World Health Organization
20, avenue Appia – CH-1211 Geneva 27 – Switzerland – Tel central +41 22 791 2111 – Fax central +41 22 791 3111
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WHO PUBLIC INSPECTION REPORT

(WHOPIR)

Finished Product Manufacturer

Part 1: General information

Name of Manufacturer	Mylan Laboratories Limited
Unit number	Mylan Nashik ("Sinnar" in CRM)
Production Block	NA
Physical address	F-4, F-12, Malegaon M.I.D.C, Sinnar, Nashik – 422103, Maharashtra state, India
Contact personand email address.	Mr. Pallab De, Sr. Vice-President and Quality Head-OSD Operations, 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 *AND* Mr. Uday Kasbekar , Vice-President Manufacturing Operations, Mylan Laboratories Limited F-4, F-12, Malegaon M.I.D.C, Sinnar, Nashik – 422103, Maharashtra state, India, Direct: + +912551304309 Mobile: +91-8888861003 Email: uday.kasbekar@mylan.in
Date of inspection	9, 10, 11, 12 June 2015
Type of inspection	Routine
Dosage forms(s) included in the inspection	Immediate and delayed release tablets and hard gelatin capsules
WHO product categories covered by the inspection	HA, MA and TB products
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

Globally, Mylan employed approximately 20,000 people. The manufacturing capacity was 45 billion dosage units. Approximately 12,000 employees were located in India. A total of 1811 employees were at the facility under inspection. The total plot area was 89,500 square meters, with approximately 22 acres of land. A neighbouring plot contained a supplementary finished product storage warehouse. A new warehouse was also under construction on the main plot of land. Production had the capacity to manufacture 6.5 billion tablets and capsules per year on a three shift basis.

History of WHO and/or regulatory agency inspections

This was the fifth inspection by WHO-PQ: the first was in July 2007, followed by inspections in July 2008 and August 2009 (special: data verification), then in June 2012. According to the company presentation, the site was also previously inspected by several stringent authorities over the last few years.

According to the company presentation and site master file, the site had a total of 1,811 employees as of 9th June 2015 distributed as:

1. Production	887
2. Quality unit (QA, QC, Stability):	516
3. Warehouse	100
4. Engineering	86
5. Process and Packaging Development	76
6. Regulatory Affairs	17
7. Others (Administration, Purchase, Accounts & Information Systems)	129

The inspection focused on the production and control of anti-HIV, anti-TB and anti-malarial products. 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

- Quality Assurance
- Sanitization and hygiene
- Qualification and validation
- Complaints
- Recalls
- Self-inspection
- Personnel
- Training
- Personal hygiene
- Premises
- Equipment
- Materials
- Documentation
- Production
- Quality control

PART 3: INSPECTION OUTCOME

3.1 PHARMACEUTICAL QUALITY SYSTEM (PQS)

Quality risk management

The standard operating procedure (SOP) for quality risk management effective from 09 June 2015, was reviewed and risk priority number was evaluated from severity of the impact, probability of occurrence and detection. The risk assessment manual dated 08 June 2015, was reviewed and functional risk identification was made in quality assurance (QA), Solid Dosage, Warehouse, Engineering, quality control (QC), Personnel and Administration and Process development. The system was well established and satisfactory overall.

Product quality review

The current version of the annual product quality review SOP was reviewed on the first day, along with annual product quality reviews for selected products. This area was considered satisfactory.

Out-of-specifications (OOSs)

These were maintained through Trackwise®. OOSs were reviewed on the first day from the actual electronic records, as these represent the true recordings, rather than the paper data.

There were 168 OOS's (opened and closed) listed for the entire site from January 2015. This was considered to be normal occurrence given the large amount of products manufactured at the site. Several examples were reviewed in detail. This area was considered acceptable overall.

3.2 GOOD MANUFACTURING PRACTICES (GMPs) FOR PHARMACEUTICAL PRODUCTS

All manufacturing processes were clearly defined, systematically reviewed for associated risks in the light of scientific knowledge and experience, and shown to be capable of consistently manufacturing pharmaceutical products of the required quality that comply with their specifications. Qualification and validation are performed; All necessary resources were provided.

