

WHO PUBLIC INSPECTION REPORT API Manufacturer
**WHO PUBLIC INSPECTION REPORT
(WHOPIR)
API Manufacturer**
Part 1: General information

Name of Manufacturer	Mylan Laboratories Limited (Unit-III)
Unit number	Unit – III
Production Block	Block 2
Physical address	Plot No 35, 36, 38 to 40, 49 to 51 Phase-IV, IDA Jeedimetla Hyderabad – 500 055, INDIA
Contact person and email address.	Dr Antony Raj Gomas antonyraj.gomas@mylan.in
Date of inspection	16 to 19 June 2014
Type of inspection	Routine inspection
Active Pharmaceutical Ingredient(s) included in the inspection	Emtricitabine (APIMF039)
Summary of the activities performed by the manufacturer	Production and control of active pharmaceutical ingredients and intermediates

Part 2: Summary

General information about the company and site

Mylan Laboratories Inc., USA was founded in 1961 and its headquarter is located in Pittsburgh, Pennsylvania, United States. The company produces generic pharmaceutical, branded generics, specialty & brand pharmaceuticals and active pharmaceutical ingredients.

The corporate office of Mylan Laboratories Limited (India) is based in Hyderabad, India and it employed more than 10,000 employees. In India, the company has several APIs and finished dosage manufacturing facilities including injectables. The company has following API manufacturing sites in India:

1. Mylan Laboratories Ltd. (Unit – 1), Kazipally
2. Mylan Laboratories Ltd. (Unit – 2), Kazipally (Astrix)
3. **Mylan Laboratories Ltd. (Unit – 3), Jeedimetla**
4. Mylan Laboratories Ltd. (Unit – 7), Pashamylaram
5. Mylan Laboratories Ltd. (Unit – 8), Vishakhapatnam
6. Mylan Laboratories Ltd. (Unit – 9), Vishakhapatnam
7. Mylan Laboratories Ltd. (Unit – 10), Vishakhapatnam
8. Mylan Laboratories Ltd. (Unit – 11), New Mumbai, Maharashtra
9. Mylan Laboratories Ltd. (Unit – 12), Vishakhapatnam

The site inspected was Mylan Laboratories Limited, Unit-3, Plot Nos. 35,36, 38 to 40 & 49 to 51, Phase-IV, IDA Jeedimetla, Ranga Reddy (Dist), Andhra Pradesh, India. The site was established in 1983 as Herren Drugs & Pharmaceuticals Ltd, acquired by Matrix Labs Ltd in 2000, Matrix was acquired by Mylan Pharmaceutical Inc. in 2007 and eventually renamed as Mylan Laboratories Limited in 2011.

From the opening meeting presentation, it was noted that the site has 5 manufacturing blocks and it operates in 3 shifts. The site employed around 590 staff who are on the company payroll. In addition, contract workers are employed for various non-critical operations.

The site has filed several drug master files (US 48, EU 11, Japan 4, EDQM 26 and WHO 1). It was noted that the site has stopped producing Lopinavir and Efavirenz and informed the WHO last year. The site produces Emtricitabine.

History of WHO and/or regulatory agency inspections

The manufacturing site was last inspected by WHO in 2011.

The site had been inspected by several regulatory authorities namely EDQM (2003), EMEA (2010), USFDA (2003, 2007, 2010 & 2014), TGA (2002, 2012), KFDA (2011), NIP, Hungary (2008) and Mexican COFEPRIS in 2013.

Focus of the inspection

The inspection focused on the production and control of Emtricitabine APIMF039. The inspection covered most of the sections of WHO GMP guidelines for active pharmaceutical ingredients, including premises, equipment, documentation, materials, validation, sanitation and hygiene, production, quality control and utilities.

