

**WHO PUBLIC INSPECTION REPORT  
(WHOPIR)  
API Manufacturer**

**Part 1: General information**

Name of Manufacturer	Mangalam Drugs & Organics Ltd
Unit number	Unit 1
Production Block	Blocks 9 and 10
Physical address	Mangalam Drugs & Organic Ltd (Unit No.1) Plot No.187, II <sup>nd</sup> Phase, G.I.D.C., Vapi -396 195 Tal. - Pardi, Dist. Valsad, State: Gujarat, INDIA.
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Date of inspection	17 – 20 January 2011
Type of inspection	Routine
Active Pharmaceutical Ingredient(s) included in the inspection	Lumefantrine (APIMF100), artemether (APIMF101, APIMF138), artesunate (APIMF135), amodiaquine HCl (APIMF134)
Summary of the activities performed by the manufacturer	Production, quality control, packaging, storage, distribution

## **Part 2: Summary**

### ***General information about the company and site***

Mangalam Drugs & Organics Ltd is a company that is specialized in the manufacturing of active pharmaceutical ingredients and their intermediates. It has manufacturing facilities located at two different sites, Unit-1 and Unit-2 in Vapi, Valsad District, Gujarat State, India. Unit-1 was the object of this inspection and is responsible for the synthesis of lumefantrine, as well as for the synthesis of artesunate and artemether from artemisinin and of amodiaquine hydrochloride. Unit-2 was briefly visited as it was used by the company for the production of key starting materials and of APIs destined to other markets, but was not covered by the scope of this inspection.

At Unit 1, there were only 2 buildings in which manufacturing was performed: Building 9 (production block 1D), an older building and Building 10 (production block 1A), a new building in which commercial manufacturing has recently started.

Other products manufactured at this site include chloroquine phosphate, Chloroquine sulphate, Hydroxychloroquine Sulphate, piperaquine phosphate, nimesulide, furosemide and allopurinol. There are no highly-sensitizing substances, antibiotics, hormones or other highly hazardous drugs being manufactured at this site.

### ***History of WHO and/or regulatory agency inspections***

This was the first WHO inspection of this site. It had been inspected by the EDQM in 2006 and a CEP had been granted for the production of nimesulide active substance.

### ***Focus of the inspection***

The inspection focused on the production and control of 4 APIs. The inspection covered all the sections of the WHO Good Manufacturing Guidelines for APIs, including:

- 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)

## *Inspected Areas*

### Day 1

After introductions and a brief company presentation, inspectors proceeded to consulting the following documents:

- Product quality reviews for lumefantrine (2009, 2010), artemether (2009, 2010), artesunate (2009, 2010) and amodiaquine HCl (2009, 2010).
- Change control SOP and registers for 2010.
- Batch release SOP.
- Out-of-specifications SOP and registers for 2010.
- Recalls SOP.
- Complaints registers.
- Deviations procedure and examples.
- SOP on corrective and preventive actions.
- SOPs on receipt, handling, storage & issuance of raw materials and packaging materials.
- Sampling procedures.

Areas visited included the warehouses for storage of the starting materials, intermediates and finished APIs, as well as the rejected material store and quarantine area. The storage area for labels was also visited. It is noted that none of the starting materials or intermediates were being refrigerated.

### Day 2

Most of the day was spent visiting Blocks 9 and 10. The state of the facilities and manufacturing/processing equipment of each API's was examined. The HVAC service floors and purified water systems were also visited on this day.

The following SOP's and documents were consulted:

- Vendor Development procedures.
- Vendor questionnaire for supplier of 4-chlorobenzaldehyde
- BMRs for selected batches of APIs and master formula cards.

### Day 3

The following documents were examined throughout the day:

- Process validation report for lumefantrine
- OQ and PQ of rotocone vacuum dryer RV1A-001, Plant 1A.
- Cleaning record forms.
- Purified water and potable water test results (including conductivity, residue on evaporation, TOC, total yeast and moulds, specified organisms for purified water and total aerobic microbial count, total yeast and mould count, specified organisms for potable water along with tests for chlorine, pH, sulfates, etc.).

-Technical agreements with the companies responsible for the calibration of various instruments and of stability chambers as well as technical agreements with a contract laboratory.

The following areas were inspected:

-QC laboratory:

- Raw data for HPLC analyses were examined in association with the audit trail. Modifications after injection were consulted in order to confirm the authenticity of data presented.
- Performance verification and calibration records for HPLC
- Daily verification records for analytical balance.
- Stability chambers.
- Retention samples storage room.

#### Day 4

Inspectors performed a brief visit of unit 2, which covered the QC laboratory, the finished API storage warehouse and the finished powder processing area. The day was ended with the closing meeting.

