



**WHO PUBLIC INSPECTION REPORT
(WHOPIR)
Active Pharmaceutical Ingredients Manufacturer**

Part 1: General information

Name of Manufacturer	Mylan Laboratories Limited
Plot number	Unit 2 (Otherwise known as Astrix Unit 2)
Production Block	All (MB-1, MB-2, MB-3, MB-4)
Physical address	Survey No. 10 & 42, Kazipally IDA, Jiannaram Mandal, Medak District, 502319 Andhra Pradesh (near Hyderabad) India
Contact address	As above
Date of inspection:	3 - 5 January 2013
Type of inspection	Routine inspection
Active Pharmaceutical Ingredient(s) included in the inspection	Didanosine, Emtricitabine, Lamivudine, Lopinavir, Nevirapine, Stavudine and Zidovudine
Summary of activities of manufacturer (e.g. manufacturing, packing).	Production, quality control, stability testing, distribution



Part 2: Summary

General information about the company and site

Mylan Laboratories Limited (hereafter MLL) is the Indian subsidiary of Mylan Laboratories, Inc., USA. MLL Inc USA was founded in 1961 and has its corporate headquarters in Pittsburgh, Pennsylvania, USA. It has a product portfolio of more than 1000 products and employs approximately 18,000 worldwide.

In India, MLL has its Corporate Office located in Hyderabad. It holds the following units:

Active Pharmaceutical Ingredients (API) manufacturing sites:

- Unit 1 Kazipally, Hyderabad
- Unit 2 Astrix Laboratories, Kazipally, Hyderabad
- Unit 3 Jeedimetla, Hyderabad
- Unit 7 Pashamylaram, Hyderabad
- Unit 8 Vizianagaram at Vishakapattanam
- Unit 9 Parawada at Vishakapattanam
- Unit 11 Taloja, Maharashtra
- China Xiamen (China)

Finished Dosage Forms (FDF) manufacturing sites:

- Sinnar, NashikWaluji, Aurangabad

FDF Research & Development site:

- Hyderabad

The Astrix 2 site which is the object of this inspection was originally known as Herren Drugs and Pharmaceuticals Ltd. It was acquired by Matrix in 2000 and re-commissioned in 2004.

History of WHO and/or regulatory agency inspections

The site has undergone the following GMP compliance inspections:

- WHO (2005)
- USFDA (2004, 2006, 2009 and 2011)
- EDQM (2009)
- ANVISA (2011)

Focus of the inspection

The inspection focused on the production and control of nevirapine, lamivudine, zidovudine, lopinavir, stavudine, didanosine, emtricitabine APIs. The inspection covered all relevant sections of ICH Q7 and of the WHO GMPs for APIs, including premises,



equipment, documentation, materials, validation, sanitation and hygiene, production, quality control and utilities. Clauses not relevant were 17, 18 and 19.

Most of the focus of the inspection was on MB-1 and MB-2 as these were the oldest blocks at the site (refurbished in 2004). MB-3 (built between 2006 and 2007) and MB-4 (built in 2008) being more recent, were not inspected due to time constraints.

Inspected Areas

The inspection covered the following sections of the WHO GMP for Active Pharmaceutical Ingredients text:

- Quality management
- Qualification and validation
- Complaints and recalls
- Self-inspection
- Personnel training
- Premises
- Equipment
- Materials
- Documentation
- Production
- Rejection and reuse of materials
- Quality control

2.1 QUALITY MANAGEMENT

Product quality reviews

These were performed for all of the products under the WHO Prequalification of Medicines Programme. This area was acceptable overall.

Out of specifications (OOS)

The standard operating procedures (SOP) for OOS and OOTs were reviewed for changes since the previous inspections along with the associated registers and examples. This area was found acceptable overall.

2.2 PERSONNEL

Training:

The training program for 2013 was reviewed in detail as well as induction and periodic training on ICH Q7. This area was considered to be acceptable overall.

