

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

Name of Manufacturer	Mylan Laboratoires Limited
Unit number	Unit-8
Production Block	MB-1, 2, 3, 4, 5, 6, 7, 8, 9, 10,11,15
Physical address	G. Chodavaram, Poosapatirega Mandal, Vizianagaram (Dist.) 535 204, Andhra Pradesh, India
Contact person and email address.	Dr Antony Raj Gomas Antonyraj.gomas@mylan.in
Date of inspection	9, 10, 11 and 12 September 2014
Type of inspection	Routine GMP inspection
Active Pharmaceutical Ingredient(s) included in the inspection	Abacavir Sulfate APIMF010 Atazanavir Sulfate APIMF095 Ritonavir Form II APIMF065 Ritonavir Form I APIMF077 Tenofovir Disoproxil Fumarate APIMF038 Efavirenz APIMF071 Lamivudine APIMF069 Zidovudine APIMF072 Ritonavir Premix (part of finished product dossier)
Summary of the activities performed by the manufacturer	Manufacturing, packaging, quality control and release of Anti-Retroviral, and other Active Pharmaceutical Ingredients (APIs) and related premixes

Part 2: Summary

General information about the company and site

The site inspected was the **Mylan (Former Matrix) Laboratories Limited (Unit 8), G. Chodavaram , Poosapatirega Mandal, Vizianagaram District - 535204, Andhra Pradesh, India**, hereafter called **Mylan Unit 8**. Mylan Laboratories Limited has a corporate office located at Plot No.564/A/22, Road No. 92, Jubilee Hills, Hyderabad - 500034, Telangana, India. Mylan has the following API facilities:

- 2 units at Kazipally Industrial area, Hyderabad, Telangana (Units 1 and 2)
- 1 unit in Jeedimetla Industrial area, Hyderabad, Telangana (Unit 3)
- 1 unit Pashamylaram Hyderabad, Telangana (Unit 7)
- 1 unit in G. Chodavaram, Vizianagaram, Andhra Pradesh (Unit 8)
- 2 units in Pharmacity, Parawada Visakhapatnam, Andhra Pradesh (Unit 9 and 10)
- 1 unit in Taloja, Maharashtra (Unit 11)

Mylan Unit 8 is located at about 70 km from Visakhapatnam airport on the Chennai - Kolkata national highway, on a 276,028.50m² plot with a built up area of 189,449.18m². The facility was established in 1993 as Vera Laboratories and was acquired by Matrix in 2004 which was in turn acquired by Mylan in 2007. The first production blocks were constructed in 1995 but have grown to include 11 production blocks (total reactor volume: 1,155 KL), one common pharma area, two solvent recovery plants, three raw material warehouses, two finished goods warehouses, one process development laboratory and one QC/QA unit.

The APIs facilities at Mylan Unit 8 are multiproduct blocks with pharma area (synthesis, purification and finishing). The pharma area has clean rooms classified as class 100,000.

According to the company presentation, the site employed a total of 1039 people distributed as follows:

<u>Department</u>	<u>Staff</u>
o Production	613
o Quality Assurance (QA)	61
o Quality Control (QC)	130
o Warehouse	46
o Engineering	113
o EHS	30
o HR and support services	25
o Technical services	21
Total	1039

History of WHO and/or regulatory agency inspections

According to the SMF and company presentation, the site was licensed by the Director, Drugs Control Administration of Government of Andhra Pradesh under licence No. 177/VN/AP/96/B/R and had been inspected and/or approved by the following:

- USFDA, 2002, 2006, 2009 and 2012
- PMDA, Japan, 2007 (site accreditation) and 2009
- AGES/PharmMed, March 2008 and 2011
- KFDA, 2011
- COFEPRIS 2013 and 2014
- EDQM 2010
- BGV Hamburg 2013

This was the seventh inspection by WHO-PQ; the previous inspections were in 2005, 2007, 2008(2), 2009 and 2011.

Focus of the inspection

The inspection focused on the production and control of Antiretroviral APIs (8) and premix (1) as outlined above.

Inspected Areas

The inspection covered most of the sections of WHO GMP for Active Pharmaceutical Ingredients (ICH Q7), including 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 and Distribution; Laboratory Controls; Validation; Change Control; Rejection and Reuse of Materials and Complaints and Recalls.

2.1 QUALITY MANAGEMENT

In general, the manufacturer has established, documented, and implemented an effective quality management system which encompasses the organizational structure, procedures, processes and resources to ensure that the API will meet its intended specifications for quality and purity. The quality unit was independent of production which fulfils both QA and QC responsibilities. The observations raised following the inspection were appropriately corrected.

2.2 PERSONNEL

There were adequate number of personnel in place with appropriate qualification and training to perform and supervise the manufacture of intermediates and APIs. The observations raised following the inspection were appropriately corrected.

2.3 BUILDINGS AND FACILITIES

Buildings and facilities used in the manufacture of intermediates and APIs were located, designed, and constructed to facilitate cleaning, maintenance, and operations as appropriate to the type and stage of manufacture.