Inspected Areas

Day 1, 16th June 2014

- Introductions
- Opening meeting
- Product quality review procedure and review of Emtricitabine produced in 2013
- Change controls & deviations
- Organization chart & job descriptions of key personnel
- Quality and production responsibilities
- Training
- Risk management
- Management review
- Calibration and maintenance

Day 2, 17th June 2014

- Feedback on day 1 observations
- Out of specifications (OOS)
- Reprocessing and reworking
- Recovery solvent management
- Handling of customer complaints
- Cleaning validation
- Inspection of warehouse covering solids, drum solvent, bulk solvent, maintenance workshop and Production Block (MB-2)

Day 3, 18th June 2014

- Feedback on day 2 observations
- Review of water system (drawings, sampling plan, SOPs)
- Inspection of water system (RO unit and purified water (PW) unit)
- Inspection of air handling units (AHUs) supplied to drier and blender room (AHU201) and filters
- Inspection of quality control laboratory including chemistry, instrumentation, stability and retention sample room

Day 4, 19th June 2014

- Feedback on day 3 observations
- Procedure for stability study of drug substances
- Review of stability study data of Emtricitabine

- Purified water trending data
- Validation strategy document
- Emtricitabine process validation
- Supplier qualification
- Caucus between inspectors
- Exit meeting with the site representatives

2.1 QUALITY MANAGEMENT

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

The observations raised from this section have been addressed satisfactorily, and will be verified during future inspections.

2.2 PERSONNEL

There was an adequate number of personnel qualified, trained and experienced to perform and supervise the manufacture of intermediates and APIs.

Training of Employees was described in SOP. The site QA head was responsible for approving training needs; content of training sessions etc but the co-ordination was conducted by Site Personnel and Administration (PNA). All new employees were given induction training and basic introduction to GMP. The training manual was thorough. In addition, there were annual GMP refresher training courses. All departments were included. The training requirements for each department were compiled in a chart. However, there was no overall chart showing the site-wide training schedule.

The observations raised from this section have been addressed satisfactorily, and will be verified during future inspections.

2.3 BUILDINGS AND FACILITIES

Buildings were constructed of rendered masonry with finishes appropriate to the activities being conducted. Overall, standards of housekeeping were adequate. The solids warehouse had internal finishes of an epoxy floor and painted walls and ceilings. MSDSs were available for each materials stored.

The observations raised from this section have been addressed satisfactorily, and will be verified during future inspections.

2.4 PROCESS EQUIPMENT

Equipment used in the manufacture of finished APIs was of adequate size, and suitably located for its intended use. Major equipment such as reactors and centrifuges

used during the production of an intermediate or API were appropriately identified. All equipment was multipurpose. The SOP for preventive maintenance was in place. The SOP included checklists for each type of equipment which included the items to be checked at monthly, quarterly, half-yearly and annually.

The observations raised from this section have been addressed satisfactorily, and will be verified during future inspections.

2.5 DOCUMENTATION AND RECORDS

Documents related to the manufacture of intermediates and APIs were prepared, reviewed, and approved. Specifications were established and documented for raw materials, key starting materials, intermediates and finished API. Acceptance criteria were established and documented for in-process controls.

The observations raised from this section have been addressed satisfactorily, and will be verified during future inspections.

2.6 MATERIALS MANAGEMENT

A common warehouse was used for storage of raw materials, starting materials and primary packaging materials. Vendor approval was conducted according to SOP. Materials covered were starting materials, general raw materials and packing materials.

The observations raised from this section have been addressed satisfactorily, and will be verified during future inspections.

2.7 PRODUCTION AND IN-PROCESS CONTROLS

Stainless steel (SS) and glass lined (GSL) reactors were used for production. The production process mainly was carried out in closed systems. The inspection of production block (MB-2) revealed that reactors were installed with overheads suitable for the activities to be conducted, such as stirring, distillation reflux etc. Standards of installation, housekeeping and maintenance were generally acceptable although some examples of poor installation and maintenance are discussed below in Part 5.

