World Health Organization

20, AVENUE APPIA – CH-1211 GENEVA 27 – SWITZERLAND – TEL CENTRAL +41 22 791 2111 – FAX CENTRAL +41 22 791 3111 – WWW.WHO.INT

Prequalification Team Inspection services
WHO PUBLIC INSPECTION REPORT
(WHOPIR)
Finished Product Manufacturer

Part 1	**General information**
Manufacturers details	
Company information	
Name of manufacturer	**Mylan Laboratories Limited, Nashik**
Corporate address of manufacturer	Mylan Laboratories Limited, Plot no. 564 / A / 22, Road no. 92, Jubilee Hills, Hyderabad - 500033, India.
Inspected site	
Address of inspected manufacturing site if different from that given above	Mylan Nashik ("Sinnar" in CRM) F-4, F-12, Malegaon M.I.D.C, Sinnar, Nashik – 422103, Maharashtra state, India
Unit / block / workshop number	NA
Manufacturing license number, (delete if not applicable)	23647 (RNW) Dated 26/6/2015 by the Food and Drugs Administration, Maharashtra State, India
Inspection details	
Dates of inspection	6-10 November 2017
Type of inspection	Routine GMP inspection
Introduction	
Brief summary of the manufacturing activities	A total of 1753 employees were at the facility under inspection. Total plot area was 89,500, with approximately 22 acres of land. A neighbouring plot contained a supplementary finished product storage warehouse.

General information about the company and site	Mylan Laboratories Limited is the Indian subsidiary of Mylan Laboratories Inc. USA. Mylan Laboratories Limited formally known as Matrix Laboratories Limited has its corporate office located at Hyderabad, India. Globally, Mylan employed approximately 30,000 people. Approximately 15,000 employees are located in India.
History	This was the sixth inspection by WHO-PQ: the first was in July, 2007, followed by inspections in July, 2008, and August, 2009, (special: data verification), then in June 2012, and June 2015. According to the company presentation, the site was also inspected by the following stringent authorities: • UKMHRA in:December 2016, November 2013, November 2012, December 2009 and October 2006 • USFDA in September 2016, March 2015, August 2012, May 2011, August 2009 and February 2007, • MCAZ in April 2017 • PMDA Japan in June 2013
Brief report of inspection activities undertaken	
Scope and limitations	
Areas inspected	The inspection focused on the production and control of anti-HIV, anti-TB and anti-malarial products. The inspection covered all the sections of the WHO GMP text, including premises, equipment, documentation, materials, validation, sanitation and hygiene, production, quality control and utilities. ***Inspected Areas*** • Quality Assurance • Sanitization and hygiene • Qualification and validation • Complaints • Recalls • Self-inspection • Personnel • Training • Personal hygiene • Premises • Equipment • Materials • Documentation • Production • Quality control

Restrictions	None
Out of scope	Products not submitted for prequalification including pilot plant were out of the scope of this inspection
WHO product numbers covered by the inspection	WHO Prequalified products Lamivudine/Zidovudine Tablet, Film-coated 150mg/300mg (HA392) Nevirapine Tablet 200mg (HA396) Efavirenz Tablet, Film-coated 600mg (HA403) Tenofovir Disoproxil fumarate Tablet, Film-coated 300mg (HA410) Lopinavir/Ritonavir Tablet, Film-coated 200mg/50mg (HA411) Lamivudine/Tenofovir Disoproxil fumarate Tablet, Film-coated 300mg/300mg (HA414) Emtricitabine/Tenofovir Disoproxil fumarate Tablet, Film-coated 200mg/300mg (HA417) Lamivudine/Nevirapine/Zidovudine Tablet, Film-coated 150mg/200mg/300mg (HA426) Lopinavir/Ritonavir Tablet, Film-coated 100mg/25mg (HA429) Lamivudine/Nevirapine/Zidovudine Tablet, Dispersible 30mg/50mg/60mg (HA433) Lamivudine/Zidovudine Tablet, Film-coated 30mg/60mg (HA437) Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate Tablet, Film-coated 600mg/200mg/300mg (HA444) Zidovudine Tablet, Film-coated 100mg (HA464) Efavirenz/Lamivudine/Tenofovir Disoproxil fumarate Tablet, Film-coated 600mg/300mg/300mg (HA466) Ritonavir Tablet, Film-coated 100mg (HA467) Atazanavir (sulfate)/Ritonavir Tablet, Film-coated 300mg/100mg (HA507) Ritonavir Tablet, Film-coated 25mg (HA621) Sofosbuvir Tablet, Film-coated 400mg (HP001) Artemether/Lumefantrine Tablet 20mg/120mg (MA099) Moxifloxacin (hydrochloride) Tablet, Film-coated 400mg (TB286) 11 Products Prequalified (under USFDA ANDA)

