

**WHO PUBLIC INSPECTION REPORT
(WHOPIR)**

Finished Product Manufacturer

Part 1: General information about the inspection

Name of manufacturer	Micro Labs Limited
Physical address	Plot No S-155 to S-159, Verna Industrial Estate, Phase III, Verna, Goa - 403722, India
Postal address	As above
Telephone number	+91-832 6686262, 6686202
Fax number	+91-832-6686203
Summary of all the activities performed by the manufacturer (e.g. manufacturing, packing).	Manufacturer and packer of oral solid dosage form products - tablets and hard gelatin capsules
Indicate dosage forms and type of products (e.g. tablets; penicillin or cephalosporin containing products)	No penicillins or cephalosporins are produced.
Scope of inspection	General and Product Specific GMP inspection with data verification.
Date of inspection	15 - 18 March 2010
Programme	Prequalification of Medicines Programme

Part 2: Summary

The manufacturing site of Micro Labs Limited, located in Goa, India was inspected by a WHO prequalification inspection team on the above mentioned days.

General information about the company and the site. History of WHO or regulatory agencies' inspections

Micro Labs limited had 14 manufacturing facilities.

The inspected site is situated in Verna Industrial Estate. The manufacturing facility was commissioned in 2004.

The Verna site previously was not inspected by the WHO.

The site was inspected and approved by:

- MHRA (UK)
- US (FDA)
- Med Safe (New Zealand)

The Mirco Labs manufacturing pharmaceutical products since 1973 for domestic and export markets. The Micro Labs facility at Verna is licensed to manufacture non-sterile oral solid dosage forms - uncoated and coated tablets and hard gelatin capsules.

100 % of products were manufactured on contract basis for other pharmaceutical companies through out the world.

In total there were approximately 170 employees working at the site of which 74 were involved in QA/QC activities and 61 in production activities.

Focus of the inspection

The focus of this inspection was to verify production and quality control activities for above mentioned products and to assess compliance with WHO GMP.

The areas inspected included the following:

- Receiving areas (raw materials and packaging materials)
- Storage areas for starting and packaging materials
- Sampling and dispensing areas
- Production areas related to the product such as granulation, compression, coating and packaging areas
- Quality control laboratory (chemical, stability testing, microbiological laboratory)
- Quality assurance and documentation
- HVAC

Documents reviewed included (but not limited to):

- Quality Risk Management
- Schematic drawings of AHUs
- Qualification protocol/report and data for specific AHU
- Batch records
- Deviations
- Complaints
- Product Quality Review
- Out of Specifications
- Equipment/instrument re-qualification schedule
- Preventive maintenance schedule for facilities and equipment
- Cleaning validation
- Cleaning of the stainless steel containers
- Cleaning performance evaluation
- Self inspection and schedule
- Vendor qualification
- Finished product testing and release
- Contracts
- Sampling tools cleaning
- Dispensing tools cleaning
- Garments laundry

- Footwear cleaning
- Temperature mapping
- Metal detector qualification
- Stability study, annual stability schedule and monthly stability planner
- Training plans and records
- Analyst certification
- Microbiological monitoring of environment
- Calibration and qualification procedures and records
- Insect and rodent control procedure
- Stability testing

2.1. Quality Assurance (QA)

A quality assurance system was implemented and maintained.

The Quality Assurance department was independent from the production. Production and control operations were clearly specified in writing. Necessary controls on starting materials, intermediate products and bulk products, in-process controls, calibrations, and validations were carried out. Quality Assurance responsibilities were specified and relevant duties were delegated to the designated persons.

Change Control

A formal system for change control was described in a written procedure and flow chart. Changes were classified as:

- Minor
- Major
- Critical

Change register was maintained.

If relevant, customers and Drug Regulatory Authorities were informed about changes. Change controls were trended yearly and trends were available for the inspection.

Deviation management

Deviation management was described in a written SOP. Deviations were investigated in accordance with the check list. Deviations were classified as:

- Minor
- Major
- Critical

Deviations were trended yearly and trends were available for the inspection.

Product Quality Review (PQR)

PQR was prepared in accordance with SOP for all products.

Products under assessment were not commercially manufactured. However PQR's were available.

Quality risk management (ORM)

A quality risk management procedure was in June 2008. Procedure was applicable to:

- Facilities
- Equipment and utilities
- Materials management
- Processing
- Laboratory controls
- Stability testing
- Packaging and labeling
- Review of existing systems

FMEA was applied as a risk assessment tool.

2.2. Good manufacturing Practices for Pharmaceutical products

Good manufacturing practices were implemented and generally maintained.

