



**WHO PUBLIC INSPECTION REPORT
(WHOPIR)**

Finished Product Manufacturer

Part 1: General information

Name of Manufacturer	Mylan Laboratories Limited
Plot number	FDF Unit 2, Aurangabad site (Plot No. H-12 and H-13)
Production Block	NA
Physical address	MIDC, Waluj Industrial Area Aurangabad, Maharashtra, 431 136, India
Contact address	As above
Date of inspection:	9 - 11 May 2013
Type of inspection	Routine inspection
Dosage forms(s) included in the inspection	Tablets, dispersible tablets and capsules
WHO product categories covered by the inspection	Tablets, dispersible tablets and capsules for treatment of HIV and influenza-specific antiviral medicines
Summary of activities of manufacturer (e.g. manufacturing, packing).	Manufacturing, quality control and batch release of FPP: solid oral dosage forms – tablets, dispersible tablets and capsules
Indicate dosage forms and type of products (e.g. tablets; cephalosporin containing products)	Hazardous or sensitizing products, including antibiotics, hormones and cytotoxins are not manufactured in facility



Part 2: Summary

General information about the company and site

Mylan Laboratories Limited (hereafter MLL) is the Indian subsidiary of Mylan Pharmaceuticals, Inc., USA. Mylan Pharmaceuticals 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 Perawada at Vishakapattanam
- Unit 11 Taloja, Maharashtra
- China Xiamen (China)

Finished Dosage Forms (FDF) manufacturing sites:

- Sinnar, Nashik
- Waluj, Aurangabad

FDF Research & Development site:

- Hyderabad

The finished product manufacturing site, located at H-12 and H-13, MIDC, Waluj, Aurangabad, was purchased from M/s Atra Pharmaceuticals Pvt Ltd in September 2010. This unit was initially constructed in 2008-2010. The facility was designed to manufacture, solid oral dosage forms i.e., immediate release & modified release tablets, powder-filled capsules, drug layered beads and pellets.

The site had recently undergone construction to enhance capacity of the warehouse, production, quality control (QC) and supportive functions (technical area, cafeteria). Further extensions of production are planned later on during the year.

The plant employed a total of 476 people: 160 in Production, and 176 in Quality Assurance (QA)/QC.



History of WHO and/or regulatory agency inspections

This was the second WHO inspection of Mylan Laboratories Limited at Waluj, Aurangabad.

The site has been inspected by international agencies, namely the US Food and Drug Administration (FDA) (February 2012) and the local FDA (December 2010).

Focus of the inspection

The inspection focused on the production and control of products under assessment and prequalified products.

The inspection covered the following sections of the WHO GMP text:

- Quality assurance
- Good manufacturing practices for pharmaceutical products (GMP)
- Sanitation and hygiene
- Qualification and validation
- Complaints
- Product recalls
- Contract production and analysis
- Self-inspection
- Personnel
- Training
- Personal hygiene
- Premises
- Equipment
- Materials
- Documentation
- Good practices in production
- Good practices in quality control

2.1 QUALITY ASSURANCE

A system for quality assurance in general was established. Production and control operations were clearly specified in written procedures, arrangements were made for the manufacture, supply and use of the correct starting and packaging materials. Necessary controls on materials, calibrations, and validations were carried out. There was a system for Quality Risk Management (QRM) in place as well as for Corrective actions and preventive actions (CAPAs).

Product Quality Reviews (PQR)

Annual Product Reviews (APR) were spot-checked. APRs should be completed maximum within the first three months of subsequent calendar year.



Examples of APRs were reviewed and were found to be adequate.

The SOP entitled “Application of statistical techniques” was spot-checked. The formula used for the Cpk (process capability) calculations was not specified in the SOP. The SOP only explained how to enter the data in the software. Minitab calculations were not verified on site.

Non-compliances observed during the inspection that was listed in the full report regarding Cpk calculations were addressed by the manufacturer to a satisfactory level.

Change Control (CC)

SOP Change Control was reviewed. It included the following attachments:

- CC flow chart
- CC form
- Justification note for CC
- Questionnaire for SOP - multiple choice questions were used for evaluation of the training on the particular SOP.
- Change notification and activity list.

The CC logbook (2012) from the solid dosage form department was reviewed. CCs should be closed within 60 days, if not; a closed justification note was raised.

The change control for the transfer of technology for specific tablets was reviewed.

The change control logbooks for 2012 were reviewed for production and engineering.

Non-compliances observed during the inspection that was listed in the full report regarding CC were addressed by the manufacturer to a satisfactory level.

Incidents

The TrackWise® global investigation system was implemented on 4 February 2013.

The SOP entitled “Incident report” was reviewed. The SOP described the process for the documentation of Incidents as a result of deviations (planned and unplanned) related to manufacture, packaging, testing or holding of drug products.

