

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

Name of Manufacturer	MICRO LABS LIMITED
Unit number	Hosur
Production Block	ML-03
Physical address	92 SIPCOT Industrial Complex Hosur - 635 126 (Near Bangalore, Karnataka) Tamil Nadu India
Contact address	Mr. S.M. Mudda Executive Director - Technical & Operations No.27, Race Course Road Bangalore 560 001, India smm@microlabs.in Tel: +91 80 22370451-7 Dir. Line: +91 80 22375649
Date of inspection	17-20 April 2012
Type of inspection	Routine
Dosage forms(s) included in the inspection	Tablets
WHO product categories covered by the inspection	Pyrazinamide 400mg tablets (TB171) Pyrazinamide 500mg tablets (TB172) Isoniazid 100mg tablets (TB 173) Isoniazid 300mg tablets (TB 174) Ethambutol 400 mg tablets (TB200) Levofloxacin 250 mg tablets (TB237) Levofloxacin 500 mg tablets (TB238) Prothionamide 250 mg tablets (TB239) Ofloxacin 200 mg tablets (TB240)

	Ofloxacin 400 mg tablets (TB241) Ethionamide 250 mg (TB242) Note: products from the MHRA were also under the scope of this joint inspection.
Summary of the activities performed by the manufacturer	Manufacturing, quality control testing, packaging and distribution of tablets and hard gelatine capsules (oral solid dosage forms)

Part 2: Summary

General information about the company and site

The Micro Labs site was located at about 35 km from Bangalore at Hosur Tamil Nadu. It has been in operation since 2003. Tablets were being produced in two different blocks (ML01 and ML03), but only the ML03 block had been inspected and registered with the WHO Prequalification Programme and the UK MHRA.

History of WHO and/or regulatory agency inspections

This was the fifth inspection of this site by the WHO Prequalification of Medicines Programme, following the last inspections of May 2011, December 2010, May 2009 (joint inspection WHO and UNICEF), August 2008 and of February 2007. The company stated that the site was previously inspected by the MHRA (UK), Health Canada and the MCC (SA).

Focus of the inspection

The inspection focused on the production and control of solid oral dosage forms. 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

2.1 QUALITY ASSURANCE

General

Batches were numbered and released as per a written procedure. The batch numbering convention followed the format “AB” where A was a five-letter code and B was a four-digit sequential serial number. The five-letter code was decomposed as follows: SVAHH, where:

The first two letters signified the active ingredient (in this case, SV = Simvastatin)

The third letter signified the strength

The fourth letter indicated the pharmacopoeial specification and

The fifth letter indicated the site (H = Hosur)

Batch Release forms were raised by production and completed for review of BMR, BPR and analytical data.

The written procedure on “Quality Risk Management” was reviewed and found to contain the expected content according to ICHQ9. An example recent risk assessment for “Prevention of Mix-Ups” was reviewed and found to be thorough and adequate.

Product Quality Reviews (PQRs)

The recently revised PQR review SOP included instructions for the review of stability test results. Positive point: PQRs were performed within 3 months at the end of the calendar year and PQRs were written for each product every year regardless of the number of batches manufactured. Summary PQRs were also prepared to cover the fact that separate PQRs are written for individual customers.

The SOP on PQRs contained a sufficient level of detail and covered all of the necessary aspects and requirements of PQRs.

A PQR example was reviewed for Simvastatin supplied to a Product License holder to the United Kingdom market. Another PQR was reviewed for Isoniazid 300 mg tablets. Minor issues were noted which were resolved in the company CAPAs.

Change Controls

The SOP for change controls was reviewed and was found to be satisfactory overall apart from some minor issues which were dealt with in the company CAPAs. The trending of change controls was requested as it is performed annually according to the SOP.

The change control registers for 2011 were examined and examples were selected for review from the list.

Deviations

The procedure on Handling of Deviations was reviewed. Both planned and unplanned deviations were appropriately defined and improvements were made after the inspection on how to deal with recurring deviations.

Several examples of deviation reports were reviewed and were found to be satisfactory overall.

The SOP on the handling of out of specification test results was reviewed. It covered OOS results for all tests performed in the laboratory. The OOS logbook for 2011 was consulted and four examples were requested and reviewed. Minor amendments to the company's OOS procedure were required and made to the company CAPAs to ensure full alignment with current MHRA guidance.

A list of batches procured by the Global Fund was provided to inspectors and it was found to include a total of 39 batches which were supplied to the IDA from May 2011 to April 2012 for pyrazinamide 400 and 500 mg tablets. 2 batches of ethionamide were seen to have been manufactured in 2011 for WHO.

2.2 GOOD MANUFACTURING PRACTICES (GMPs) FOR PHARMACEUTICAL PRODUCTS

There were no significant or systemic problems seen with GMP in production.

2.3 SANITATION AND HYGIENE

The level of sanitation and hygiene appeared to be appropriate in general and covered personnel, premises and equipment.

2.4 QUALIFICATION AND VALIDATION

Process validation was covered for the commercial batch size of selected products.

Cleaning validation was reviewed and was found acceptable.

2.5 COMPLAINTS

The SOP for market complaints was reviewed and was found to be acceptable.

2.6 PRODUCT RECALLS

The SOPs for ADRs and recalls were reviewed. Minor issues raised with regards to mock recalls were addressed in the company CAPAs.

