

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
Unit number	NA
Production Block	NA
Physical address	F-4, F-12, Malegaon M.I.D.C, Sinnar, Nashik – 422103, Maharashtra state, India
Contact person and email address.	Mr. Pallab De, Sr. Vice-President, Corporate Quality Assurance, Mylan Laboratories Limited, Plot no. 564 / A / 22, Road no. 92, Jubilee Hills, Hyderabad - 500033, India. Tel: +91-40-30866410, Fax: +91-40-30866699 Mobile: +91-8008001497 Email: Pallab.De@mylan.in
Date of inspection	25 to 28 June 2012
Type of inspection	Routine
Dosage forms(s) included in the inspection	Direct and delayed release Tablets and Hard Gelatin Capsules
WHO product numbers covered by the inspection	HA391: Lamivudine 150 mg Film coated Tablets HA392: Lamivudine/Zidovudine 150/300 mg Film coated Tablets HA393: Abacavir 300 mg Film coated Tablets HA394: Stavudine 30 mg Capsules HA395: Stavudine 40 mg Capsules HA396: Nevirapine 200 mg Tablets HA403: Efavirenz 600 mg Tablet HA404: Zidovudine 300 mg Tablet HA405: Lamivudine/Stavudine 150/30 mg Tablet HA406: Lamivudine/Stavudine 150/40 mg Tablet HA407: Lamivudine/Nevirapine/Stavudine, 150/200/30 mg Tablet HA408: Lamivudine/Nevirapine/Stavudine 150/200/40 mg Tablet HA410: Tenofovir disoproxil fumarate 300 mg Tablet HA411: Lopinavir/Ritonavir 200/50 mg Tablet

	15. HA414 : Lamivudine/Tenofovir disoproxil fumarate 300/300 mg Tablets 16. HA417: Emtricitabine/Tenofovir 200/300mg Film-coated Tablets 17. HA420: Lamivudine 300 mg Tablets 18. HA426: Lamivudine/Nevirapine/Zidovudine 150/200/300 mg Tablets 19. HA429: Lopinavir/ritonavir 100/25 mg Tablets 20. HA433: Lamivudine/Nevirapine/Zidovudine 30/50/60 mg Dispersible Tablet 21. HA435: Abacavir 60 mg Tablets 22. HA436: Abacavir/Lamivudine/Zidovudine 60/30/60 mg Tablet 23. HA437: Lamivudine/Zidovudine 30/60 mg Tablet 24. HA444: Efavirenz/Emtricitabine/Tenofovir 600/200/300 mg Tablets 25. HA451: Emtricitabine 200 mg Capsules 26. HA456: Abacavir Sulfate/ Lamivudine 60mg/30 mg Tablets 27. HA464: Zidovudine 100 mg Tablets 28. HA466: Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate 600/300/300mg Tablet 29. HA467: Ritonavir 100mg Tablet (Heat Stable) 30. HA471: Didanosine 125 mg Capsule Delayed Release 31. HA472: Didanosine 200 mg Capsule Delayed Release 32. HA473: Didanosine 250 mg Capsule Delayed Release 33. HA474: Didanosine 400 mg Capsule Delayed Release 34. HA477: Atazanavir 300 mg Capsule 35. HA478: Atazanavir 150 mg Capsule 36. HA501: Tenofovir disoproxil fumarate/Lamivudine + Nevirapine 300/300 + 200mg Co-Blistered tablets 37. HA505: Abacavir sulfate/Lamivudine/Zidovudine 300/150/300 mg Tablet 38. HA507: Atazanavir/Ritonavir 300/100mg Tablet 39. HA512: Atazanavir + Lamivudine/Tenofovir Disoproxil Fumarate + Ritonavir 300+ 300/300mg + 100mg Co-Blistered tablets
Summary of the activities performed by the manufacturer	Production, packaging, quality control testing and release of finished pharmaceutical products.

Part 2: Summary

General information about the company and site

The facility inspected was **Mylan Laboratories Limited F-4, F-12, Malegaon M.I.D.C, Sinnar, Nashik – 422103, Maharashtra state, India**, here after referred to as **Mylan Nashik**. 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., UDA, with headquarters at Pittsburgh, Pennsylvania, USA.