If the incident was related to the product impact and patient safety incidents were classified as:

- Severe
- Major
- Medium
- Minor
- Negligible



Complexity of investigation was defined as:

- Low
- Medium
- High

Relevant data was entered in the system by Quality Assurance (QA) manager (Quality approval persons). Afterwards the system automatically calculates the risk associated with the event. Risk levels were defined as:

- Critical,
- Major followed by the investigation
- Minor

CAPA was generated if required.

A specific Deviation report was spot checked, process validation was carried out on 3 consecutive batches.

A specific Incident/failure reports were spot-checked. In general, the reviewed SOP and Incidents/failure reports were found to be adequate.

Management review (MR)

SOP “Management review” was reviewed. Formal MR shall be performed monthly and formal MR report was written. Management review committee included:

- Site head
- Head of QA & QC
- Heads of manufacturing, engineering, process development, regulatory affairs, warehouse and supplier chain management/logistic, process development and packing development. Quality indicators were reviewed.

MR meeting minutes contained:

- A review of action items from the previous management
- Verification that each topic required to reviewed

In general reviewed procedure was found to be adequate; MR minutes were not reviewed as those were considered to be confidential.

Quality Risk Management (QRM)

SOP “Risk management (RM)” was reviewed. The SOP was applicable for:

- Product
- Specific process
- System
- Equipment’s
- Instruments



FMEA using 10 score system was used for risk assessment. Complaints, recalls, CC, incidents and QA were not listed in the SOP.

Specific examples were reviewed and found to be comprehensive. In general RM was implemented and found to be adequate.

CAPAs

CAPAs from last year's inspection were reviewed. The SOP on CAPAs was modified by the company to adapt it to the use of TrackWise[®]. The implementation of the TrackWise[®] system was done in February 2013. Afterwards CAPAs were implemented monthly.

Apart from CAPAs, the TrackWise[®] system was also used to track:

- Laboratory incidents (and OOS since February 2013).
- General incidents
- Complaints

TrackWise[®] validation was performed at Global Headquarters in the US.

2.2 GOOD MANUFACTURING PRACTICES (GMPs) FOR PHARMACEUTICAL PRODUCTS

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.

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.

2.4 QUALIFICATION AND VALIDATION

The company identified what qualification and validation work was required. The key elements of a qualification and validation programme were defined and in the validation master plan (VMP).

Process validation

A specific tablets process validation protocol/report and some analytical raw data (HPLC) were reviewed. Reviewed process validation was found to be adequate.

SAP[®] system validation

The SOP entitled "Computer Systems Validation" was reviewed. The validation strategy document for the SAP[®] global template validation strategy document was reviewed as well.



A local validation summary report was generated, summarizing the development and testing activities that occurred prior to the release of SAP for production use.

Non-compliances observed during the inspection that was listed in the full report regarding SAP were addressed by the manufacturer to a satisfactory level.

A risk assessment was done with regards to the implementation of SAP at Mylan laboratories in Aurangabad based on FMEA.

Cleaning validation

Re-validation criterion was specified in Cleaning validation Master plan and was the following:

- Changes in manufacturing process
- Changes in cleaning methodology
- Changes in acceptance criteria for chemical and microbiological (MB) analysis
- Changes in equipment design or equipment train
- Changes in analytical method or sampling method

The cleaning validation master plan was presented. The company had plans to adopt requirements from the upcoming European Medicines Agency (EMA) guidelines when adopted. The latest assessment of worst case was last done in April 2013.

Swab recovery studies were carried out for all molecules for the following surfaces:

- Stainless Steel (SS) 316 surfaces
- Silicon
- Teflon
- Neoprene
- Viton
- Acryl
- Polycarbonate

Swab recovery criteria were set up NLT 70 %.

The change control SOP clearly states that when a new product is introduced, the cleaning validation has to be assessed.

Cleaning validation was found to be acceptable overall.

Non-compliances observed during the inspection that was listed in the full report regarding cleaning validation were addressed by the manufacturer to a satisfactory level.

Holding time study

The report was reviewed for specific tablets. Reviewed report was considered to be acceptable.



Installation qualification (IQ), operational qualification (OQ) and performance qualification (PQ) of equipment

The IQ/OQ/PQ reports were reviewed for a recently installed tablet compression machine.

Representative from the company who manufactured the compression machine was present during qualification of the tablet press along with a Mylan staff member who was responsible for qualification of new equipment (this was verified in his job description).