Necessary resources were provided, including qualified and trained personnel, adequate premises and space, suitable equipment and services, appropriate materials, containers and labels, approved procedures and instructions, suitable storage, adequate personnel, laboratories and equipment for in-process controls.

Manufacturing steps were recorded in batch manufacturing and packaging records; records were made during manufacture.

Instructions and procedures were generally written in clear and unambiguous language.

Qualification and validation were performed.

2.3 Sanitation and Hygiene

The topic was not specifically covered during the inspection; no notable concerns were identified during the inspection. The hygiene measures in place were generally found to be sufficient to assure the prevention of contamination of the premises and product.

2.4 Qualification and Validation

The key elements of the qualification and validation program were defined and documented in Validation Master Plan (VMP). VMP was revised once per year.

Cleaning validation

The "worst case scenario" was applied for the cleaning validation studies and MAC was calculated. The products and equipment were grouped using matrixes. Swab and rinse samples were collected for the analysis. Sample locations were identified on the equipment drawings.

HVAC qualification re-qualification SOP and specific AHU qualification and re-qualification reports and raw data were reviewed in details.

The procedure for the classification of the clean room area was according with ISO standard 14644.

2.5. Complaints

Dealing with complaints was specified in a written SOP. The complaints register was maintained. A person responsible for the handling of complaints was designated. Attention was given to counterfeiting. If a product defect was discovered or suspected in a batch, consideration was given to whether other batches should be checked in order to determine whether these were affected. If required, recall should be initiated. Complaints were classified into three categories:

- Critical
- Major
- Minor

Complaints regarding adverse drug reactions were investigated by the medical department.

2.6 Product Recalls

The system to recall the products from the market was in place. The authorized person responsible for the execution and coordination of recalls was designated and was the Head of QA. Recalls were classified as:

- Class I
- Class II
- Class II

In case there are no recalls, a mock recall should be carried out every three years according to the company SOP.

2.7 Contract production and analysis

Manufacturing activities were not contracted out.

Five contract laboratories were used for some analytical tests.

2.8 Self inspection and Quality Audits

Self inspection was carried out once in six months for all departments according to a written SOP and audit schedule. Audits were carried out by suitable trained personnel. Check lists were used to carry out audits. Critical, major and minor observations were identified. Corrective Actions (CA) were proposed after the audit and follow-up was carried out by the QA.

Supplier audit and approval

The vendor approval procedure was based on the questionnaires and audits. Mostly audits were carried out by the corporate Head QA. API materials vendor audits, printed packaging materials and primary packaging materials vendor audits were carried out in accordance with the audit schedule. An audit schedule was available for the inspection.

2.9 Personnel

In general, the personnel met and interviewed during the inspection were experienced, skilled and conscientious.

The following Job descriptions were reviewed:

- Head QA
- Head QC
- Sr. G. M. Technical & Operations

2.10 Training

The training needs were identified and training was organized as per the written SOP. The training effectiveness was evaluated by questionnaires and some open questions. Training records and annual training plan were maintained. A training schedule was available for the inspection.

The analyst certification procedure was reviewed and found to be satisfactory. An analyst competency list was available.

2.11 Personal Hygiene

No notable concerns were identified during the inspection of the production areas and the level of hygiene observed was considered satisfactory. Direct contact was avoided between operators' hands and starting materials, primary packaging materials and intermediate or bulk product.

All changing rooms were provided with photographs which described the gowning procedures.

2.12 Premises

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. Production areas had adequate space around equipment and acceptable material flow to prevent mix-ups and contamination, with separate entrances for personnel and materials. Premises used for the manufacture of finished products were suitably designed and constructed to facilitate good sanitation. Premises were cleaned according with validated cleaning procedures, cleaning was recorded. Premises were protected against the entry of insects, birds or animals. A pest control procedure was in place.

Storage areas

Receiving and dispatch areas had measures to protect materials and products from adverse weather conditions. Storage areas were of sufficient capacity to allow orderly storage of various materials and products with proper separation and segregation. Sampling of starting materials was carried out in two separate areas designed for the purpose. Sampling and dispensing of primary packaging materials and printed packaging materials was carried out in separate sampling and dispensing rooms.

Production areas

Production areas were laid out in a way to provide logical flow and required cleanliness level. Production areas were effectively ventilated.

Quality control (QC) areas

Quality control laboratories were separated from production areas. Sufficient space was given to avoid mix-ups and cross-contamination. Sufficient space was provided for samples, reference standards, solvents and reagents.