Mylan Laboratories Limited, India has the following sites:

API sites:

1. Unit I: Kazipally, Hyderabad, India
2. Unit II: Astrix Laboratories, Kazipally, Hyderabad India.
3. Unit III: Jeedimetla, Hyderabad, India
4. Unit VII: Pashamylaram, Hyderabad, India
5. Unit VIII: Vizianagaram, at Vishakapatnam, India
6. Unit IX: Vishakapatnam, India
7. Unit XI: Taloja, Maharashtra, India
8. China: Xiamen, China

FPP Sites:

1. Sinnar, Nashik, India
2. Waluj, Aurangabad, India

FPP R&D:

1. Hyderabad, India

According to the Site Master File MLLNSK/SMF/01, Revision 02 and the company presentation, Mylan Nashik, was located on a 49.701m² (approx.. 12 acres) piece of land, 40,000m² of which was occupied by the production facility.

The site is dedicated to the manufacture of conventional tablets and capsules filled with powder, drug layered beads and pellets for human use only. No toxic or hazardous substances were used or manufactured on the site.

The site was licensed by the Food & Drug Administration, Nashik 25-NKD/89 and 28-NKD/43, valid up to 03/08/2015. It had a GMP certificate No. WHO-GMP/CERT/NKD-New-183-2011/2404/11 issued by the Food and Drug Administration, Maharashtra State and valid up to 14th November 2013.

According to the company presentation and SMF, the site employed a total of 1,542 people as of 31st May 2012 distributed as:

1. Production	719
2. Quality unit (QA, QC, IPQA, stability):	462
3. Warehouse	89
4. Engineering	75

5. Process and packaging development	58
6. Regulatory affairs	17
7. Others (Admin, Purchase, Accounts & ISD)	122

History of WHO and/or regulatory agency inspections

This was the fourth inspection by WHO-PQ, the first was in July 2007, then in July 2008 and August 2009 (special: data verification). According to the company presentation, the site was also previously inspected by the following authorities:

1. MCC, South Africa: March 2011
2. FBD, Ghana: Nov, 2009 and April 2012
3. NAFDAC, Nigeria: July 2009
4. FDA, India: Feb. 2007, April 2009, Nov. 2011
5. FDA, Nepal: April 2009
6. MCC, Namibia: Feb. 2008
7. MOH, Malawi: Dec. 2008
8. PPB, Kenya: March 2008, Aug. 2011
9. DRU, Botswana: Jan. 2008
10. MCAZ, Zimbabwe: Dec. 2007
11. DACA, Ethiopia: Nov. 2007
12. TFDA, Tanzania: Nov. 2007
13. MOH, Ivory Coast: Oct. 2007
14. NDA, Uganda: Sept. 2007
15. FDA, Thailand: Aug. 2007
16. FDA, USA: Feb. 2007, Aug. 2009, May 2011
17. MHRA, UK: Oct. 2006, Dec. 2009

The changes since the last inspections were summarised as:

1. Facility expansion:
 - a. RM warehouse
 - b. Pellet manufacturing, wet granulation, roller compaction, compression and coating
 - c. Blister packaging and bottle packaging
 - d. Quality control, stability laboratory
2. Equipment:
 - a. Balancing equipment, instruments and utilities in line with product mix.
3. Computer Systems:
 - a. LIMS
 - b. Documentum - SOP
 - c. Track wise – Complaints

Changes being proposed included:

1. Pilot packaging

Focus of the inspection

The inspection focused on the production and control of ARV tablets and capsules in general and the above listed products in particular. 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: 25 June 2012

The inspection opened with a meeting which included introductions; brief on WHO Medicines Prequalification Programme (WHO-PQ) and procedures; company and site presentation.

The inspection of the following aspects of the quality management system followed:

1. Annual product review:
 - a. SOP on annual Quality Product Review.
 - b. APQRs for selected products for the period January to December 2011.
 - c. APQR for Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate 600/300/300mg Tablet (HA466) for 2011.
2. Change control:
 - a. SOP on change control.
 - b. Register for changes related to production, QC and QA in 2011.
3. Handling of complaints
 - a. SOP on handling customer complaints.
 - b. The investigation reports of 4 Complaints were assessed
 - c. Quarterly complaint trends reports for 2011 were assessed.
 - d. SOP on CAPA.
4. Handling of deviations
 - a. SOP on handling deviations.
5. Warehouse, sampling and dispensing areas:
 - a. The inspection of the warehouse followed the flow of materials covering with receipt of raw materials, inspection, sampling, status labelling, sampling, storage and dispensing.
 - b. There were 3 sampling rooms fitted with RLAR cabins: 2 for APIs, colours and flavours and 1 for excipients.
 - c. There were 2 dispensing areas: one for API with 2 RLAF cabins and another for excipients with 3 RLAF cabins.

