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Prequalification Team
WHO PUBLIC INSPECTION REPORT
(WHOPIR)
Active Pharmaceutical Ingredient Manufacturer

Part 1	**General information**
Manufacturers details	
Company information	
Name of manufacturer	Mylan Laboratories Limited
Corporate address of manufacturer	House No 8-2-293/82/J-III, Plot No 564//22, Road No 92, Jubilee Hills, Hyderabad-500 034 Telangana, India
Inspected site	
Address of inspected manufacturing site if different from that given above	Survey No.10/42, Gaddapotharam, IDA Kazipally Medak District, Telangana– 502319 India
Unit / block / workshop number	Unit 2, Prodution Block: MB I, II, III, IV, V &VI
Manufacturing license number	Manufacturing Licenses in Form-25 bearing No. 66/MD/AP/95/B/CC and Form-28 bearing No. 66/MD/AP/04/B/CC
Inspection details	
Dates of inspection	18 to 21 April 2016
Type of inspection	Routine inspection
Introduction	
Brief summary of the manufacturing activities	Production and quality control of APIs.
General information about the company and site	Mylan Laboratories Limited (India) has its corporate office in Jubilee Hills, Hyderabad, India. Mylan Laboratories Limited (India) has nine API manufacturing sites in India. The site inspected was renamed as Mylan laboratories limited, Unit-2 in 2015 (which previously was named Matrix Laboratories limited and Astrix Laboratories limited). The site is located in Survey No.10/42, Gaddapotharam, IDA Kazipally Medak District, Telangana, 502319 India. Key intermediates and APIs are manufactured at this site. The number of personnel at the time of the inspection was approximately 323 including

	QA: 22, QC:49, Production: 134, Warehouse:12 and Others. Penicillin and Cephalosporin APIs were not manufactured on the site.
History	This was a third WHO inspection with previous inspections by the WHO performed in 2005 and 2013.The site had been inspected by US FDA in 2011 and 2013.
Brief report of inspection activities undertaken	
Scope and limitations	
Areas inspected	The inspection covered the following sections of the WHO GMP for Active Pharmaceutical Ingredients text: • Quality management • Personnel • Buildings and facilities • Process equipment • Documentation and records • Materials management • Production and in-process controls • Packaging and identification labelling of APIs and intermediates • Storage • Laboratory controls • Validation • Change control • Rejection and reuse of materials • Complaints and recalls • Contract manufacturers (including laboratories)
Restrictions	No
Out of scope	No
WHO product numbers covered by the inspection	Nevirapine APIMF70 Lamivudine APIMF69 Zidovudine APIMF072 Lopinavir APIMF050 Stavudine APIMF068 Didanosine APIMF087 Emtricitabine APIMF 039

Abbreviations

AHU	air handling unit
ALCOA	attributable, legible, contemporaneous, original and accurate
API	active pharmaceutical ingredient
APQR	annual product quality review
BDL	below detection limit

BMR	batch manufacturing record
BPR	batch packaging record
CAPA	corrective actions and preventive actions
CC	change control
CFU	colony-forming unit
CoA	certificate of analysis
CpK	process capability index
DQ	design qualification
EM	environmental monitoring
FAT	factory acceptance test
FBD	fluid bed dryer
FMEA	failure modes and effects analysis
FPP	finished pharmaceutical product
FTA	fault tree analysis
FTIR	Fourier transform infrared spectrometer
GC	gas chromatograph
GMP	good manufacturing practice
HACCP	hazard analysis and critical control points
HPLC	high-performance liquid chromatograph
HVAC	heating, ventilation and air conditioning
IR	infrared spectrophotometer
IQ	installation qualification
KF	Karl Fisher
LAF	laminar air flow
LIMS	laboratory information management system
LoD	limit of detection
LOD	loss on drying
MB	microbiology
MBL	microbiology laboratory
MF	master formulae
MR	management review
NMR	nuclear magnetic resonance spectroscopy
NRA	national regulatory agency
OQ	operational qualification
PHA	process hazard analysis
PM	preventive maintenance
PpK	process performance index
PQ	performance qualification
PQR	product quality review
PQS	pharmaceutical quality system
QA	quality assurance
QC	quality control
QCL	quality control laboratory
QRM	quality risk management

RA	risk assessment
RCA	root cause analysis
SOP	standard operating procedure
TAMC	total aerobic microbial count
TFC	total fungi count
TLC	thin layer chromatography
URS	user requirements specifications
UV	ultraviolet-visible spectrophotometer

Part 2	Brief summary of the findings and comments (where applicable)

Brief summary of the findings and comments

1. Quality management

Principles

The quality management system was generally well established, documented and implemented.
The site organizational structure was presented and was generally acceptable. Quality-related activities were defined and documented. The Quality Assurance department was independent from production.

Product quality review (PQR)

A SOP for annual product quality review was reviewed.

The 2015 PQR for Didanosine, Emtricitabine (WHO grade) and Nevirapine were reviewed. There was no batch of Didanosine manufactured in the year. Non-compliances observed during the inspection that was listed in the full report regarding PQR were addressed by the manufacturer to a satisfactory level.