2.3 BUILDINGS AND FACILITIES

In general, buildings were constructed of painted, rendered masonry. Internal finishes were suitable for the nature of the work being conducted. Rodent and pest control measures were seen to be in place at suitable locations. Maintenance of utilities and



equipment was covered under the same SOP. A separate SOP existed for building maintenance. This was acceptable overall.

2.4 PROCESS EQUIPMENT

Design and construction of equipment was acceptable overall. Product-contact surfaces were suitable for the reactions being conducted. Reactors systems were designed and installed to acceptable standards to permit the processes to be conducted as required. Adequate control systems were in place for the utilities supplied to reactors and for the addition of liquids.

Maintenance of equipment was done in accordance with a pre-established schedule which covered every piece of equipment at the site for all blocks and the solvent recovery plant. Different frequencies were set for different types of maintenance (monthly, quarterly, half-yearly, annually). The preventative maintenance and checks for glass lined reactors (verifications of integrity of the lining) were reviewed.

Gauges (e.g. pressure, vacuum) that were inspected were observed to be calibrated and in date.

2.5 DOCUMENTATION AND RECORDS

In general, documentation was adequate as part of the QMS. SOPs were generally available within ready access.

2.6 MATERIALS MANAGEMENT

Sampling was conducted using appropriate sampling plans in the mostpart.

Issues were raised regarding the adequacy of verification of the GMP compliance status of vendor/suppliers.

2.7 PRODUCTION AND IN-PROCESS CONTROLS

Inspectors reviewed the manufacturing process along with the company's identification of critical in-process parameters and associated justifications. This area was considered to be acceptable overall.

2.8 PACKAGING AND IDENTIFICATION LABELLING OF APIs AND INTERMEDIATES

Packaging materials and the company's system for labelling of materials was inspected. No apparent issues of concern were noted.



2.9 STORAGE AND DISTRIBUTION

The different warehouses used for storage of starting materials, solvents and finished APIs were inspected. Temperature and humidity monitoring was done through the BMS. No apparent issues of concern were noted.

2.10 LABORATORY CONTROLS

Inspectors reviewed purified water testing, including microbial analysis, HPLC analysis, audit trails and computer access rights, gas chromatographic analysis, reference standards, analytical worksheets and LIMS, as well as stability testing. Quality controls performed by the laboratory were found to be generally acceptable.

2.11 VALIDATION

Cleaning validation was reviewed. The current policy in place was that all product change-overs should be supported by cleaning verification. In the examples seen, all results were below the set acceptance criteria for rinse and swab samples.

Equipment qualification was reviewed. In the example seen, all of the necessary systems were covered within appropriate ranges.

Qualification for the computerized system for valve control was also reviewed.

2.12 CHANGE CONTROL

The Change Control procedure was reviewed. The issues raised were addressed in the company CAPAs.

2.13 REJECTION AND RE-USE OF MATERIALS

Materials were recovered on a routine basis using validated processes. This area was considered acceptable overall.

2.14 COMPLAINTS AND RECALLS

The procedures for handling of customer complaints and market returns were reviewed. This area was considered to be acceptable overall.

2.15 CONTRACT MANUFACTURERS (INCLUDING LABORATORIES)

Issues were raised regarding contract manufacturers and the manner in which internal audits were conducted. This was adequately addressed in the company's corrective and preventive actions.



Part 3: Conclusion

On the basis of the findings of the inspection and these subsequent responses the inspectors have recommended that the site **Astrix Unit 2, Survey No. 10 & 42, Kazipally IDA, Jiannaram Mandal, Medak District, 502319 Andhra Pradesh (near Hyderabad), India**, can be considered to be compliant with WHO GMPs for Active Pharmaceutical Ingredients published by WHO for the scope activities listed below:

- Manufacture, packaging, quality control and storage of Didanosine, Emtricitabine, Lamivudine, Lopinavir, Nevirapine, Stavudine and Zidovudine 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.