

**Prequalification Team
WHO PUBLIC INSPECTION REPORT
(WHOPIR)
Active Pharmaceutical Ingredient (API) Manufacturer**

PART 1: GENERAL INFORMATION

Name of Manufacturer	MICRO LABS LIMITED
Unit number	ML_15
Production Block	Production A, B
Physical address	API -Bommasandra (ML-15) Plot No.43-45, KIADB, Jigani -Bommasandra Link Road Anekal Taluk, Bangalore, Karnataka, India
Contact person and email address.	Mr N. B. Shenoy, Vice President – Technical and Operations (Site Head)
Date of inspection	8-10 December 2015
Type of inspection	Follow-up inspection
Active Pharmaceutical Ingredient(s) included in the inspection	Lumefantrine (APIMF217) Artemether (APIMF259) Ethambutol Dihydrochloride (APIMF273)
Summary of the activities performed by the manufacturer	Production and quality control of APIs

PART 2***General information about the company and site***

Micro Labs Ltd (hereafter MLL) was established in 1973 by the late Shri. G. C. Surana. MLL is engaged in manufacturing of Medicinal products since 1973 for domestic and export regulated markets. Presently Micro Labs Ltd exports to over 40 countries. The MLL group export to the regulated markets and also to South East Asia, Africa, CIS States, Middle East and Latin America.

The MLL API manufacturing facility set up in Bommasandra Industrial area was established in the year 2007, about 25 Km from Bangalore city. The site area is 24,000M². The company is engaged in the production of APIs in segments of Anti-histamines, Ophthalmology, Anti-hypertensive, Anti-malarial, Anti-inflammatory, Anti-depressants, Anti-diabetics, Antipsychotic, Antiviral, Antibacterial, Anti-ulcerate etc. Facility does not manufacture any cytotoxic, hormones, penicillin's, Cephalosporins or steroids.

The facility has four manufacturing blocks, (Production Block-A & B, Pilot Plant & Kilo Lab) one Hydrogenation Block, and one Solvent recovery plant. The plant is equipped with 100L to 3KL reactors. There are five finishing areas meeting ISO Class 8 and manufacturing facility has the capabilities to process reactions requiring temperatures – 80° C to + 155° C. The reactors are made of Glass Lined and SS 316L.

History of WHO and/or regulatory agency inspections

The API manufacturing site was first inspected by WHO-PQT in 2013. This is a follow-up inspection. In addition, the site was inspected / approved by following authorities:

- Manufacturing Site approved by **EDQM & ANSM** in the year 2014.
- Manufacturing Site approved by **USFDA** in the year 2015.
- Manufacturing site approved by **TGA** in the year 2015 based on document Review.

Focus of the inspection

The inspection focused on the production and control of Lumefantrine, Artemether and Ethambutol Dihydrochloride. The inspection covered all the sections of WHO good manufacturing practices for active pharmaceutical ingredients including premises, equipment, documentation, materials, validation, sanitation and hygiene, production, quality control and utilities.

Note: The scope of this inspection was limited to data verification and verification for the implementation of CAPA from previous WHO inspection; hence this inspection did not cover all aspects of two new APIs. A routine inspection will be conducted earlier than the schedule period to cover these two additional APIs.

Inspected Areas

The inspection covered some of the following sections of the WHO GMP for Active Pharmaceutical Ingredients text:

- Quality management
- Personnel
- Buildings and facilities
- Process equipment
- Documentation and records
- Materials management
- Production and in-process controls
- Packaging and identification labelling of APIs and intermediates
- Storage and distribution
- Laboratory controls
- Validation
- Change control
- Rejection and reuse of materials
- Complaints and recalls
- Contract manufacturers (including laboratories)

PART 3: INSPECTION OUTCOME**3.1 QUALITY MANAGEMENT (QM)**

The Company's Quality Management System is designed to meet the CGMP requirements as per WHO good manufacturing practices for active pharmaceutical ingredients. The designated documentation ensuring QMS is implemented in general. The scope of the Documentation System covers preparation, approval, issuance, changes / modifications and review of documents.