Quality Risk Management

Quality risk management and risk assessment procedure and reports were reviewed. Various approaches to risk assessment were allowed by the procedures.

Deviations

A procedure for handling and investigation of incident/deviation was reviewed, as well as CAPA trend analysis. Non-compliances observed during the inspection that was listed in the full report regarding deviation management were addressed by the manufacturer to a satisfactory level.

2. Personnel

Personnel qualifications

An organization chart was available. There was an adequate number of personnel, suitably qualified by education and training, to perform and supervise the manufacture of APIs. The personnel met during the inspection were experienced and appeared to be knowledgeable about GMP.

Training

Training was inspected.

Personnel Hygiene

Personnel hygiene requirements were available and documented. The requirements for entry into the Grade D cleanrooms were documented, including by approved photographs on change room walls. Staff observed in these areas wore appropriate protective clothing.

3. Buildings and facilities

Design and construction

Production blocks for the production and packaging were not dedicated to any of the APIs in the inspection scope. Micronization and common packaging area were shared by all APIs when necessary.

The facilities were generally located, designed, and constructed to facilitate cleaning, maintenance and operations as appropriate to the type and stage of manufacture of the APIs. Non-compliance observed during the inspection that was listed in the full report regarding material movement was addressed by the manufacturer to a satisfactory level.

Adequate space was provided for production and QC activities. Contamination during the final stages of production was minimized by these activities taking place in a suitably controlled Grade D environment.

Utilities

Ventilation, air filtration and exhaust systems were provided. A HVAC system providing filtered air to Grade D cleanrooms was reviewed and discussed during the inspection.

Purified Water

Purified water was produced from bore well water by pretreatment followed by RO. Distribution was at ambient temperature and the loop was sanitized weekly. Temperature and conductivity were monitored on line. TOC and PH were monitored off line. PW was used for final purification of the APIs, as well as cleaning of equipment.

A change control regarding PW distribution loop in 2013 was reviewed. PW testing results, design qualification and operation qualification were reviewed.

Lighting

Lighting was considered to be adequate in all areas visited during the inspection.

Sanitation and maintenance

All areas visited appeared to be clean. Cleaning procedures were available and records were maintained.

4. Process equipment

Design and construction

The equipment used to manufacture different APIs were not dedicated to specific steps of each process. The equipment viewed appeared to be of suitable design and construction for the allocated process in general.

Equipment maintenance and cleaning

Equipment maintenance Procedure for plant maintenance (PM) module was followed. The equipment viewed during the inspection appeared to have been suitably maintained and in acceptable condition.

Although documented procedures and records for equipment preventive maintenance were generally available in the SAP system.

Cleaning records were available for equipment and those reviewed were satisfactory. The time frame for cleaning of equipment and its subsequent release for use in the manufacture of the API were stated on the equipment status labels.

Calibration

Measuring equipment was labelled with a calibration status label and all viewed were within recalibration date during the inspection.

Computerized systems

Computerized systems were used in the warehouse, production, QA and QC labs including SAP, PLC, Track Wise and LIMS etc. HPLC and GC instruments in QC were networked by computer system.

5. Documentation and records

Materials management was controlled by a SAP system. Change control, deviation and complaints were controlled by Track Wise system. QC documents were controlled by LIMS system and the data was manually uploaded in the computerised system.

Documentation control was found adequate according to those being reviewed during the inspection. SOPs and records were generally available near the point of use in production. Several in-process batch records were inspected during the visits to a production block and all were up to date and had been properly filled in.

6. Materials management

General controls

Suppliers of materials were required to be approved according to a SOP. Flow charts for approval of starting material of new and existing API were available for review. Materials were classified into API starting material, general material and packaging material. An annual audit schedule was available. Critical suppliers were required to be evaluated every 3 years.

Examples of suppliers control for key starting material used in Lamivudine manufacturing was reviewed in the SAP system. The code management in the SAP system showed that the procedure had been followed.

Sampling and testing of incoming production materials

Sampling of starting materials was performed by QC personnel according to a documented sampling plan. Appropriate environmentally controlled sampling areas were available in the warehouses.

The material was released or rejected after testing and controlled by the SAP system with bar code reader.

Storage

There were separate warehouses for the storage of solid raw materials, packaging materials and finished APIs. These areas were included in the inspection and generally found acceptable. Storage conditions were specific in a SOP and where necessary were monitored with records maintained.

7. Production and in-process controls

Production operations

The production of Emtricitabine and Lamivudine were in operation at the time of inspection. Production block for Lamivudine was inspected.

In-process sampling and controls

Requirements for in-process sampling were described in the BMRs and acceptance criteria included. In-process sampling were done by Manufacturing and testing were performed by QC lab, and there was no IPC lab located in production area.

Contamination control

There were two production bays in a common chemical area of a block inspected and two bays in Grade D clean area which were physically separated. Each bay had two separate drying rooms. The operation procedure regarding cross contamination control was reviewed and discussed during the inspection.

8. Packaging and identification labelling of APIs and intermediates

Packaging materials

Packaging materials were purchased from approved suppliers and placed in quarantine before sampling, testing and release by QC. The storage and labelling of these materials was spot checked and discussed.