Day 2: 26 June 2012

The Inspectors gave feedback on the observation of the previous day and the company was given opportunity to make clarifications.

The inspectors then inspected and reviewed the following areas and aspects:

1. Production area.
 - a. Change rooms.
 - b. Production procedures, controls and segregation of operations.
 - c. BMRs and log book.
 - d. SOP on cleaning procedures.
 - e. The preventive maintenance of the tray dryer.
 - f. Handling of materials and intermediates
 - g. Focus on hot-melt extrusion process.
 - h. Qualification, care and use of punches and dies.
 - i. The primary and secondary packaging.
2. Deviation related to a batch of bulk tablets which exceeded hold time by 49 days (NMT 60 days). The product was reanalysed before approval for packaging.
3. Validation Master Plan.
4. HVAC system:
 - Design, operation, control and monitoring.
 - AHUs were inspected with focus on AHU for the Granulation suite 8 (AHU51) and FBD: CSD408. The area and procedure for filter cleaning were reviewed.
 - The results of the last qualification of AHU and area for Granulation suite 8 and related preventive maintenance were reviewed. No significant issue was noted.
5. Purified water system:
 - Treatment, purification storage distribution and monitoring.
6. Compressed air:
 - Design, monitoring and testing.
 - Results of the last sample from one of the coating machines.
7. Packaging material warehouse, sampling (3 x RLAFs) and dispensing (3 x RLAFs).
8. Warehouse for raw materials.

Day 3: 27 June 2012

The Inspectors gave feedback on the observation of the previous day and the company was given opportunity to make clarifications.

The inspection of the following areas and aspects followed:

1. Quality control laboratory:
 - a. Sample receipt, registration and allocation procedure.
 - b. Calibration and care of pH meter electrodes
 - c. Preparation of HPLC reagents.
 - d. Handling, preparation, storage and use of analytical chemicals, reagents and volumetric solutions.
 - e. Reference standard:
 - i. Sourcing, standardisation and use of reference and working standards.
 - ii. Preparation of one of the working standards.
 - f. Water for analysis: Elix – Millipore
 - g. LIMS: use, details entered and controls: allocation of samples, selection of tests and preparation of analytical reports.
 - h. Review of selected tests: Identity by IR, dissolution, assay and related substances by HPLC.
 - i. Qualification/Calibration of IR instrument.
 - j. Microbiology: with sections for microbial enumeration (RM, FPP, stability and hold time), testing of utility (water and compressed gases) and environmental monitoring. Media preparation and control. Reference culture sub-culturing and control. Double door autoclave under installation.
 - k. Testing of packaging materials: font patterns and colour; test for pin holes in aluminium foil.
2. Stability chambers (25⁰C/60%RH; 30⁰C/75%RH; 40⁰C/75%RH) and testing programme for selected products.
3. Qualification of FBD (ESD 408) in Granulation suite Number 8.
4. Process validation of one of the products from both the solvent process and hot melt extrusion process.
5. Cleaning validation
 - a. Review of site matrix approach to cleaning validation.
 - b. Calculation of MACO and determination of the residual limits.
 - c. Swab recovery test.
6. Purified water trends for 2011.
 - a. The July August trends for potable water and purified water.
 - b. Results of annual full testing of source water (2011).

7. Validation of FTNIR analytical method used for identification testing of received raw materials in their containers.
 - a. Report of building the model and the library.
8. Review of BMR and analytical reports of selected batches of selected products.
9. Assessment of the Active Substance testing
 - a. The inspectors assessed the testing of different batches of selected products.

Day 4: 28 June 2012

The Inspectors gave feedback on the observation of the previous day and the company was given opportunity to make clarifications.