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

1. Pharmaceutical quality system

The facility used Mylan global quality assurance system, whose implementation at the facility level was reviewed and found robust. The global procedures in place were for handling complaints, notice of rejection, handling incident and laboratory investigation reports, corrective/preventive actions (CAPA) with effectiveness checks, for reporting of analytical results and for preparing issuance of technical (quality) agreements. There was extensive use of computerized systems for deviation management, CAPA, change control, complaints, testing, reporting of quality control results and training and they were all validated and under control. The following software systems were in place: Trackwise, LIMS, Empower, SAP and My University (LMS). Incidence and complaints were adequately investigated and trended periodically. The quality system was adequately resourced with experienced and trained personnel.

Quality Risk Management (QRM)
QRM procedure was available.

Management review (MR)
MR was in place.

Deviations and corrective and preventive actions (CAPA)
Deviations and CAPA procedures were available.

Change control
CC procedure was available.

Product Quality Review (PQR)
PQR according to SOP Annual product quality review SOP was mostly similar to the items requested in chapter Pharmaceutical Quality System of the WHO good manufacturing practices for pharmaceutical products: main principles.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

2. Good manufacturing practices for pharmaceutical products

Good manufacturing practices were implemented and followed. Required staff and system resources were provided. Manufacturing processes were clearly defined and documented. Qualification and validation were performed. Operators were trained to carry out procedures correctly, and comprehensive records were made during manufacture. Some minor deficiencies were noted.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

3. Sanitation and hygiene

In general, premises and equipment were maintained at a satisfactory level of cleanliness. The company had a standard operating procedure as the basis for its approach to personal hygiene and sanitation in its production facility, with appropriate changing rooms.

4. Qualification and validation

The company approach to validation was documented and explained in the Validation Mater Plan (VMP) and the VMP was briefly reviewed by the inspectors. The key elements of a qualification and validation programme were defined.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

5. Complaints

Complaints were being handled through SOP. The actual recording, investigation and tracking was being handled through the software system Trackwise. Complaints were logged in the Trackwise by Mylan affiliates in South Africa, Australia, Japan, America and Japan. The complaints for the remaining markets were reported to the sites by email through the business development unit.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

6. Product recalls

Product recalls were being handled through SOP, which provided for classification of recalls as Class I, initiated within three (3) days, Class II , initiated within seven (7) days and Class III, initiated with fifteen (15) days and the respective levels of recalls were defined and typical examples were provided against each category.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

7. Contract production, analysis and other activities

No analysis and other activities were contracted-out.

This section was not inspected in detail due to time constraint.

8. Self-inspection, quality audits and suppliers' audits and approval

The procedure for internal quality audits, was in place and provided for internal audits to be conducted twice a year for all departments. Audits were conducted by at least three members, one of which was from Quality Assurance and there were detailed checklist which covered all essential principles for each department. The team composition for auditing of the quality assurance department was not defined, taking into consideration the majority of the auditors were in the same department. The qualification criteria to be an internal auditor was clearly defined, at least the auditor was expected to have 5 years industrial experience, graduate and was appointed after completion on the relevant training module. A calendar was in place and planned audits were executed as planned. There was a clear reporting process with fixed timelines.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

9. Personnel

The manufacturer had an adequate number of personnel with the necessary qualifications and practical experience. Responsibilities of staff, and their specific duties were recorded in written job descriptions. An inconsistent behaviour was noted during some manufacturing activities such as during spooning materials from the bins into the sifting.

10. Training

Training was performed according to SOP. SOP included planned training (induction, introductory, job specific, cGMP training, and SOP revision), additional training (in case of particular needs) and re-training (after long leave and at least more than 6 months). Software Learning Management System LMS, in force since 2015, managed personal training records, training material (in case of e-training), final evaluation for each session and personal training curricula. All self-reading training courses required an evaluation with a minimum score at least 80%.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

11. Personal hygiene

Changing and washing before entry to production areas followed a written procedure. Direct contact was avoided between the operator's hands and starting materials, primary packaging materials and intermediate or bulk product. The approach to sanitation and hygiene was in general acceptable; during the inspection in the production areas, personnel wore adequate clothes related to the activities to be performed.