The process to make Emtricitabine was followed from the starting material, through the technical area and into the controlled area. Final crystallisation was conducted in reactor RE226 and this was inspected.

The observations raised from this section have been addressed satisfactorily, and will be verified during future inspections.

2.8 PACKAGING AND IDENTIFICATION LABELLING OF APIs AND INTERMEDIATES

Packing was conducted in the controlled area of Production after the completion of milling sifting and blending operations, as required. No packing activities were being

conducted at the time of the inspection. Finished goods were stored in rooms allocated for the purpose. Labelling issuance and control was by means of the SAP system

2.9 STORAGE AND DISTRIBUTION

Materials were held under quarantine until they were sampled, tested and released for use. Separate room was provided for storage of rejected starting materials. At the time of the inspection, this room was empty and kept locked. Rodent and pest control was contracted to an outside party. Insectocutors and rodent/pest traps were observed to be installed satisfactorily. Sampling and dispensing operations were conducted in dedicated rooms. The use was recorded in registers.

2.10 LABORATORY CONTROLS

Procedures describing sampling, testing, approval or rejection of materials and recording and storage of laboratory data were available. Laboratory records were maintained. Specifications included testing of impurities - organic impurities and residual solvents.

Overall, the laboratory was adequately equipped to conduct the analyses required. It was noted that in addition to the usual range of instrumentation (chromatography, IR & UV spectroscopy etc) there was an XRPD instrument and also a NMR instrument. Sample notification was done via the SAP system. SOP was Sampling, Testing and Release of Raw Materials and Packing Materials available. Each container of API starting materials was tested for identification and full testing done on a $0.4\sqrt{N}$ composite. General raw materials were tested according to a $(\sqrt{N} + 1)$ plan. For API starting materials and APIs, these were dedicated. AR numbers were generated in the LIMS system which then allowed the sampling sheet to be printed. On allocation of work, the analyst would log into LIMS which would then issue the relevant work sheet(s). Sampling and Testing of Intermediates and APIs were conducted according to SOP. All containers of APIs were sampled and a composite made for testing. Quantities required were stated in the STPs (Standard Test Procedures). Results were checked by QCD before being sent to QAD for review.

The observations raised from this section have been addressed satisfactorily, and will be verified during future inspections.

2.11 VALIDATION

The Validation Master Plan was document following SOP. QA were overall responsible. Topics covered included all relevant aspects of GMP, such as cleaning validation and process validation.

The observations raised from this section have been addressed satisfactorily, and will be verified during future inspections.

2.12 CHANGE CONTROL

Change management process was available which provided detail on handling change controls. The flow chart did not provide any detail on risk assessment and impact assessment. The procedure did not state at which stage risk assessment and impact assessment should be conducted. The changes were not divided into any category. The timelines for the initiation of changes were stated in the SOP ranging from 3 days (critical) to 7 days (minor). Trackwise prioritised changes into low, medium, high and emergency.

The observations raised from this section have been addressed satisfactorily, and will be verified during future inspections.

2.13 REJECTION AND RE-USE OF MATERIALS

The SOP on reprocessing stated the procedure for reprocessing of intermediates and finished products.

The observations raised from this section have been addressed satisfactorily, and will be verified during future inspections.

2.14 COMPLAINTS AND RECALLS

The SOP on handling of customer complaints was available. The complaints were handled through Trackwise system whereby all of the complaints were routed to site QA either through CQA, customers, business development or any other source. The complaints were classified into critical, major and minor with timelines for response of 2, 7 and 15 days respectively. The SOP referred to related documents including product recall.

2.15 CONTRACT MANUFACTURERS (INCLUDING LABORATORIES)

Some of the key starting materials were procured from contract manufacturers. There was a system in place to evaluate such contract manufacturers before qualification.

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, as well as the corrective actions taken and planned, APIs manufactured at *Mylan laboratories limited, Unit-III, Phase IV, IDA Jeedimetla, AP, 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.