The inspection of the following areas and aspects followed:

1. Validation of the testing method for impurities for one of the products.
 - a. The validation report for HPLC method for the determination of related substances and the method transfer report.
 - b. New HPLC method to capture two other impurities.
2. Supplier qualification
 - a. SOP on supplier qualification policy.
 - b. The qualification file of the supplier of one of the APIs.
3. Stability testing programme:
 - a. SOP on stability testing.
 - b. Stability data a batch of one product following increase of batch size.
4. Validation of media (by GPT) after exposure for 4 hours.
5. XRD for selected batches of one product.
6. Handling OOS:
 - a. SOP on handling OOS.
 - b. Review of OOS registers for 2011 and 2012.
 - c. Review of selected examples and report of review of trends.

2.1 QUALITY ASSURANCE

Mylan Nashik had in place arrangements for evaluations and monitoring of the quality of the systems, procedures and products through self-inspection procedures and annual product reviews. There were procedures for equipment and systems qualification and validation of procedures and processes. There were written and approved procedures to investigate, assess the impact of control changes, deviations and Out-of-Specification results.

Annual Quality Product Review (AQPR)

Annual Quality Product Review (AQPR) was performed according to an approved. This SOP described the different heading of the AQPR. The SOP stated that the AQPR takes into account the production of the calendar year.

APQRs for selected products were reviewed and no major issues were observed.

Change control:

This was managed under an SOP which indicated that changes had to be closed within 90 days, otherwise justification had to be given before an extension was formally granted. There were 235 changes related to production, 14 in QC and 337 in QA in 2011. The impact of the changes on the qualification, validation and approved regulatory status was reviewed. Change of vendor of raw materials had to be followed by validation.

Minor issues related to the design, maintenance and closure of registers for changes were noted but appropriate CAPAs were subsequently proposed.

Inadequate clarity was noted in the documentation of several changes related to change to manufacturing instructions (MIs) and a number of these changes had not been closed since November 2011. These issues were subsequently addressed by the company.

Deviations

Deviation were handled according to the an SOP. This SOP described the recoding process of the deviation and it assessment or investigation.

Deviations were classified as planned or unplanned deviation. They were categorized as critical, major deviation. Deviations were logged into a manual logbook by department. Any CAPA associated with the deviation investigation was handled through the CAPA system.

Deviation related to a batch of bulk tablets which exceeded hold time by 49 days (NMT 60 days) was reviewed. The product was reanalysed before approval for packaging.

2.2 GOOD MANUFACTURING PRACTICES (GMPs) FOR PHARMACEUTICAL PRODUCTS

There were facilities and procedures for the production and quality control of the products in focus and their level of execution and/or maintenance was generally adequate to ensure products of consistent quality.

Nevertheless, a few minor observations were noted that required attention to ensure continuous improvement.

2.3 SANITATION AND HYGIENE

The site had facilities and procedures for sanitation and hygiene. Materials for production, containers and products for cleaning were handled in a manner to minimize their chances of becoming a source of contamination to the product. There was need to ensure that these materials (e.g. disinfectants) are approved by QC and evidence for that maintained. Appropriate CAPAs were subsequently proposed.

Cleaning procedures for equipment and premises in place were adequate to enhance hygiene on the site. Personnel were trained on how to maintain good hygiene. There were comprehensive factory entrance and changing procedures.

Manufacturing areas, corridors and change room were cleaned.

2.4 QUALIFICATION AND VALIDATION

Validation Master Plan (VMP)

The VMP was discussed. This VMP described the different heading of the qualification and the validation policies. Each system was then described in a specific system validation master plan (for instance cleaning validation and qualification master plans).

Cleaning validation

For the cleaning validation purpose, the site ranked first all the 110 products based on their solubility level and then ranked the “insoluble” and “very slightly” soluble products based on their toxicity level. Three products were highlighted as the worst case scenario.

MACO was calculated and the residual limit was determined. Based on that, the site swabbed the equipment train and tested the swabs for the residual limit or 10 ppm whichever was lower. A cleaning verification study was performed for each product.

After validation on the three worst case scenarios, any new product was evaluated to ensure if the matrix was still valid and a cleaning verification study was performed during the exhibit batch manufacture.

The matrix took into account the products manufactured but not the equipment used. For example the three worst case scenarios were tablets so the validation study did not focus on the cleaning validation of the capsule filling equipment.

Equipment qualification and process validation

Qualification included User Requirements Specification (URS), Design Qualification (DQ), Factory Acceptance Tests (FAT), Installation Qualification (IQ), Operation Qualification (OQ) and Performance qualification (PQ).