The observations raised following the inspection were appropriately corrected.

2.4 PROCESS EQUIPMENT

Reactors were either of stainless steel or glassed lined steel, with overheads to allow to usual range of organic reactions requiring distillation/reflux from atmospheric pressure to full vacuum. Materials of construction were suitable and nitrogen was available to provide inert atmospheres. Gauges inspected at random were all seen to be within calibration date.

The observations raised following the inspection were appropriately corrected.

2.5 DOCUMENTATION AND RECORDS

The documentation system at the site included SOPs, manufacturing procedures, log books, testing procedures, records, specifications and related documentation, approaches and policies. These were designed, approved and controlled according to an established SOP.

The observations raised following the inspection were appropriately corrected.

2.6 MATERIALS MANAGEMENT

The procedure was in place which described the receipt, identification, quarantine, storage, handling, sampling, testing, and approval or rejection of materials. There was a system in place to evaluate suppliers of critical / key starting materials (KSM). The intermediates and key starting materials were stored under ambient condition without any control (temperature noted 32.8°C).

SOP on Vendor Approval was reviewed and noted that it had been recently revised after taking comments from recent WHO inspection of Unit-3. The procedure provided a flow chart for vendor qualification of API starting materials (no process flow chart for contract manufacturing units). It is noted that a separate procurement provision (with sample, COA, questionnaire and without sample but with COA & questionnaire) was provided for general raw materials (all other than SM).

The observations raised following the inspection were appropriately corrected.

2.7 PRODUCTION AND IN-PROCESS CONTROLS

Production processes were guided by documented procedures and instructions. Some production processes were conducted on campaign basis in multipurpose workshops and equipment. There were in-process controls conducted at appropriate stages to monitor the processes plus the quality of the intermediates and APIs.

The observations raised following the inspection were appropriately corrected.

2.8 PACKAGING AND IDENTIFICATION LABELLING OF APIs AND INTERMEDIATES

Label reconciliation was conducted according to the requirements of the procedure. This step is done through SAP e1 system.

The observations raised following the inspection were appropriately corrected.

2.9 STORAGE AND DISTRIBUTION

In general, facilities were available for the storage of all materials under appropriate conditions (ambient, controlled room temperature and 2-8°C). Separate storage areas were assigned for the storage of quarantine, approved and rejected materials.

The observations raised following the inspection were appropriately corrected.

2.10 LABORATORY CONTROLS

In general, the laboratory facility was adequate and equipped with various equipment and instruments. It was noted that laboratory had recently implemented LIMS. Currently, there was no interfacing between SAP and LIMS and between Empower software and LIMS.

The observations raised following the inspection were appropriately corrected.

2.11 VALIDATION

The company's overall policy, intentions and approach to validation was described in the validation master plan. Cleaning verification or validation provided procedure for cleaning verification or validation of the equipment used in the manufacturing process of APIs or intermediates to prevent cross contamination. The procedure is applicable to all critical equipment used in the manufacturing process. The procedure is applicable to batch to batch and product change over cleaning during manufacturing process at Mylan Labs Unit-8. Product changeover cleaning is done using purified water/ suitable solvent depending upon the solubility of product or intermediate. In general, 10ppm criteria was set for individual equipment from one stage to another, one intermediate to another intermediate/API and from one API to another API. Maximum allowable carryover shall be calculated in respective cleaning validation

protocol by using therapeutic dosage or LD50. The procedure provided how samples are collected using swab and rinse.

The observations raised following the inspection were appropriately corrected.

2.12 CHANGE CONTROL

A change control system was in place to evaluate all changes that could affect the production and control of intermediates and APIs. A corporate procedure titled “Change Management Process” provided change control process, responsibilities and requirements for the management of GMP changes through Trackwise software.

The observations raised following the inspection were appropriately corrected.

2.13 REJECTION AND RE-USE OF MATERIALS

It was noted that recovered solvents were used back in the same stage for number of APIs. Recovery Solvent Management procedure described procedure for recovery of solvents. It was stated that recovered solvents are used at the same or previous stage. Also, if route of synthesis is different, recovered solvents should be used in same process only.

The observations raised following the inspection were appropriately corrected.

2.14 COMPLAINTS AND RECALLS

A procedure on the “Handling of Customer Complaints” was applicable to APIs of Mylan Group of companies. The complaints were classified into critical, major and minor whereas critical complaints have to be investigated within 2 working days while major/minor in 7 working days. The complaints have to be closed within 60 days. No recall in 2011, 2012, 2013 and 2014 (till now). It is told that mock recall (paper based for domestic & export) was done in 2013.

The observations raised following the inspection were appropriately corrected.

2.15 CONTRACT MANUFACTURERS (INCLUDING LABORATORIES)

SOP on Handling of Contract Manufacturing Units (CMUs) for Manufacturing of API Starting Materials / Raw Materials and Intermediates were reviewed. Based on questionnaire and on-site assessment of the CMUs, CMUs are approved in SAP (no provisional approval). The CMUs are periodically monitored at least once a year.

The observations raised following the inspection were appropriately corrected.

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-8* 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.