

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

Name of Manufacturer	Mylan Laboratories Limited
Unit number	Unit-1
Production Block	Manufacturing Blocks (MB-01 to 09)
Physical address	Mylan Laboratories Ltd. Survey No. 10 Gaddapotharam, IDA, Kazipally Medak (Distr.) Pin: 502319 Telangana, INDIA
Contact person and email address.	Dr Antony Raj Gomas Antonyraj.Gomas@mylan.in
Date of inspection	21-24 January 2015
Type of inspection	Routine inspection
Active Pharmaceutical Ingredient(s) included in the inspection	1) Artemether APIMF153 2) Artesunate APIMF161 3) Darunavir Ethanolate APIMF214 4) Dihydroartemisinin APIMF178 5) Lamivudine USP APIMF069 6) Lopinavir APIMF050 7) Moxifloxacin Hydrochloride APIMF228 8) Nevirapine USP (Anhydrous) APIMF070 9) Oseltamivir Phosphate USP APIMF211 10) Pyronaridine Tetrphosphate APIMF190 11) Tenofovir Disoproxil Fumarate APIMF038 12) Zidovudine USP APIMF072
Summary of the activities performed by the manufacturer	Production and quality control of APIs

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

Mylan Laboratories Ltd, Unit-1, Survey No:10, Gaddapotharam, Kazipally Industrial Area, Medak District, Telangana- 502319 is located in Kazipally industrial area which is approximately 60 KM away from Hyderabad International Airport. The manufacturing site has nine Manufacturing Blocks (MBs) and it operates in three shifts. The site was originally known as Vorin Laboratories Ltd and was established in 1984. The site was eventually acquired by Matrix Group in year 2000 and renamed as Matrix Labs Ltd Unit-1 in year 2003. Matrix Labs was eventually acquired by Mylan Inc. USA in year 2007 and renamed as Mylan Labs Ltd (Unit-1) in October 2011.

History of WHO and/or regulatory agency inspections

- This was the fourth WHO inspection of this site. Previous inspections took place in April 2012, 2011 and 2006.
- The site had been inspected by USFDA in 2007, 2009, 2011 and 2013.
- The site had been inspected by AGES Austria in 2008 and 2011.
- The site had been inspected by COFEPRIS, Mexico in 2014 and KFDA in 2011.

Focus of the inspection

The inspection focused on the production and control of APIs listed above. It was noted during the opening meeting that Nevirapine Hemihydrate USP (APIMF147) has been withdrawn from WHOPQ in January 2015, hence not covered. The inspection covered all the sections of WHO good manufacturing practices for active

pharmaceutical ingredients including premises, equipment, documentation, materials, validation, sanitation and hygiene, production, quality control and utilities.

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

Generally, quality management system (QMS) procedures are well executed. The site had an acceptable documentation system consisting of procedures, records, specifications and related documentation, approaches and policies to support quality management and quality assurance. The responsibilities of the Quality and production units were defined. There was a system and records for self-inspection and Annual product quality review.

The organizational structure, procedures, processes and resources provided were generally satisfactory. Quality-related activities were defined, documented and were seen to be recorded at the time they were performed.

Regular quality reviews of APIs were conducted per SOP on product annual quality management procedure. The results of this review were evaluated and an assessment made of whether corrective action or any re-validation should be undertaken.

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

2.2 PERSONNEL

Generally, the site had adequate numbers of qualified and experienced personnel to carry out the tasks in accordance to the applicable GMP. The heads of production and Quality Unit were independent of each other.

Personnel interviewed reflected that they were aware of the principles of GMP. Entry to critical production, storage and quality control areas was restricted to only authorized personnel. Personnel were provided with appropriate protective clothing.

2.3 BUILDINGS AND FACILITIES

Buildings and facilities were generally well designed and were adequately cleaned. The clean areas for purification stage were separate from those for the synthesis stages and floors, walls and ceilings were smooth to facilitate cleaning. These

purification areas were supplied with adequately filtered air and pressure differential to prevent cross contamination.

Water used in the manufacture of APIs was suitable for its intended use. Appropriate specifications were established and monitored.

Buildings used in the manufacture of intermediates and API were generally well maintained, in a good state of repair and being maintained in a clean condition.

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

2.4 PROCESS EQUIPMENT

Equipment used in the manufacture of intermediates and API in focus were of appropriate design, adequate size, and suitably located for its intended use.