Validation and qualification were guided by approved protocols. The schedules and frequencies for executed and planned requalification, validation and revalidation were outlined in annexes to the VMP.

Selected examples were reviewed, e.g. qualification/Calibration of IR instrument and qualification of FBD (ESD 408) in Granulation suite Number 8. No observations were made.

2.5 COMPLAINTS

Complaints were handled through an approved SOP. This SOP described the recording of the complaint the categorization of the complaint as critical, major or minor. It described also the investigation process. Major complaints were stipulated to be handled in 30 days and minor complaints were to be handled in 45 days. The SOP prescribed also that, since 10th of June 2012, CAPA issued at the outcome of the investigation should include a target date for its implementation.

CAPAs were then recorded in an Excel sheet according to the SOP and were monitored each month for implementation. A trend report of the complaint was issued each quarter. The reports of 2011 were assessed.

The investigation of 4 complaints was assessed.

2.6 PRODUCT RECALLS

This was not reviewed in details but the APQRs reviewed indicated that there had been no recall for those products.

2.7 CONTRACT PRODUCTION AND ANALYSIS

The SMF listed a number of outside laboratories that were approved to conduct contract analysis for the site. This area was not reviewed in detail.

2.8 SELF INSPECTION AND QUALITY AUDIT

There were procedures to conduct self-inspection at regular intervals for the purpose of monitoring the quality system and continuous improvement of the procedures. Auditors had the skills and training to conduct the internal audits. Reports were written with follow up actions and timelines. The implementation of CAPAs and its effectiveness was regularly reviewed by management.

Supplier qualification

The supplier qualification policy was highlighted through an SOP. This SOP stated that for all suppliers, a questionnaire was completed and assessed. The testing was performed by the R&D department to assess the compliance to its specifications. The two criteria were processed during development of the product or the transfer.

Before manufacture of the exhibit batch, the SOP stated that for:

- Active Substance (AS) and printed packaging materials supplier, an audit must be conducted,
- Other products suppliers, an audit should be conducted if necessary.

The SOP stated also that the site could rely on the audit outcome of the corporate quality group.

The qualification file of the supplier of one of the Active Substances was assessed without raising any comment.

An assessment of the qualification status of the supplier taking into account event occurring during the year or any outstanding issue was performed yearly.

2.9 PERSONNEL

The site engaged adequate numbers of skilled personnel to conduct production and quality control procedures. There was an organizational chart and job description to guide personnel. These indicated independence of quality control from production. The responsibility for batch review and release was assigned to Quality Assurance.

2.10 TRAINING

There was a system designed to ensure that newly recruited staff members received orientation plus training in basic GMP, hygiene & safety, written procedures, technical skills and SOP training as well as continuous training for continuous improvements and new procedures. Personnel interviewed and the records checked reflected that initial and continuing training was provided.

2.11 PERSONAL HYGIENE

There were facilities and procedures for changing and entrance into production areas which required staff members to wash their hands/feet and change into clean factory garments. The facilities and procedures were generally adequate, although the company should reconsider the practice of walking bare footed in the first change room from the wash areas across the bench before picking and putting on shoes.

Production staff were required to undergo health checks on recruitment and thereafter regularly as required.

2.12 PREMISES

Production areas:

The premises were located, designed, constructed and maintained to suit storage, manufacturing, quality control and related operations. The layout and design of premises facilitated the logical flow of materials and personnel to minimize the risk of errors and permitted effective cleaning and maintenance. The areas where dust was generated were fitted with dust containment and extraction systems.

The management was advised to watch the capacity of the product facilities so that they are not over-stretched.

Warehouse:

There were separate warehouses for raw materials, packaging materials and finished goods. They were generally well designed, controlled and monitored to provide appropriate temperature and Relative humidity conditions.

The warehouse for raw materials was crowded and materials were stacked in the corridors obstructing free movement. Empty Hard Gelatine Capsules had been purchased from Capsugel USA and Associated Capsules India Ltd, but the suppliers had not been contacted to assess the possible impact of the current alert on contamination with high levels of chromium.

There were 3 sampling rooms each fitted with a RLAF cabin: 2 for APIs, colours and flavours and 1 for excipients.