3.3 SANITATION AND HYGIENE

The site had adequate procedures for sanitation and hygiene. This area was considered acceptable overall.

3.4 QUALIFICATION AND VALIDATION

Validation Master Plan (VMP)

The Validation Master Plan, approved 8 June 2015, was reviewed. 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. This area was considered acceptable after CAPAs.

Process validation (PV)

Selected exampled were reviewed. No observations were made.

Equipment qualification

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

Computerized systems

Caliber LIMS was the system in use and was initiated in January 2012. The server capacity was further enhanced in 2013. The documentation relating to the rollout of LIMS was reviewed. System design qualification, dated from 6 November 2013, was reviewed; this was a general overarching document. The sample information is manually entered in LIMS by the quality control user. The analyst entered the analytical observation manually, LIMS calculates the results and generated the certificates of analyses. Goods receipt was done in SAP. An inspection lot was generated in SAP. This goods receipt is done for a raw material, and packing material. Batch release is done in SAP through the inspection lot (which automatically generated by SAP). This inspection lot was manually fed into LIMS. There, LIMS generated an AR Number, which was associated to the multiple tests conducted for a particular lot. Once the certificate of analysis is generated and the LIMS process is completed. Then, the inspection lot is manually released in SAP. Quarantine status, in SAP, was identified as "quality inspection". When a lot was released, in SAP it was identified as "unrestricted". Any lot that was in an unrestricted status could be processed for further stages of execution. The company was still in the strategy alignment phase when it comes to fully integrating SAP with LIMS.

The qualification of the ability of LIMS to calculate test results, was reviewed. A script was used to execute the test. The expected value was verified against the expected value. The tool used was camera enabled and took screen shots of each step. The validation of calculations for analytical reports, was done in the Test Environment. Electronic signatures were used.

The tool formulas were verified each and every time at the time of master creation. The master formulas are registered under the test types. The person who is entering the variables into the master formula, has verified the results with the calculator.

The ability of LIMS to record OOS results and investigations was verified by the inspector randomly picking and example, and verifying it against information earlier recorded from the Trackwise system for OOSs.

3.5 COMPLAINTS

Handling of complaints SOP Version 7.0 effective as of 03 Sep. 2014, was reviewed. This SOP described the recording of the complaint the categorization of the complaint as critical, major or minor. This area was acceptable overall.

3.6 PRODUCT RECALLS

Product recall and withdrawal SOP MLLNSK-SOP-QA-GMP-0021 Version 5.0 effective as of 10 Nov. 2013, was reviewed. There were 4 classes for recalls, class I (within 3 days), class II (within 7 days) and class III (within 15 days), mock recalls were performed on a yearly basis. This area was acceptable overall.

3.7 CONTRACT PRODUCTION AND ANALYSIS

The SOP on the approval and evaluation of outside testing laboratories, Version 3.0, was reviewed. Amongst approved outside labs, four of them were Mylan groups. Vimta laboratories and Analytical solutions were third party laboratories.

3.8 SELF INSPECTION AND QUALITY AUDIT

This area was generally considered acceptable.

3.9 PERSONNEL

This area was generally considered acceptable.

3.10 TRAINING

Training was being managed through the "My university" electronic system, which had just recently been fully implemented. There were 1835 total records, which matched the total number of employees reported to be employed at the site during the opening meeting.

According to the system, there were 258 employees in quality control. One of the senior chemists, was selected as an example. He had been trained on HPLC operation and calibration for the pump, on waters equipment, on GLPs on safety, and on operation and calibration of dissolution testing apparatus.

A paper-based training matrix was used. The scheduled date of training was set and was respected. A number of employees were marked as "resigned".

Training records were reviewed and considered acceptable.

3.11 PERSONAL HYGIENE

The various changing areas inspected were clean, gowns used by personnel, were clean and free of product residue. There were no visible instructions on how to perform proper hand sanitization with isopropyl alcohol.

3.12 PREMISES

General

Premises were generally in an excellent state of maintenance and control.

Ancillary areas

These were satisfactory overall. Enough space was allocated for all of the required activities.

Storage areas

The finished product's offsite warehouse was inspected. It contained a large number of anti-ARV products, most of them manufactured in May 2015.

Weighing areas

Weighing areas were generally acceptable.