Schedules and procedures were established for the preventive maintenance of equipment. Written procedures were established for cleaning of equipment and were available where requested for review.

Control, weighing, measuring, monitoring and test equipment were calibrated according to written procedures and an established schedule was in place.

Computerized systems were not used in the inspected API production operations.

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

2.5 DOCUMENTATION AND RECORDS

There was a system for documentation in form of SOPs, manufacturing procedures, log books, specifications, testing procedures. These were designed, approved and controlled according to established SOPs.

Records of raw material, intermediates, APIs, labelling and packaging materials were maintained and when requested made promptly available to the inspection team.

In general, the batch production records for the products reviewed were concentrate and included relevant and complete information relation to the production and control of each batch.

Laboratory control records included data derived from tests conducted to ensure compliance with established specifications and standards. Out-of-specification (OOS) investigations were performed per SOP on OOS procedure.

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

2.6 MATERIALS MANAGEMENT

Materials were sourced from approved suppliers. On receipt they were quarantined, sampled and tested before acceptance into approved stores for subsequent use. The storage of starting materials, intermediates and finished APIs was generally adequate and the storage conditions were regularly monitored. Materials under a different status and stage of processing were adequately segregated.

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

2.7 PRODUCTION AND IN-PROCESS CONTROLS

Production procedures were generally well executed. Processes were guided by well documented procedures and detailed instructions. Different production stages were conducted in segregated facilities. There were in-process controls conducted at appropriate stages of synthesis to monitor the quality of the intermediates and APIs. The process used was generally similar to those outlined in dossiers submitted to WHO. The cleaning procedures, design of the buildings and equipment, plus the planning of production facilitated prevention of possible contamination.

Examination of the flow of the manufacturing process and relevant equipment was in line with the BPR examined in general compliance with the details in the submissions to WHO PQT. That equipment used in different step of the manufacturing process that was inspected was satisfactory. Majority of the equipment used for production of the APIs in focus were not dedicated.

Production flows were generally well laid out and logical. The production areas were in good condition and appropriate to their application.

2.8 PACKAGING AND IDENTIFICATION LABELLING OF APIs AND INTERMEDIATES

Packaging and labeling materials were managed through SOP for reception, identification, and release. Packaging and labeling operations procedure and records were in place.

2.9 STORAGE AND DISTRIBUTION

Mylan Unit I had appropriate and separate storage warehouses and areas for starting materials, packaging materials, solvents, intermediates, and finished APIs. Conditions of storage were monitored and appropriate records for stock and distribution were maintained.

2.10 LABORATORY CONTROLS

There was a separate block for QC department. The premises, facilities and utilities were separate from production and were in a good state of repair. There were adequate pieces of equipment with up to date calibration status.

A SOP on management procedure of stability studies was available.

Retention samples were available and stored under appropriate conditions.

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

2.11 VALIDATION

The company's overall validation policy had not been changed since last inspection. The system is comprehensive and adequate.

Written validation protocols specifying critical processes steps and acceptance criteria were established and available where requested.

In general appropriate qualification of critical equipment and ancillary systems were carried out.

The cleaning validation was performed with worst case approach. Records and performance of the studies reviewed were satisfactory.

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

2.12 CHANGE CONTROL

There was a procedure for change control which included evaluation of the validation status of the system and prescribed appropriate control measures to preserve the validated status. Change controls were managed through Track wise software and appropriate records were maintained. Several changes were reviewed which proved that the change control in place was designed and adequately implemented.

2.13 REJECTION AND RE-USE OF MATERIALS

Not inspected

2.14 COMPLAINTS AND RECALLS

There were procedures for handling customer and market complaints and product recall. The authorized person responsible for the execution and coordination of recalls was designated.

2.15 CONTRACT MANUFACTURERS (INCLUDING LABORATORIES)

The site used contract manufacturing units (CMUs) to manufacture API starting materials and intermediates for various APIs under contractual agreements with CMUs.

The observations raised from this section have been addressed satisfactorily and will be verified during future 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 observations listed in the Inspection Report, as well as the corrective actions taken and planned, APIs (Artemether, Artesunate, Darunavir Ethanolate, Dihydroartemisinin, Lamivudine, Lopinavir, Moxifloxacin Hydrochloride, Nevirapine (Anhydrous), Oseltamivir Phosphate, Pyronaridine Tetraphosphate, Tenofovir Disoproxil Fumarate and Zidovudine) manufactured at *Mylan Laboratories Limited, Unit-1* 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.