12. Premises

The facility was designed in a unidirectional flow with epoxy floored floors and the walls were painted with polyurethane paint. The facility was fitted with separate air handling units for clean corridors, maintained overpressure respect to the production rooms, and for each processing area and the same were interlocked in case of fan failure for air handling units supplying the clean corridor.

Three warehouses were in use. Two warehouses were located inside the production building at ground floor and they were used to store raw materials; they were both equipped with sampling areas (3+2 for API and 2+2 for excipients) and dispensing areas (4 for API and 5 for excipients).

A new warehouse building was used for storage the finished products / primary and secondary packaging materials; it was equipped with separate rooms to sample primary packaging materials and QC lab for performing testing on packaging materials. All printed materials were stored in locked areas. The temperature mapping studies for new warehouse and for raw materials store were reviewed.

The warehouse temperature (15-25°C) was monitored via a data loggers located in the hottest and coldest location, 24 hours recording; the min / max values were recorded manually every 24 hours. Sampling and dispensing area were maintained overpressure respect to warehouse and were equipped with material and personnel airlocks.

The production areas including granulating step, encapsulation, coating and primary/secondary packaging were performed on the ground floor of the production building.

On the first floor, with a separate access, there was a pilot plant for the manufacture of exhibit and commercial scale with small batch size (company claimed this plant was not used for the manufacturing of WHO products) and three (3) QC laboratories (for stability/validation studies; for analytical tests and microbiological tests; area with stability chambers).

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

13. Equipment

The machinery were modern and were not all equipped with closed system for all operations from sifting to tableting, the in-process controls allow for automatic printing of all in process control tests. The utilities were all modern, qualified and in a state of control.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

14. Materials

Materials were sourced from approved vendors, quarantined, sampled and tested prior to use and all this was controlled using the SAP system. The materials were adequately segregated, labelled and stored in a controlled environment. Hold time for in process materials were monitored through tracking forms which were part of the BMR and generally manufacture of products was being completed with 30 days and the manufacturer was in the process of initiating hold time studies.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

15. Documentation

The quality system was well documented with manuals, policies, master documents and procedures based on standard formats controlled through software system and approved by quality assurance and regularly approved. Computer systems in place were validated and periodically reviewed at a frequency based on risk assessment. The company had a well detailed procedure and training material on data integrity which explicitly covered the concepts of ALCOA and personnel were trained on the same. Quality assurance personnel involved in review of electronic data were trained in basic understanding of how computerized systems work and on how to efficiently review the electronic data, which included metadata and audit trails

16. Good practices in production

The manufacturing premise was in a good state of repair. There were adequate gowning procedures in place. There were dedicated places for storage of in-process materials, granulation areas, blending areas, compression areas, coating areas, tablet inspection areas, in-process control areas, washing areas and packaging areas. Tableting rooms had provisions for in-process monitoring of all parameters except for the disintegration and friability tests which were carried out the in-process control laboratory by IPQA personnel. There were detailed procedures for line clearance, cleaning and operating machines. There was a robust process for verification of dispensed material when they were received and issued out of the storage areas.

The pressure differentials and manufacturing conditions were all with limits.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

17. Good practices in quality control

The QC function was independent of other departments. Adequate resources were available to ensure that the QC arrangements are effectively and reliably carried out in general.

The movement of samples and analysis was being traced through the Laboratory Information Management System (LIMS) and all HPLC were connected using Empower 3 software. All the systems were validated with audit trail functionality. The laboratory was equipped with adequate modern instruments that were regularly qualified. There were adequate personnel who were qualified for the quality control various activities carried out by the manufacturer. There were separate quality control facilities for routine testing and for stability and validation studies.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

PART 3
Conclusion

Based on the areas inspected, the people met and the documents reviewed, and considering the findings of the inspection, including the observations listed in the Inspection Report, Mylan Laboratories Limited, Nashik, located at F-4, F-12, Malegaon M.I.D.C, Sinnar, Nashik – 422103, Maharashtra state, India was considered to be operating at an acceptable level of compliance with WHO good manufacturing Practices for pharmaceutical products.

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

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.
   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.
   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
   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. Fiftieth 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. Fiftieth 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. Fiftieth 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. Fiftieth 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