- IQ: A complete set of diagrams, drawings and user specification requirements was available and verified by both the Mylan and company representative.
- OQ: this included screen reading verifications, verifications of the SOPs on operation and cleaning of the tablet press. The SOP for maintenance was the same for all compression equipment. The SOP for operation was different. The adequacy of the SOPs relative to maintenance and operation of new tablet presses was not necessarily verified with the assistance of specialized personnel from the supplier. The OQ was executed by the vendor along with the personnel from Mylan.
- PQ: covered in process parameters of compression, AWC challenge test, speed of the machine, smooth operation of the machine. Thickness, hardness, average weight, weight variation, friability, disintegration and appearance are verified as well as the rejection mechanism.

The reviewed IQ/OQ/PQ reports were found to be acceptable overall.

Transfer of technology (ToT)

ToT of specific tablets was performed in 2011, but the final summary report was written retrospectively in March 2012. The Sending unit was the Nashik site and the receiving unit was the Aurangabad site.

The feasibility batch report was reviewed. The comparative summary report for the WHO/PEPFAR market was reviewed as well.

The analytical method transfer protocol and report was reviewed for another product as an example of the CAPAs brought further to the last WHO inspection.

Non-compliances observed during the inspection that was listed in the full report regarding ToT were addressed by the manufacturer to a satisfactory level.

PW system validation

A new Purified water (PW) system was installed for extended production facilities. Phase I, Phase II and Phase III validation reports were reviewed. All test results were within specified limits.

Welder/welding operator performance qualification reports were reviewed and were found to be acceptable overall.



Reviewed PW system validation (Phase I and Phase II) was found to be carried out adequately.

AHU qualification

Performance Qualification protocol/report for specific AHU was spot-checked.

Air was recirculated; intake of fresh air was more than 10 %. Qualification was carried out by a third party.

The following filter cascade was installed in the AHU: G4 → F6 → F9. Terminals HEPA filters H13 were installed in the production suites.

The following tests were carried out according with ISO 14644 requirements:

- HEPA filter integrity (PAO)
- Air velocity / air changes per hour
- Different pressure gradient
- Airborne particle count
- Environmental monitoring temperature & humidity
- Air flow visualisation
- Recovery / decontamination rate test
- Viable particulate matter

Measuring equipment calibration certificates were presented and were traceable. In general HVAC system qualification was found to be adequately carried out.

2.5 COMPLAINTS

The complaint SOP was last revised in May 2013. Changes made since the last WHO inspection were reviewed.

This procedure incorporated the tracking of complaints using TrackWise[®] since its inception.

The closing time for minor complaints which were not likely to pose a significant hazard to health was reduced from 45 days to 30 days of receipt since the last WHO inspection.

Non-compliances observed during the inspection that was listed in the full report regarding complaints were addressed by the manufacturer to a satisfactory level.

2.6 PRODUCT RECALLS

No recalls had been performed since the last inspection. See previous report for a description of the company's means of conducting recalls.

2.7 CONTRACT PRODUCTION AND ANALYSIS

Production activities were not contracted out. Some analysis was carried out on contract basis. This area was not inspected during this inspection



2.8 SELF INSPECTION AND QUALITY AUDIT

Self-inspection was not inspected during this inspection. For details see previous inspection report.

2.9 PERSONNEL

The manufacturer had an adequate number of personnel with the necessary qualifications and practical experience. Responsible staffs, specific duties were recorded in written job descriptions. Personnel were aware of the principles of GMP and received initial and continuing training, including hygiene instructions, relevant to their needs. Steps were taken to prevent unauthorized people from entering production, storage and QC areas.

2.10 TRAINING

Non-compliances observed during the inspection that was listed in the full report regarding training were addressed by the manufacturer to a satisfactory level.

Contract workers

The contract workers' entrance register was spot-checked. Training files for some contract workers employed in the secondary packaging area were spot-checked. Training for the contract workers was given in the local language in several different GMP topics and SOPs.

2.11 PERSONAL HYGIENE

An adequate level of personal hygiene was observed by all of those concerned with the manufacturing processes. Direct contact was avoided between the operator's hands and starting materials, primary packaging materials and intermediate or bulk product. Smoking, eating, drinking, chewing, and keeping plants, food, drinks, smoking material and personal medicines was not permitted in production, laboratory and storage areas. Wrist-watches, cosmetics and jewelry were not being worn in clean areas. Personnel were wearing clean body coverings appropriate to the duties they performed, including appropriate hair covering.

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.

Storage areas

Warehouse for the storage of different materials was found to be adequate. Appropriate storage conditions were provided. Temperature mapping was carried out though it was not reviewed.



Production areas

Production area was laid out to allow the production 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

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

2.13 EQUIPMENT

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

Calibrated standard weights used for in-house checking of balances were available. Standard weights calibration certificate were presented to the inspectors.

Daily verification as well as quarterly and annually calibration of dispensing and analytical balances was carried out using calibrated standard weights.

Preventive maintenance

The SOP “Preventive Maintenance Plan (PMP) and the schedule (production & engineering) for January – June 2013 were reviewed. PMP was prepared twice per year. PMP SOPs and check lists were available for respective equipment. Spot-checks performed on the schedule revealed that it had been adequately followed.