2.7 CONTRACT PRODUCTION AND ANALYSIS

This area was reviewed within the scope of the MHRA inspection.

2.8 SELF INSPECTION AND QUALITY AUDIT

The written procedure on Self Inspection was reviewed. The audit teams for inspections of each area were listed in an annexure and non-conformances were required to be classified as critical, major or minor. The audit team was allowed seven days to issue the audit report and the auditee ten days for development of CAPAs. The audit schedule for 2012 was reviewed and seen to be up to date as regards progress.

2.9 PERSONNEL

In general, the personnel met during the audit were experienced, skilful and conscientious. Adequate numbers of personnel were present to ensure completion of all necessary tasks.

2.10 TRAINING

The written procedure on Training of Personnel, was in place and adequately described how new recruits to the company should be inducted and trained in their roles. Training for established employees, including the requirement to review the training needs of workers returning to work after a period of absence were also described. Most training required assessment of competency, with an 80% pass mark to be achieved. The training plan for 2012 was reviewed and indicated monthly training in various GMP subjects in the General Plan. Separate plans were in place for SOP-based training for each department. The training records for an individual working in primary packaging were reviewed and found to be in good order. Training

was done according to an annual schedule. Records of training were verified in a few instances.

A new training centre was inaugurated during the inspection.

2.11 PERSONAL HYGIENE

Personal hygiene was found to be satisfactory.

2.12 PREMISES

Premises were generally well designed and maintained. Environmental monitoring was reviewed. A new procedure was in process of being implemented to enumerate microorganisms in the manufacturing area and microbiology section by settle plate, volumetric air sampling and swab testing method.

2.13 EQUIPMENT

A description of changes in equipment and at the facility was given by the company. New HPLC software had been installed on all HPLCs.

One new high performance compression machine was recently installed. Five metal detectors and nine dedusters were added. The new compression machine was fully qualified.

NIR was being used for 100% identification of raw materials. Qualification was examined along with positive and negative recognition tests done in front of inspectors.

2.14 MATERIALS

General

The control of materials as well as their flow were generally found to be adequate.

Control of vendors was documented in the SOP on Vendor Approval. Approved Supplier Lists (ASLs) were in place for each material type e.g. Active Ingredients, Packaging Materials and were prepared by QA. Updates to ASLs were prompted by receipt of new supplier approval forms. The procedure required all API manufacturers to be audited and re-assessed on a three-yearly frequency. The process for delisting poorly-performing vendors was well described. No reduced testing was done for APIs.

Compliance with TSE Guidelines : API Compliance

The documents associated with the approval of a supplier for supply of Simvastatin were reviewed and found to be thorough and comprehensive. A vendor audit schedule for 2012 was in place and satisfactory progress was noted. The audit reports for six approved API manufacturers were requested and were noted to be available.

Packaging materials: The company was requested to consider more secure methods of tamper evidence for product shippers.

2.15 DOCUMENTATION

Documentation was generally found adequate. The company has addressed issues raised in this area in their CAPAs.

2.16 GOOD PRACTICES IN PRODUCTION

Environmental controls, processes and practices appeared to be generally acceptable. General controls for calibration were outlined in a written procedure. Scheduling of calibration activities was documented in the Annual Calibration Plan. The procedure included an appropriate level of detail on actions to be taken in the event of a calibration failure. Instrument calibration was outsourced to a third party. Minor issues were raised with regards to the verification of the qualification of the 3rd party performing this work.

Maintenance of equipment was managed by a written procedure. Maintenance frequencies were defined in the maintenance plan with different tolerances for annual, six-monthly and three-monthly maintenance intervals. Qualification of equipment was documented in written procedure and seen to require the expected flow of documents from User Requirements Specification (URS) to Performance Qualification. The URS, Installation Qualification and Operational Qualification documents for a compression machine were reviewed and found to be generally in good order apart from the absence of definition of maintenance requirements as detailed in the SOP. This was addressed in the company CAPAs.

2.17 GOOD PRACTICES IN QUALITY CONTROL

Quality Control activities were performed in several small laboratories on two floors which were organised for instrumental, wet chemistry and microbiology tests respectively. 34 staff were employed in QC with a number of these staff working on shifts.

Samples for testing were received into the QC Manager's office and booked into a register according to type of material.

A formal specification was in place for testing of simvastatin for supply to a particular distributor for the UK market. A selection of tests was chosen from the specification for verification of equipment, calibration and associated documentation e.g. TLC equipment, a microbalance and one HPLC system. HPLC columns were dedicated and use was recorded in individual log sheets together with cumulative injections, theoretical plates and tailing factor, etc. Mobile phases were given a default 48 hr usage period.

Authentic Ph. Eur. Chemical Reference Standards were seen to be available e.g. for Simvastatin, lot number 4 was seen to be the current version.

Retention samples were stored in a locked room at 25°C and ambient humidity.

Stability chambers were available for storage at all of the required ICH conditions and ample back-up capacity was available. The actions to be taken in the event of chamber failures were described in writing.

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, *MICRO LABS LIMITED Hosur, ML-03, located at 92 SIPCOT Industrial Complex, Hosur - 635 126 (Near Bangalore, Karnataka), Tamil Nadu, 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.