

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

Name of Manufacturer	Mylan Laboratories Limited, Pithampur
Unit number	FD3
Production Block	NA
Physical address	Phase No: 11, 12 & 13, Indore Special Economic Zone, Pharma Zone, Phase-II, Sector-III, Pithampur – 454775, Dist. Dhar, Madhya Pradesh, INDIA
Contact address	Mr Pallab De, Quality Head (Formulations) pallabde@mylan.com
Date of inspection	7, 8, 9, and 10 October 2014
Type of inspection	Routine inspection
Dosage forms(s) included in the inspection	Oral solid dosage forms (tablets)
WHO product categories covered by the inspection	Prequalified products - HA433 Lamivudine, Nevirapine, Zidovudine Dispersible tablets 30/50/60mg - HA444 Tenofovir Disoproxil Fumarate/Efavirenz/ Emtricitabine 300mg/600mg/200mg tablet - HA466 Tenofovir Disoproxil Fumarate / Lamivudine / Efavirenz 300mg/300mg/600mg tablet
Summary of the activities performed by the manufacturer	Manufacturing, quality control and batch release of FPP oral solid dosage forms (tablets and capsules)

Part 2: Summary

General information about the company and site

The facility inspected was **Mylan Laboratories Limited, Plot No 11, 12 & 13, Indore Special Economic Zone, Pharma Zone, Phase-II, Sector-III, Pithampur, District Dhar, Madhya Pradesh, India**, here after referred to as **Mylan Pithampur**. The site belongs to Mylan Laboratories Limited, India (the former Matrix laboratories Ltd) with corporate offices at Jubilee Hills, Hyderabad, India which in turn is fully owned by Mylan Laboratories Inc., USA, with headquarters at Pittsburgh, Pennsylvania, USA.

Mylan labs Ltd have four finished pharmaceutical product facilities namely FDF 1, 2, 3, 4 and 8 API sites in India.

Mylan Laboratories Limited had acquired *Unichem Laboratories Limited*, Pithampur in March 2013 and transition phase was completed in January 2014. Mylan Pithampur is capable to manufacture solid orals (tablets and capsules).

According to the company presentation, the site employed a total of 318 people as of 30th Sept 2014 distributed as:

1. Production: 98
2. Quality unit (QA, QC, IPQA, stability): 82
3. Warehouse: 33
4. Engineering: 36
5. Process and packaging development: 16
6. Regulatory affairs: 4
7. Training/OE: 5
8. Others (HR, Admin, Purchase, Accounts etc): 44

There is an increase in number of personnel from 106 (last WHO inspection) to 318 as of 30/9/2014.

History of WHO and/or regulatory agency inspections

This was the second WHO inspection. The site was first inspected by WHO in October 2013. The site was also inspected by UKMHRA (Feb 2014), USFDA (Mar 2014), PPB Kenya (Apr 2014), NDA Uganda (Sept 2014) and CDSCO/FDAIndia (July 2012, Feb, Dec 2013 and Jun 2014).

Focus of the inspection

The inspection focused on the production and control of finished pharmaceutical products listed under Part 1.0. The inspection covered all the sections of the WHO GMP text, including premises, equipment, documentation, materials, validation, sanitation and hygiene, production, quality control and utilities.

Inspected Areas

Day 1, 7th October 2014

- Introductions
- Site presentation
- Update on WHO Prequalification Programme
- Product quality review (PQR) procedure
- PQR of LNZ tablets (HA433)
- Laboratory investigation report
- Training procedure and training schedule
- Organization chart and job descriptions
- Sanitation and personal hygiene
- Medical checks
- Self-inspection

Day 2, 8th October 2014

- Feedback on observation of day 1
- Inspection of laboratory covering verification of integration parameters, audit trail and access rights for two OOS, sample management using LIMS, dissolution, microbiology lab
- Procedure for handling of complaints
- Product recall and withdrawal
- SOP on vendor approval and evaluation
- Inspection of raw material and packaging material store
- Separate gowning area for visitors, male and female
- Receipt of raw materials, warehouse management procedure, walk-in chamber (2-8°C)
- Inspection of SAP
- Quick round of production at the end of day 2 including packaging material store

Day 3, 9th October 2014

- Feedback on observation of day 2
- Discussion on Track wise including how it was qualified for electronic signatures, audit trail, how patches & errors will be handled through change control, GAMP 5 used as reference document to validate Track wise
- Inspection of production area

Day 4, 10th October 2014

- Feedback on observations of day 3
- SOP on quality risk management
- Cleaning validation methodology
- Inspection of microbiology laboratory covering microbiologist certification, autoclave qualification, media, culture handling
- Inspection of retention samples room, QA documentation cell and stability section
- Inspection of water system
- Inspection of air handling units and dust collector units
- Exit meeting with site representatives

2.1 QUALITY ASSURANCE

The organisation chart was available and reviewed. Job descriptions of Quality Assurance Manager, Quality Control Manager, Production Manager and Engineering Manager were reviewed.

