

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-9
Production Block	MB-1, MB-2, MB-3, MB-4 and MB-5
Physical address	Plot No: 5, Road No: 12, Jawaharlal Nehru Pharma City, Tadi Village Parawada Mandal, Visakhapatnam 531021 Andhra Pradesh, INDIA.
Contact person and email address.	Dr Antony Raj Gomas Antonyraj.Gomas@mylan.in
Date of inspection	16, 17, 19 and 20 January 2015
Type of inspection	Routine GMP inspection
Active Pharmaceutical Ingredient(s) included in the inspection	1. APIMF 072, Zidovudine 2. APIMF 155, Lumefantrine 3. APIMF 166, Piperaquine Tetraphosphate
Summary of the activities performed by the manufacturer	Production and quality control of intermediates and finished 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 Limited Unit 9 is located at Plot No 5, Road No 12, J.N. Pharma City, Tadi Village, Parawada Mandal, Visakhapatnam, Andhra Pradesh-531021, India was the focus of this inspection. The plant is located at 25 km away from Visakhapatnam Airport. The manufacturing site was established in June 2009 as Vivin Laboratories Pvt Ltd (Unit-2), acquired by Matrix in December 2009, renamed as Matrix Unit-9 in January 2010 and again renamed as Mylan Laboratories Ltd Unit-9 in October 2011. The site has 5 Manufacturing Blocks (MB). The facility operates in 3 shifts and a general shift. The site employed 302 personnel as on 1 January 2015 and their break-up were as follows:

S/No.	Department	No. of Employees
1	Production	157
2	Engineering	39
3	Stores & Commercial	19
4	Quality control	47
5	Quality assurance	19
6	E.H.S	06
7	Human resource	07
8	Information systems	01
9	Security	05
10	Finance	02
	Total Workforce	302

History of WHO and/or regulatory agency inspections

The site was first inspected by WHO-PQ in December 2011. This was the second WHO Prequalification inspection on the above mentioned site. During the opening meeting, it was noted that the site had been inspected by AGES, Austria in November 2011; TGA, Australia in December 2013 and the USFDA in July 2012.

Focus of the inspection

The inspection focused on the production and control of Lumefantrine, Zidovudine and Piperaquine Tetraphosphate APIs. The inspection covered most of 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

In general, all required quality management systems and elements were established, documented and implemented. The QMS is generally mature with a strong corporate element. 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.

Responsibilities of the quality unit (personnel) and the responsibility of the production unit (personnel) activities were available for inspection. The responsibilities of the quality Unit are independent of production Unit. Appropriate job descriptions and role definitions were documented.

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

2.2 PERSONNEL

There was adequate number of personnel qualified to perform and supervise the manufacture of intermediates and APIs. The responsibilities of personnel engaged in the manufacture of intermediates and APIs were documented in written job descriptions.

Sanitation was at an acceptable level in general on the site. Smoking, eating, drinking, chewing and the storage of food was restricted from the manufacturing areas. The gowning areas were fit for purpose and under good levels of control. General gowning levels and procedures were appropriate to the production activities and the discipline of compliance was being maintained.

2.3 BUILDINGS AND FACILITIES

In general the buildings and facilities used in the manufacture of intermediates and APIs were located, designed, and constructed to facilitate appropriate cleaning and maintenance. The manufacturing facilities were not dedicated to the inspected APIs.

Adequate ventilation, air filtration and exhaust systems were provided and these were also designed and constructed to minimize risks of contamination and cross-contamination. Permanently installed pipework was generally appropriately identified.

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.

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.

2.5 DOCUMENTATION AND RECORDS

Documents related to the manufacture of APIs were sampled and reviewed though out the inspection and were found to have been prepared, reviewed, approved and distributed according to SOP and effectively handled. Production, control and distribution records were retained for at least one year after the expiry date of the batch. Specifications were established and documented for raw material, intermediates, finished APIs etc.

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.

2.6 MATERIALS MANAGEMENT

Procedures for the receipt, identification, quarantine, storage, handling, sampling, testing and approval or rejection of materials were inspected. The finished APIs' log book and the traceability were checked.

Materials were stored under appropriate conditions to prevent degradation, contamination and cross-contamination. Materials stored in fiber drums, bags or boxes were stored off the floor.

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

2.7 PRODUCTION AND IN-PROCESS CONTROLS

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.

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

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

Facilities were available for the storage of all materials and those observed were under appropriately controlled and monitored conditions. The receiving and distribution of the finished API products were inspected and found satisfactory.

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

2.10 LABORATORY CONTROLS

The QC laboratory premises, facilities and utilities were separate from production. There were dedicated rooms for activities like sample receipt and storage, wet chemistry, hot areas and instrumentation. 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.

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.

2.12 CHANGE CONTROL

A change control system was established. The system is comprehensive and according to corporate guidance.

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

2.13 REJECTION AND RE-USE OF MATERIALS

SOPs required intermediates and APIs failing to meet established specifications to be rejected. There was adequate space available for the segregation of rejected material prior to disposal. The reprocessing was considered satisfactory.

2.14 COMPLAINTS AND RECALLS

Quality-related complaints were recorded and investigated according to a written procedure SOP on complaint management procedure. The written procedure SOP to recall products from the market was reviewed. The SOP was adequate. The authorized person responsible for the execution and coordination of recalls was designated.

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

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.

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 (Zidovudine, Lumefantrine and Piperaquine Tetraphosphate) manufactured at *Mylan Laboratories Limited, Unit-9* 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.