Packaging and labeling operations

Packaging and labelling was performed in areas dedicated for this purpose. The design and temperature control of the common packing area were briefly inspected. There was no packaging and labelling operation performed in the area at the time of inspection.

9. Storage and distribution

Starting materials and APIs were stored in temperature controlled and monitored areas. The records of monitoring reviewed were spot checked. Temperature mapping of a finished product warehouse was reviewed.

10. Laboratory controls

General controls

The company had an organized and suitably equipped QC laboratory. Equipment included HPLC, GC and other testing instruments. All HPLC and GC workstations were equipped with Empower 3 software and networked. LIMS system in the QC laboratory was installed with server located in the corporate office.

Microbiological lab was separate to the Chemical QC lab. Mylan Unit I also use this Micro lab for testing.

Testing of intermediates and APIs

QC testing was conducted as specified in relevant specifications and according to documented test methods.

The computer and software Empower 3 access control, authorization of the functions and batch testing result were checked during the inspection. Guest account's approval and traceability were also checked.

Microbiological limit testing of purified water was checked. R2A media was used for testing. Alert limit, action limit and specification limit for PW Microbiological test were established and documented.

Handling of out of specification (OOS) results

There was an OOS procedure for handling chemicals and instruments. A separate SOP was in place for handling microbiological OOS result. The OOS handling procedures were reviewed and discussed. The 2015 OOS records were available in the Track Wise System for review.

11. Validation

Cleaning validation and qualification

Cleaning verification was performed according to a cleaning SOP. The cleaning verification for the micronization block was reviewed. Micronizer was regarded as standalone equipment and cleaning verification was separated with other equipment. Non-compliances observed during the inspection that was listed in the full report regarding cleaning validation were addressed by the manufacturer to a satisfactory level.

Computerized system validation

The company's validation policy was described in a SOP for validation of computerized system. A computerised system validation master plan and initial risk assessment were reviewed and discussed during the inspection.

Process validation

Process validation was not reviewed in detail during this inspection. The blending process validation was ongoing at the time of inspection.

12. Change control

Change control was handled according to a SOP. Examples of change control were reviewed. Non-compliances observed during the inspection that was listed in the full report regarding change control were addressed by the manufacturer to a satisfactory level.

13. Rejection and re-use of materials

Rejection

Rejects were appropriately controlled and there was a locked dedicated area in the warehouses for rejected materials.

Reprocessing

Reprocessing was handed according to a SOP. Reprocessing required prior approval.

Reworking

Reworking was handed according to a SOP. No reworking batches had been processed in 2015.

Recovery of materials and solvents

Solvents and materials were recovered in the process on a routine basis using a validated process.

Returns
A SOP for handling of returned goods was reviewed and discussed.

14. Complaints and recalls
Complaints were handled according to a written procedure and controlled by Track Wise system.

An example of complaint about a API that failed customer testing was reviewed. Non-compliances observed during the inspection that was listed in the full report regarding deviation investigation were addressed by the manufacturer to a satisfactory level.

15. Contract manufacturers (including laboratories)
No routine QC testing was contracted out.
Some intermediates manufacturing were contract out and not reviewed in this inspection.

PART 3

Conclusion
Based on the areas inspected, the people met and the documents reviewed, and considering the findings of the inspection, including the deficiencies listed in the Inspection Report, as well as corrective actions taken and planned. The APIs listed in the inspection scope manufactured at Unit 2, Mylan Laboratories Limited located at Survey No.10/42, Gaddapotharam, IDA Kazipally Medak District, Telangana– 502319 India were considered to be manufactured in compliance with WHO GMP for Active Pharmaceutical Ingredients.

All the non-compliances observed during the inspection that were listed in the full report as well as those reflected in the WHOPIR, were addressed by the manufacturer, to a satisfactory level, prior to the publication of the WHOPIR

This WHOPIR will remain valid for 3 years, provided that the outcome of any inspection conducted during this period is positive.

PART 4

List of GMP guidelines referenced in the 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.
   http://www.who.int/medicines/publications/44threport/en/

2. WHO good manufacturing practices for pharmaceutical products: main principles. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-eight Report Geneva, World Health Organization, 2014 (WHO Technical Report Series, 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-six Report. Geneva, World Health Organization, 2012 (WHO Technical Report Series, 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
http://whqlibdoc.who.int/trs/WHO_TRS_929_eng.pdf?ua=1

5. WHO guidelines on good manufacturing practices for heating, ventilation and air-conditioning systems for non-sterile pharmaceutical dosage forms. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 5
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

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
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
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 2
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
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
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
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 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 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 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 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 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 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 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 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 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 http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

21. WHO good manufacturing practices for biological products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifties Report Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 3 http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex03.pdf

22. Guidance on good data and record management practices. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifties Report Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 5 http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex05.pdf

23. WHO general guidance on variations to multisource pharmaceutical products. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifties Report* Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 10 http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex10.pdf

24. WHO good manufacturing practices for biological products. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifties Report* Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 3 http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex03.pdf