The SOP “Preventive Maintenance of Air Handling Units, forced draft ventilation system and dust collectors” and PM checklist for specific AHU were reviewed. PM was found to be carried out adequately.

The SOP entitled “Calibration management” and schedule (production & engineering) for January – June 2013 were reviewed. Instruments were classified as:

- Product critical instruments
- Non-critical instruments
- Monitoring instruments / for indication purpose

The Calibration Master List was presented. It specified:

- Name of instrument
- Location
- ID of the instrument



- Range
- Operation range
- Least counts
- Calibration points
- Acceptance criteria
- Method
- Calibration frequency

Instruments calibration was contracted out to one calibration agency. On spot-checks calibration schedule was followed

Heating Ventilation and Air Conditioning system

HVAC system was not inspected on site during this inspection. For more details see previous report.

Compressed air

Compressed air system was not inspected on site during this inspection. For more details see previous report.

Water system

Water system was not inspected on site during this inspection. For more details see previous report.

2.14 MATERIALS

Starting materials were quarantined, sampled and tested before approval for use. All containers of active pharmaceutical ingredients were sampled individually and tested for identity while full testing was done on a composite sample.

Non-compliances observed during the inspection that was listed in the full report regarding sampling of starting materials were addressed by the manufacturer to a satisfactory level.

Materials in the warehouse (WH) were stored in the high bay racks. Temperature in the WH was monitored using 2 sensors.

Dispensing was carried out in 7 dispensing booths under RLAF. 4 dispensing booths were dedicated for excipients dispensing and 3 booths for API dispensing.

Packaging materials were quarantined, sampled and tested before release for use.

It was said to inspectors that printed roll labels vendors had been audited. Audit reports were not reviewed during the inspection. In case if several rolls were spliced together the



splicing place was indicated by the label manufacturer. Printed labels were 100 % checked in the WH using label counter for labels counts and bar code verification.

Materials were identified by a unique number and tracked using SAP[®] which was also used for material control

Reprocessing and reworking

SOP “Handling of rejects” and SOP “Reprocessing and reworking” were reviewed. Reprocessing was allowed only for packed materials, for example changing of secondary packing material.

2.15 DOCUMENTATION

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.

2.16 GOOD PRACTICES IN PRODUCTION

Handling of materials and products were carried out in accordance with written procedures. Checks on yields and reconciliation of quantities were carried out. During processing, all materials, bulk containers, major items of equipment and rooms were labeled. Equipment spare parts such as FBE filter bags, sieves, and screens were stored securely in locked cabinets. Punches and dies were product dedicated and rotation was ensured. Food grade lubricant was used for lubricating of punches and dies.

The production procedures were established and controlled and had been validated. The various manufacturing stages were performed in segregated areas. The rooms, equipment and containers were appropriately labelled with status, content and stage of processing.

Line clearance checks were conducted before the start of production and packaging.

Inspection of production activities was focused on activities carried out at new/extended production suites that were in use after previous inspection.

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. Sufficient samples of starting materials and products were retained to permit future examination of the product.



Stability studies:

Specific products stability data were reviewed and found to be adequate,

Stability chambers:

For more details see previous report.

Retention samples:

For more details see previous report.

Reference / working substances:

Working reference standards were dispensed in the microbiological laboratory RLAF cabinet. For more details see previous report.

Microbiology (MB) laboratory

MB media preparation

The SOP “Preparation and disposal of Microbiological culture media” was reviewed.

Non-compliances observed during the inspection that was listed in the full report regarding media sterilization were addressed by the manufacturer to a satisfactory level.

Out of specifications (OOS) and out of trends

These were tracked using TrackWise® and were covered under the wider category of laboratory investigations. A flow chart was shown for how Laboratory Investigations were performed. The SOP for laboratory investigations is site specific, but based on the Global procedure.

Non-compliances observed during the inspection that was listed in the full report regarding OOS were addressed by the manufacturer to a satisfactory level.

Laboratory Information Management System (LIMS)

LIMS contained the re-transcribed analytical results, which were taken from the analysts’ worksheet.

Electronic data and HPLC

The data was verified in the LIMS system against the data in the HPLC for 1 batch.

Identity (ID) testing

NIR was implemented in May.

Non-compliances observed during the inspection that was listed in the full report regarding ID were addressed by the manufacturer to a satisfactory level.



**World Health
Organization**

20, avenue Appia – CH-1211 Geneva 27 – Switzerland – Tel central +41 22 791 2111 – Fax central +41 22 791 3111 – www.who.int

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, **Mylan Laboratories Limited, FDF Unit 2, Aurangabad site (Plot No. H-12 and H-13), Aurangabad, 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.