2.13 Equipment

Process equipment was installed and maintained in a manner that minimized the risk of error and contamination. Balances and other measuring equipment with appropriate range and precision were available for production and control operations and were calibrated on a scheduled basis. Calibrated standard weights used for in-house checking of balances were available.

Calibration due date labels was attached to the equipment.

Production equipment was cleaned on a scheduled basis.

Laboratory equipment and instruments were suited to the testing procedures undertaken. A planned preventive maintenance program of equipment and systems was in place. The critical equipments were identified. On spot checks the schedules and SOPs generally had been followed and records were maintained.

2.14 Materials

Materials were stored in high bay racks. Materials were properly quarantined, stored and released by QC. Temperature and RH was controlled in all warehouses, sampling and dispensing units. Temperature mapping was carried out.

Upon receipt, materials were checked against purchase orders. Starting materials were sampled 100% for identity tests and labeled with "sampled" labels.

Entrance to the sampling units was via airlocks, separate for personnel and materials. Line clearance was carried out before sampling using check list.

Entrance to the dispensing rooms was via airlocks, separate for personnel and materials. Dispensing was done under LAF. Balances were verified daily using appropriate range of calibrated standard weights.

2.15 Documentation

In general, the documentation system was established and maintained, documents were approved, signed and dated by appropriate responsible persons, regularly reviewed and kept up to date. Alterations made to documents were signed and dated. Specifications and testing procedures were available.

Batch related documents were kept for 7 years.

2.16 Good practices in production

Handling of materials and products was done in accordance with written procedures and was recorded, checks on yields and reconciliation of quantities were carried out. During processing, materials, bulk containers, equipment, rooms and packaging lines being used were labeled. Access to production premises was restricted. In-process controls were performed within the production area.

Temperature and relative humidity in the production rooms were controlled.

The general design of the facilities was appropriate. Premises maintenance should be improved.

Processes were generally under good control.

Food grade lubricants were used for punches and dies.

FBE finger bags were dedicated for each product and were stored in locked cabinets.

Cleaned equipment hold time was specified.

- Holding times for intermediate products were specified.

PW was used for final rinsing of the equipment. Equipment was dried using filtered compressed air or left to dry in ambient conditions.

IPQC room was provided with instruments for controlling compression parameters such as thickness and hardness, disintegration and friability.

Primary and secondary packaging

The primary and secondary packaging process was inspected and in general found to be satisfactory.

2.17 Good practice in Quality Control

Good Practice in Quality Control were generally implemented and maintained. Adequate facilities, personnel and approved procedures were available. Records of analysis were checked.

Instruments were calibrated by the laboratory personnel on regular intervals following the calibration schedule. Instruments were identified by unique numbers. Log books were available for all instruments and HPLC columns.

Reagents and mobile phases were appropriately labeled and stored. Expiry dates were specified for reagents.

KBr used for identity tests was dried before use.

Glassware SOP was available for the inspection. PW was used for the final rinse.

Out of Specification (OOS) results were investigated in accordance with a written SOP, which included a flow chart. OOS results were registered in the log book. A number of OOS investigation reports were reviewed.

Reference substances:

Pharmacopoeial and primary reference standards and working standards were stored under appropriate storage conditions in the fridge. Working standards (WS) were dispensed in vial for single use. Working standards were dispensed in separate glove box. Standards were registered and their usage was traceable. WS were standardized against the Pharmacopoeial standards. Reference standards were managed satisfactory.

Microbiology

The laboratory conducted water and environment monitoring, starting material, finished product and stability testing.

Settle plates for the environmental monitoring were exposed for 2 hours. Settle plates and air sample locations were identified. Action and alert limits were specified.

PW and environmental monitoring trends were reviewed and found to be satisfactory.

There were separate autoclaves for media sterilization and for destruction. Autoclave validation using thermocouples was carried out and the results were available. The autoclave was re-validated every year.

The pH of media was checked before and after sterilization. Growth promotion checks, positive and negative controls were carried out.

Stability studies

The procedure for stability monitoring defined the time tolerances for loading, unloading and analysis of samples. Records for the different activities were available for the inspection. Activities were planned in schedules, responsibilities for the collection of on-going stability samples were assigned. For every product in production at least one batch per year was taken into the on-going stability program.

Part 3: Conclusion

Based on the facilities inspected, the personnel met and the documents reviewed, and considering the inspection observations listed in the inspection report, Micro Labs Limited, located at Plot No S-155 to S-159, Verna Industrial Estate, Phase III, Verna, Goa - 403722, India, was considered to be operating at an acceptable level of compliance with WHO GMP.

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.