The SOP on annual product review (APR) was available and APRs were prepared in accordance to the procedure. The APRs of Artemether and Ethambutol HCl were reviewed.

Management review meetings are conducted once every three months, and it is chaired by Site Head and Head CQA. A SOP on quality review meeting was in place. Several of the quality metrics such as OOS, change controls, complaints, recalls, OOT, non-conforming products, stability studies, internal audit, vendor development, environmental review, new product scale up, regulatory issues, corrective action & preventive actions, PQR etc were part of the review. In general, the procedure was found to be satisfactory.

3.2 PERSONNEL

An organization chart was available. The quality assurance and quality control department were independent from the production department. It was noted from the organogram that the regulatory department was parallel to the QA department. The site distribution of staff is as follows:

- Production: 51
- QA/QC Staff: 60
- Support Staff: 36
- Total Strength: 147

3.3 BUILDINGS AND FACILITIES

Production blocks (PB-A and PB-B) were briefly inspected, and in general found adequate for the type of products produced on site.

3.4 PROCESS EQUIPMENT

The equipment used to manufacture the inspected three APIs were not dedicated.

3.5 DOCUMENTATION AND RECORDS

The site documentation system was paper based. There was no major change made since the last WHO-PQT inspection.

3.6 MATERIALS MANAGEMENT

The receipt, identification, quarantine, storage, sampling, testing and approval or rejection was conducted according to approved documented procedures. The Vendor qualification procedure and approved vendor list were reviewed.

3.7 PRODUCTION AND IN-PROCESS CONTROLS

The production of Lumefantrine was in operation at different stage at the time of inspection. Processing took place according to the instructions in the BMR. The steps reviewed indicated that the BMR had been kept up to date. Each major piece of equipment was appropriately labelled with a status label.

3.8 PACKAGING AND IDENTIFICATION LABELLING OF APIs AND INTERMEDIATES

Not inspected

3.9 STORAGE AND DISTRIBUTION

Not inspected

3.10 LABORATORY CONTROLS

The SOP for handling of OOS was in place which was applicable to RM, PPM, intermediates, stability samples and water samples. The procedure described investigation into Phase-I, hypothesis testing, Phase-II (full scale investigation including retesting, resampling and manufacturing investigation. An OOS investigation flowchart was part of the

procedure. It was noted that reanalysis was done in triplicate by two analysts, there was no consideration given on statistical review of 6 results.

Upon inspection of HPLC systems, it was noted that three administrator user type were available without any justification. It is important to note that the roles of each type must be defined and appropriately assigned independent of the analyst.

It was noted during inspection that audit trails were fully enabled for projects and instruments.

3.11 VALIDATION

The validation master plan (VMP) for the year 2015 was available. The planner included HVAC performance verification, nitrogen and compressed air, thermal mapping (dryers, warehouse, and stability chambers), raw water, and equipment requalification. It was noted that process validation is tracked through change controls. Similarly, new SSR-12 procured in 2015 was handled through change control.

Process validation protocol for Ethambutol HCl was available which provided process flow diagram including in-process and critical process parameters, status of qualification of equipment, name of the raw materials, specification, key starting materials etc.

The validation sampling plan and critical process parameters, drying process parameters, in-process controls, and standard output were reviewed. The PV report was reviewed.

Process validation of Artemether was performed in 2013. The process validation protocol, report and analytical method validation associated to the following batches were reviewed.

Equipment cleaning validation SOP was in place which described cleaning procedure following respective equipment cleaning procedure, calculation of MACO, sampling method (rinse & swab), selection of cleaning agent and revalidation criteria (introduction of new product, change in equipment design, major modification, change in cleaning procedure, change in method of testing and change in batch size). In general, the procedure appears satisfactory.

Cleaning validation protocol for production block-B, bay 1 and bay 2 were available which essentially described equipment list with names of the products produced in respective bays. It is noted that Lumefantrine is produced in Bay 1 and equipment used were listed and compared with information provided in process flow which is part of the batch record. It is noted that Bay 2 is also used for Lumefantrine as RCVD, MM and Sifter of bigger capacity are available. Artemether is included in Bay 2. An addendum was prepared due to the introduction of Ethambutol HCl and removal of Escitalopram Oxalate in PB-B, bay 2 dated 27/9/2014.