There were 2 dispensing areas: one for API with 2 RLAF cabins and another for excipients with 3 RLAF cabins. Each had a dedicated vacuum cleaner and wash area with an oven for drying utensils. The limits of pressure differential for one of the washing areas were not indicated on the Magnehelic gauge.

HVAC system:

Several AHUs were on site to supply filtered air to process rooms. Filtration system included G4, F7, terminal HEPA (H13) and G4 on return riser. The G4 and F7 filter were HDPE cleanable filters. They were cleaned and dried in a dedicated area. HEPA filters were replaced whenever pressure differential across the filter exceeded 60mm water gauge.

There was a dust extractor for each room that generated dust which was coupled to the respective AHU and the exhaust from the coating machine was treated through a water scrubber.

The company stated that AHUs were never switched off except for filter cleaning (monthly) and preventive maintenance (6 monthly). AHUs serving rooms around the corridor were designed to trip to prevent reverse air flow should the AHU of the corridor go off.

AHUs were inspected with focus on AHU for the Granulation suite 8 (AHU51) and FBD: CSD408. The area and procedure for filter cleaning were reviewed.

The results of the last qualification of AHU and area for Granulation suite 8 were reviewed. No significant issue was noted.

Each FBD was serviced by a dedicated air handling unit which processed air through G4, F7 and HEPA filter. To avoid clogging of the filter a differential pressure was transferred to the PLC of the FBD and an alarm was set. This was tested during operational qualification in 2009.

Purified water system:

The system included water from municipal supply collected in underground tank, then filtering it through multi-grade sand filter, softener, UV, Double RO system, EDI and UF to produce PW stored in a 4500L heat jacketed tank with a spray ball and steam sterilised vent filter. The distribution loop had a well monitored UV lamp, online TOC and conductivity meters and the flow rate in the return was controlled to NLT 7.1m³/hour.

A new water system was under installation to serve the new section for Wurster Coaters.

Results of annual full testing of source water (2011) and trends for potable water and purified water for the months of July and August (monsoon period) were reviewed. No observation was made.

Compressed air:

This had an oil free compressor, alternate dryers, receiver and filters of 5µ, 1µ and 0.2µ. The filter integrity of the final filter was regularly checked and compressed air was sampled annually from user points and tested for particulates, oil mist concentration, moisture content, hydrocarbons, dew point and microbial contamination. Results of the last sample from coating machine CA27 were reviewed and results were within acceptance limits.

2.13 EQUIPMENT

There were adequate numbers of equipment for the production and testing products manufactured at the site. For tablets and hard gelatine capsule manufacturing, which were the focus of this inspection, these included RGMs, vibratory sifters, Fluid Bed Processors, Roller compactors, Hot-melt Extruders, Fitz mills, Comils, Bin blenders, Single or double rotary compression machines some with PLC integrated weight checks, Automatic capsule filling machines, metal detectors, dedusters, Auto-coater, Wurster coaters, blister and bottle packing equipment with batch coding printers and an online NFD devices (camera) and multiple sensors. The product contact parts for all equipment were made up of SS316.

The QC laboratory had enough glassware for wet chemistry and other instruments like HPLCs, UPLC, RRLC, GCs, FTIR, UV/VIS Spectrophotometer, Dissolution Test Apparatus, Particle Size Analyser, Melting Point Apparatus, TOC Analyser, Karl Fisher Apparatus, High Precision Micro Balance, Analytical Balances, Coulometer and Auto-Titrators.

The equipment reviewed were well designed, qualified and were regularly calibrated. Balances were calibrated and records of daily verification using standard weights were available. There were procedures and records for equipment use, cleaning and maintenance.

Cleaning procedures provided for 3 types of cleaning: Type A for batch to batch cleaning; Type B for end of the day cleaning; and Type C for product change cleaning and after maintenance work. During product change over, the filter in the air return rise (G4) was cleaned with compressed air and purified water.

The records for use and cleaning of movable equipment should be adequately maintained to highlight the location of equipment for particular operation. The current system gave an impression that different products were being processed at the same time in the same room (*see example under section 2.16*).

The preventive maintenance of the tray dryer ESD445 was not performed adequately as some nuts were found to be loose and others had been replaced with non-stainless steel ones which showed signs of rust. Adequate CAPAs were subsequently put in place.