2.2 GOOD MANUFACTURING PRACTICES (GMPs) FOR PHARMACEUTICAL PRODUCTS

In general good manufacturing practices were implemented. The necessary resources were generally provided. Manufacturing steps were recorded in batch manufacturing and packaging records. Instructions and procedures were generally written in clear and unambiguous language. Qualifications and validations were performed, adequate premises and equipment were available for production, in-process controls and storage, and operators were trained.

Change controls, incidents, and investigation were handled through Trackwise system.

SOP on Risk Management was available which provided scope, responsibility, definition of various terms used and procedure. FMEA tool was used to evaluate risk using severity of impact, probability of occurrence, and level of detection which is subsequently categorised in five categories.

2.3 SANITATION AND HYGIENE

Premises and equipment were maintained at an acceptable level of cleanliness. The company had a standard operating procedure as the basis for its approach to personal hygiene and sanitation in its production facility.

There were documented procedures for which covered the cleaning of equipment and premises. There were logs that were kept for cleaning of equipment and apparatus, premises and containers. These were also included as part of the batch manufacturing record as part of line clearance. There were equipment and container labels that were in use.

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

2.4 QUALIFICATION AND VALIDATION

The Validation Master Plan was a general document and stated the company's validation policy. Re-validations were conducted based on the change control and annual review. A validation plan for 2014 was available. The materials hold time studies were scheduled to be conducted in October 2014

2.5 COMPLAINTS

SOP on handling of complaints was in place which is handled through Trackwise system. The procedure provided scope, responsibility and process of handling complaints received for Mylan Pithampur site. The procedure provided definition of adverse drug reaction, adverse event, complainant etc. A flow chart for handling of complaint was in place which provided an overview on handling of complaints.

There was no complaint received in 2013 and 2014.

2.6 PRODUCT RECALLS

SOP on product recall and withdrawal was in place. The procedure provided instructions for handling of recall including identification, initiation, monitoring and follow up, evaluation of root cause and corrective action plan. The responsibility to recall product rests with the Head QA in consultation with Regional QA Head. The recalls are classified as Class I, II and III. The procedure also described instructions for mock recall which is performed on dummy and or commercialised batches.

There was no recall performed in 2013 and 2014.

2.7 CONTRACT PRODUCTION AND ANALYSIS

It is noted that no manufacturing activity is outsourced. Some of the analytical tests are performed by outside laboratories.

2.8 SELF INSPECTION AND QUALITY AUDIT

SOP on Internal Quality Audits was in place. It is noted that there were quarterly self-inspections conducted of each department. These were conducted by certified auditors who were heads of the departments. There was use of checklists which were department specific.

There was an annual quality audit conducted by the corporate office.

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

2.9 PERSONNEL

The organisation's organogram was reviewed and it had provision for the different duties and departments within the organisation. There were job descriptions for personnel available. There was a documented training programme in place for both employees of Mylan and contract workers which covered GMP, good documentation practices, sanitation and hygiene and the job specific procedures. There were training modules for the employees for each department and there was a documented schedule available.

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

2.10 TRAINING

There was a training programme in place for both employees of Mylan and contract workers i.e. Fixed Term Employees (FTE). There were training modules available for each department and the modules included basic GMP, sanitation and hygiene, good documentation practices in addition to the job specific SOPs. Training records were kept for each employee and the effectiveness of the training was assessed through questionnaires.

2.11 PERSONAL HYGIENE

There were training modules on personal hygiene in the training module. There were relevant standard operating procedures on personal hygiene, entry and exit procedures into the critical areas in the plant. The SOP for personal hygiene also covered issues to do with illness and any medical conditions which were to be reported to the supervisors. Protective clothing was also used when entering production areas and other areas.