Protocol for dirty hold time study of equipment was available which identified reactor as worst case equipment and Lumefantrine was identified as worst product for dirty hold time based on difficult to clean criteria, coloured product and sticky nature. The dirty hold time was set for 24 hours and samples were taken for swab and microbiological testing. The dirty hold time was completed.

Protocol for clean hold time study of equipment was available. The reactor and Lumefantrine were identified and selected for clean hold time as for dirty hold time. The study was performed for 3 days and clean hold time of 3 days was established. The report was available dated 20/1/2015 which confirmed 3 days clean hold time.

The SOP for transfer of analytical methods was reviewed and noted that procedure was applicable to assay, related substances, residual solvents, chiral purity and content analysis which was performed in ARD and transferred to QC. The ARD will visit QC and perform joint analysis before method is transferred to QC. If it is a pharmacopoeial method, verification will be performed.

Method transfer for Lumefantrine for related substances (Ph. Int.) by HPLC was performed in August 2013. Lumefantrine CRS 1.0 was used for the test and testing was jointly performed by ARD & QC in QC lab. The related substance test was performed in triplicate (three separate preparations) by analytical research development (ARD) on and then by QC. In general, the results reported were comparable. It was however noted that integration parameters and audit trail related documents were not retained.

Analytical method validation /verification report of Ethambutol HCl for related substances test (Ph. Eur.) by HPLC was reviewed and noted that method was verified by ARD. The recommendations were made on mobile phase stability, sample solution stability and RRT for impurity B. the processing method including integration parameters were part of the chromatograms. It was however noted that method was not transferred to QC as ARD/QC had verified the same method in June 2014. The recommendations given by ARD were taken into account and analytical method was revised accordingly.

Artemether Ph. Int. was validated in December 2013 by ARD for related substances test by HPLC. The method was also transferred in December 2013 to QC. The ARD revised specification of Artemether Ph. Int. and included related substances test, acetyl chloride content, benzene content and polymorphism by PXRD. It is noted that the revised specification will be implemented and will be filed with WHO-PQT.

3.12 CHANGE CONTROL (CC)

The change control (CC) procedure was revised which provided clarification on major and minor changes as commented in previous WHO inspection. The batch size increase to 10 fold is classified as major and procedure is supported with list of typical changes.

The CC regarding the new vendor of Artemisinin and CC regarding Lumefantrine Master Batch Record which was triggered by the equipment change were reviewed and discussed.

3.13 REJECTION AND RE-USE OF MATERIALS

Not inspected

3.14 COMPLAINTS AND RECALLS

There was no recall in 2014. In 2015, the company recalled Lumefantrine and two other products. Lumefantrine was supplied to Micro Labs, and was recalled as batch was produced using recovered solvent and or alternate vendor. Since API is to be used for WHO submission batches, and use of recovered solvent / and or alternate vendor was not part of APIMF submission, hence it was recalled. The company has taken CAPA by introducing specific code to APIMF grade and this code was extended to the site now. Other products were recalled due to stability failure as these were supplied to Micro Labs for submission batches.

3.15 CONTRACT MANUFACTURERS (INCLUDING LABORATORIES)

Not inspected

PART 4: CONCLUSION

Based on the areas inspected, the people met and the documents reviewed, and considering the findings of the inspection, including the deficiencies listed in the Inspection Report, as well as corrective actions taken and planned:

- *Lumefantrine (APIMF217)*
- *Artemether (APIMF259)*
- *Ethambutol Dihydrochloride (APIMF273)*

manufactured *Micro Labs Limited*, Plot No.43-45, *KlADB, Jigani -Bommasandra Link Road Anekal Taluk, Bangalore, Karnataka, India*, was considered to be manufactured in compliance with WHO GMP for Active Pharmaceutical Ingredients.

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 2 years, provided that the outcome of any inspection conducted during this period is positive.