Production areas

Production areas were generally acceptable.

Quality control areas

Spacious, temperature/humidity controlled and adequately maintained premises were provided for all of the quality control activities performed at the facility.

3.13 EQUIPMENT

An example of a rapid mixer granulator used in the manufacturing of the LNZ product, was seen to have heavily scratched surfaces. Most of the equipment seen in production, was nevertheless in an acceptable state of maintenance.

3.14 MATERIALS

A SAP system was used to manage materials electronically. SAP showed a place called "Interim Goods". In the example of Batch 3007835, it was stored in the finished goods antiretroviral store. The system showed that only retention samples were left (fourteen of them).

Starting materials and packaging materials were received following acceptable procedures.

Intermediate and bulk products were kept within the appropriate environmental conditions and within their approved hold periods.

A validity period of 15 days was assigned to working standards – these were clearly labelled. Those seen stored at 2-8^{o}C were in boxes with desiccant. Many resolution solutions were seen in the refrigerator. The laboratory would run stability tests on these to verify that their use was acceptable.

3.15 DOCUMENTATION

The electronic documentation systems of Mylan Corporate were used for management of SOPs and of other documents at the site. This was done through a database called Documentum® (version 5.0), that had been in use since June 2012. SOPs were routed for approval through this software. Once approved, the SOPs were still nevertheless implemented and distributed as a paper based system at the Mylan Nashik site, since the full electronic system has not yet been implemented at Nashik. SOPs have a new format compared to previous inspections, with includes version number, validity period at corporate, validity period at the Nashik site (three years, vs. 24 hours only at corporate/ Mainland sites), as well as the list of changes.

3.16 GOOD PRACTICES IN PRODUCTION

Prevention of cross-contamination and bacterial contamination during production

There were provisions in place to regularly clean the production equipment and premises (floors, ceilings, etc.). Dust extraction systems were in place to prevent accumulation of dust resulting from the various production activities (sifting, sieving, compression).. The controls in place were generally considered rigorous.

Processing operations

Processing operations were adequately performed. Only one product was manufactured in each room at any one time.

Packaging operations

Primary packaging operations were inspected in process for the filling of bottles. Modern, state-of-the-art equipment was in place with controls for tablet count, bottle weight, labelling and metal contamination (this was tested in front of inspectors). Only 1 product and batch was packaged in a primary packaging room at one time and adequate procedures for line clearance were in place.

3.17 GOOD PRACTICES IN QUALITY CONTROL

The quality control department was divided into two laboratories. The stability laboratory was equipped with 87 HPLC systems, and all of them were visible on the network. These systems were controlled using Empower 2. The release testing laboratory contained approximately 63 HPLCs and 11 GCs. All instruments were networked.

On Day two, product lots found in the various warehouses at the site were verified against their status and test results in LIMS. It was noted that for the LNZ product, the specifications used specified dissolution test conditions of NLT 75% Q should be dissolved in 45 minutes for the three active ingredients that it contained.

On Day three, the quality control stability laboratory was inspected. This laboratory was also used to perform comparative dissolution profiles.

Analytical reports were generally detailed and were found to be filled contemporaneously during the inspection. Several reports were randomly selected and reviewed.

For instance, the Niacin extended release tablets 750 mg dissolution profile was seen to be under way for the third commercial validation batch (batch No. 3039405) at the coating stage for the US market. Samples were taken through automated sampling equipment on a Lab India DS14000 12 vessel dissolution testing apparatus. The nine hour dissolution sample time-point was witnessed by the inspector.

The samples from the subsequent time-points would be taken in test tubes until 24 hours would be reached. The process validation protocol, clearly stated that dissolution profiles time-points should be 1, 2, 3, 4, 6, 9, 12, 15, 20 and 24 hours. With limits of NMT 20% for 1 hour, NLT 25% and NMT 50% for 6 hours, NLT 45% and NMT 75% for 12 hours and NLT 80% for 24 hours for coated tablets with immediate filtration.

The calibration records showed that the sample volume taken was within ± 5% of the set volume for sample volume values of 5 mL, 10 mL and 10 mL (replenishment volume calibration).

A few other dissolution test results and their procedures were reviewed by inspectors.

PART 4: 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 Nashik, 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.