2.14 MATERIALS

The inspection of the warehouse followed the flow of materials covering receipt of raw materials, inspection, sampling, status labelling, sampling, storage and dispensing. There was an approved vendor list against which orders were placed and received consignments were verified. Storage areas included ambient, below 25°C and 2° to 8°C.

Consignments of certain Raw Materials were received with target samples taken by the supplier. This area had an FTNIR for identity (ID) tests in situ for each container and a composite sample was made from samples taken from $\sqrt{N+1}$ containers for other tests. In case NIR was not applicable, samples were taken from all containers for ID tests.

There was no evidence that the disinfectants (Dettol, Teepol and Phenol) used in on site were approved by QC.

2.15 DOCUMENTATION

A documentation system was in place to guide production and control of products. These included: Site Master File (SMF); Validation Master Plan (VMP); standard operating procedures (SOPs); Batch Manufacturing and Packaging Instructions and records (MIs, BMRs, BPRs); specifications of starting materials, packaging materials, packaging components and finished products; standard testing procedures, analytical records and certificates of analysis; qualification and validation protocols, schedules and reports; training schedules and records. There were corresponding records in form of reports, forms, checklists, logbooks, registers maintained as evidence of compliance with the procedures and specifications.

Most documents were maintained electronically on a computer server and there was a daily and weekly back up.

QA department was responsible for the coordination and control of preparation, review, approval, distribution and review of documents. The system was generally comprehensive and well managed.

2.16 GOOD PRACTICES IN PRODUCTION

Production operations were guided by approved written procedures in form of manufacturing instructions (MIs) and batch manufacturing records (BMRs). Records reviewed and practices witnessed indicated that records were made promptly in the BMRs and any deviations were also recorded and handled in accordance with an approved procedure.

Line clearance was conducted before and after production and packaging operations. The check list used was not detailed enough to highlight all the checks that needed to be done.

In-process controls were performed and documented at appropriate stages and intervals. There were provisions for checks on yields and reconciliation of quantities. Materials and equipment were adequately labelled with identity, stage of processing and status as appropriate.

In some instances, input materials, materials in hoppers and output materials were over-exposed to the room environment. For example, materials before and/or after hot-melt extrusion were not well protected from potential contamination as powder in a container from which the hopper for machine ESD572/SD061 was vacuum fed was not covered while the hopper on machine ESD238/SD022 was not covered and the hot-melt strip produced was collected in a container which was not covered. Moreover, the latter machine was not installed in a way to facilitate easy charging of the hopper. Adequate CAPAs were subsequently put in place to address these issues.

The maintenance of log books of movable equipment did not give confidence that one batch at a time was processed in a room that had more than one equipment, e.g. granulation suites. For example, at the time of inspection granulation suite 1 hosted a sifter (No. ESD1052), mixer (No. xxx) and FBD (No. ESD006). Review of the use and cleaning log books indicated that the sifter was in use when the FBD in the same room was used to process another product which would pose a risk of cross contamination. However, it was later established from the BMR and the environmental records of the room used that the sifter was used in a different room (SD002). Adequate CAPAs were subsequently put in place.

During inspection, granules for were being processed in granulation suite 17 and no similar observations were noted.

In granulation suite IX, the room was congested with equipment and drums, some of which blocked the air return riser RSD018. The log book for a sizer mill ESD559 indicated that it had been used on 25th June 2012 from 23.00 to 23.50 and had been cleaned (type A) on 26th June 2012 from 00.58 to 01.20 but was found during the plant inspection to have crumbs of white powder. This posed a risk of contaminating the next batch with potentially degraded material.

Tubes used for powder vacuum feed and FBD finger bags were dedicated to specific products and identified as such.

Punches and dies were qualified on receipt, used on rotational basis to ensure uniform ware and tare, inspected before and after use, adequately cleaned and lubricated with food grade oil before storage.

The tooling for primary packaging of one of the products under focus had not been purchased, though it was stated to be on order.

The primary and secondary packaging was controlled with a number of automatic sensors based on photography, weight and bar codes.

2.17 GOOD PRACTICES IN QUALITY CONTROL

Quality control laboratories were separate from production areas and their functions were independent of other units including production. They were manned by qualified analysts and had adequate facilities in form of space, equipment, reagents and chemicals to test all starting material, packaging materials, intermediates and finished products before release for use or distribution.

