bitstream/handle/10665/312316/9789241210287-eng.pdf?ua=1

7. Good manufacturing practices: guidelines on validation. *WHO Expert Committee on Specifications for Pharmaceutical Preparations*. Fifty-Third Report Geneva, World Health Organization, 2019 (WHO Technical Report Series, No. 1019), Annex 3. **Short name: WHO TRS No. 1019, Annex 3**
https://apps.who.int/iris/bitstream/handle/10665/312316/9789241210287-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. 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 3. ***Short name: WHO TRS No. 957, Annex 3***
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. 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. 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

24. 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