2.12 PREMISES

In general the buildings and facilities used for manufacture and quality control were located, designed, and constructed to facilitate proper cleaning, maintenance and production operations. Premises were designed to ensure the logical flow of materials and personnel. In-process laboratory was located in the production block. Quality control laboratories were separated from production areas. Sufficient space was given to avoid mix-ups and cross-contamination. Premises were protected from entry by insects, birds and animals. Premises were clean and well maintained.

Receiving and dispatch bays protected materials and products from the weather. Segregation was provided for the storage of rejected, recalled, or returned materials or products. Warehouse for the storage of different materials was found to be adequate. Temperature mapping was performed.

In general, the production area was laid out to allow the production steps to take place in a logical order. In general the surfaces were smooth and free from cracks. Equipment and materials were orderly positioned to minimize the risk of confusion between different pharmaceutical products or their components. Temperature, relative humidity and pressure differentials were regularly monitored.

Quality control areas were separated from production areas. Sufficient space was provided for samples, reference standards, solvents and reagents.

The floors were coved to facilitate cleaning.

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

2.13 EQUIPMENT

The equipment seen in production, quality control, warehousing and utilities was found in an adequate state of function and maintenance.

Balances and other measuring equipment were available for production and control operations and were calibrated on a scheduled basis. Calibration due-date labels were attached to the equipment.

Calibration schedule for the laboratory equipment for the year was reviewed as was the preventive maintenance schedules. They were the responsibility of the manager responsible for validation and GLP. The tolerance in terms of timelines between the scheduled and the actual date of calibration were also included on the schedule. Monthly checks were conducted of both schedules and signed.

2.14 MATERIALS

Materials in the warehouse were appropriately stored in a clean and orderly manner. The receiving and dispatch bays were separated. Procedures describing the receipt, quarantine, storage, handling, sampling, testing and approval or rejection of materials were available.

SOP on vendor approval and evaluation was reviewed and noted that Head QA together with purchase, R&D responsible for approval of vendors. Qualification of vendors for commercial batches done based on filled questionnaire and on-site assessment. It is noted that vendor audit is applicable to APIs and printed packaging materials and are done by Global QA. For excipients and unprinted materials, vendors are qualified based on the filled questionnaire.

2.15 DOCUMENTATION

In general documents were designed, prepared, reviewed and distributed with care. In general, documents were approved, signed and dated by the appropriate responsible

persons. Documents were laid out in an orderly fashion and were easy to check. Reproduced documents were clear and legible. Documents were regularly reviewed and kept up to date.

Document control procedure provided for the development, distribution and destruction of all documents; both controlled and uncontrolled. There was a procedure on document control which provided for the development, distribution and destruction of all documents; both controlled and uncontrolled. The revision and change of document was captured through a process of forms at each stage.

2.16 GOOD PRACTICES IN PRODUCTION

Attention to the production activities and equipment was limited to the rooms where the product of interest was manufactured. In general the surfaces were smooth and free from cracks. Equipment and materials were orderly positioned to minimize the risk of confusion between different pharmaceutical products or their components. Temperature, relative humidity and pressure differentials were regularly monitored.

It was noted from the discussion and inspection of production areas that the site divided whole of the production areas into general production area and MPB4 (Mylan Product Band 4). MPB4 products does not include WHO products but based on Mylan's internal requirement, the area was split to produce "certain" products in MPB4.

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

2.17 GOOD PRACTICES IN QUALITY CONTROL

The QC function was independent from other departments. Samples of starting materials, packaging materials, intermediate products, bulk products and finished products were taken by approved methods.

The LIMS system was installed in July 2014 which had been validated and it is in use since 1st August, 2014. The LIMS system was used to issue the analytical numbers and also to allocate work, track analysis and control the versions of the specifications and standard test protocols used. There were no individual analyst work books as all information was inputted into the LIMS using the standard work sheet for each product. The release of the CoA was the responsibility of the QC manager. There were different user types with different privileges in LIMS. Access was user specific and password controlled. The audit trail was enabled and could be modified by the manager QC. There was a procedure for Operation of Sample flow Module in LIMS Application.

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, ***Mylan Laboratories Limited, Plot number 11, 12, 13 Indore SEZ, Pithampur- 454775, Dist. Dhar, Madhya Pradesh, India***, was considered to be operating at an acceptable level of compliance with WHO GMP guidelines.

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.