Received samples were registered in a registers before entering the records in LIMS which resulted in double AR numbers for each sample without adequate guidance on cross-referencing them. The selection of the tests to perform and allocation of the analysts was done via LIMS but guidance for this was inadequate as the parameters where skip testing was possible were not highlight and LIMS could not facilitate

identification of the batch due for testing under skip testing. In addition, there was no competence matrix to facilitate allocation of tests to individual analysts.

Reference standards

Primary reference standards were supplied from USP and EDQM (Ph.Eur and Ph.Int) when available or from the specific supplier with the certificate of analysis. Primary reference standards were used when working standards cannot be used.

Working standards were taken from specific received batches. The working standards were tested versus the primary reference standard. For instance, an example of working reference standard reviewed was tested versus the primary reference standard and was packaged into 48 multiple use vials. Each vial was used for a maximum of 15 days. However, vial of the working standard was securely closed by tape. The closing system put in place should be enhanced to avoid any risk of degradation during the multiple use periods.

Assessment of the AS testing

The inspectors assessed the testing of different batches of one of the active substances. The HPLC analysis performed was also assessed together with the logging of the results into LIMS and the verification process.

XRD analysis for several batches of one tablet product was reviewed. It was noted that XRD on the premix was limited to the validation batches but has been part of the FPP release specifications since February 2010.

FTNIR

In February 2011, the site implemented the identification process of received containers by FT NIR system. This implementation started in 2009 by building the model and the library. According to the protocol, the library built used at least three batches and for each batch 5 spectrums were captured. Then, the site used three different products from the library as a negative test. A report was issued and approved on 6th September, 2009.

The protocol stated also that for each new material 10 spectrums of the same batch and even the same container is considered sufficient.

Validation of the testing method for product impurities

During the Hot-melt process, impurities due to heat were expected. For the determination of related substances of one of the active substance, an HPLC method was developed in 2005 in Mylan Hyderabad (formerly Matrix Laboratories) and was transferred to Mylan Nashik in 2007.

The validation report and the method transfer report were assessed.

During 2012, the site developed a new HPLC method to capture two other impurities of another active substance and during the testing using this method, the level of one impurity was not accurate as the technician added to the peak area of this impurity a peak area for unknown impurity with close RT (retention time were 37min and

38min). This resulted in a high level of the impurity and an erratic variation of this level during long term stability testing due to error acquisition of the peak area.

OOS Investigation:

This was controlled under a SOP with 3 phases of investigation:

- Phase I: laboratory investigation: In case an assignable cause was observed, a reverse hypothesis was evaluated while in case no assignable cause was observed but suspected, hypothesis testing followed.
- Phase II: Evaluation of the manufacturing and allied processes.
- Phase III: conclusion

There were 77 OOS in 2011 (66 in stability, 7 in FPP, 2 RM and 2 PM) while in 2012 there were 49 so far (36 stability, 2 FPP and 11 RM). Several batches were recorded under one reference number and the trend analysis was not accurate with respect to number of batches/lots involved in a particular OOS. Selected cases were reviewed.

Microbiology laboratory:

The microbiology laboratory included sections for microbial enumeration (RM, FPP, stability and hold time), testing of utilities (water and compressed gases) and environmental monitoring. There were adequate facilities and procedures for media preparation and control. Reference culture sub-culturing and control was adequate with maximum 5 passages allowed. There were separate autoclaves for sterilisation (EQC035) and decontamination. A double door autoclave for sterilisation was under installation.

The report of validation of media (by GPT) after exposure for 4 hours was reviewed, which indicated that media could support growth up to 4 hours, but this duration was only routinely used for monitoring LAR but not in other environments.

Stability testing:

The SOP on stability testing provided for a window for withdrawal of samples from chambers as: 0 to 6m - +5 days; >6m - ±15 days and testing to be initiated within 30 days of withdrawal and completed within 60 days of withdrawal. It was recommended that the window for completion of analysis during the period of 0 to 12 months should be reduced from 60 days so as to reflect the actual situation at the time point.

The site has stability chambers for the following conditions: 25⁰C/60%RH, 30⁰C/75%RH and 40⁰C/75%RH.

Stability data one batch of a product following increase of batch size to 500,000 tablets was reviewed. Testing had been completed up to T24M.

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 F-4, F-12, Malegaon M.I.D.C, Sinnar, Nashik – 422103, Maharashtra state, 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.