### **2.1 QUALITY MANAGEMENT**

The quality assurance system was presented. Mangalam Drugs & Organics Ltd., performs manufacturing, testing, packaging and holding of artemether, artesunate, lumefantrine and amodiaquine HCl APIs in accordance with the requirements of the GMP principles at Unit-1. Unit-2 is used for the manufacturing of key starting materials and is also used by the company to manufacture APIs for other markets. A different batch numbering system was used for APIs manufactured at Unit-2 compared to Unit-1.

All changes which directly or indirectly have the potential to affect product quality were reviewed and approved by the quality management department.

Some laboratory tests were also carried out by the quality control laboratory in Unit-2 depending on workload of the QC laboratory at Unit-1 and some were being outsourced.

Internal audits and self-inspections are covered by adequate standard operating procedures. The self inspection plan for 2010 was presented and reviewed.

Product quality reviews were presented for lumefantrine, amodiaquine HCl, artemether and artesunate. These were considered to be acceptable except for issues which have been addressed through the company's corrective actions.

### **2.2 PERSONNEL**

The number of staff and organizational structure were presented and found to be acceptable. Quality control was independent from production. The list of modules of training for year 2011 and the training plan for 2010/2011 were presented.

The training records of a laboratory analyst and of production operator were reviewed. Job descriptions of different management levels (e.g., QA manager, QC manager, production manager, general manager Engineering & Services) were presented and reviewed.

### **2.3 BUILDINGS AND FACILITIES**

Blocks 1D and 1A used to manufacture Lumefantrine, Artemether, Artesunate and Amodiaquine Hydrochloride active substances were inspected. The workshops and the facilities associated were clean and well maintained. The last stages of the process were carried out in clean isolation areas which were equipped with terminal HEPA filters. Issues which had been noted regarding washing areas for dispensing utensils were addressed by the company after the inspection.

The company addressed issues related to the replacement of filters being used in various utility systems (e.g., purified water and compressed air) with corrective actions.

Production Blocks 1D and 1A were equipped with a purified water system with a multi-media filter, carbon filter and a 2 pass reverse osmosis system for purification followed by an electro deionization unit. The potable water was sourced from the GIDC. The purified water circulation was continuous over 24 hours. The system has a production output of 2 tons/hr.

Warehouse and production areas were generally clean.

### **2.4 PROCESS EQUIPMENT**

The process equipment were designed and installed to facilitate containment and logical flow of production. They were regularly cleaned and maintained according to approved procedures and records were maintained. There was a system to indicate the status of the equipment although its implementation needed to be more consistent.

The last stages of the processes were carried out in clean isolation areas with air supplied through terminal HEPA filters. The company did not claim that the areas met class 100,000 and therefore, the observations regarding the clean area were not reported in the present report.

The preventative maintenance schedule of 1D plant was presented.

Calibration of devices (temperature, pressure etc.) was conducted according to the established program. The certificate of calibration of temperature indicator MDOL-1/TI-06 and temperature sensor MDOL-1/TS-06 were checked.

Only the HPLC, FTIR, GC and UV instruments were computerized. These instruments operate with commercially "off the shelf" software running on individual desktop computers.

## **2.5 DOCUMENTATION AND RECORDS**

The company had a documentation system in place consisting of organization charts, SOPs, protocols, records, reports, computer printouts etc. SOPs and specifications for the product existed. Several SOPs were reviewed pertaining to the activities associated with the product processing, cleaning of equipment. All SOPs were covered by a master list.

Equipment cleaning and use records were generally in place. Some discrepancies were however noted such as the missing status of reactor RE1A-106 which was idle. These discrepancies were addressed in the company's proposed corrective and preventive actions.

Records including an approved vendors list (listing general raw materials and key materials respectively) were available. However, some observations were made with regards to the audit of the key material suppliers.

Batch production records, as well as the relevant SOP “Batch Numbering System for API’s” were reviewed and found to be acceptable in general.

Laboratory control records were revised and were found to be acceptable.

## **2.6 MATERIALS MANAGEMENT**

Materials were received and checked prior to storage. On receipt they were quarantined, sampled and tested before acceptance into approved stores for subsequent use. An approved vendors list existed and the company has committed to qualify all vendors of key raw materials.

## **2.7 PRODUCTION AND IN-PROCESS CONTROLS**

Production processes were guided by documented procedures and detailed instructions. Production processes were conducted in non dedicated facilities and with non dedicated equipment. There were in-process controls conducted at appropriate stages of synthesis to monitor the quality of the intermediates and APIs. The processes used were generally similar to those outlined in the dossiers submitted to WHO. Reactors and vessels were capable to carry out or hold reaction mass during reaction and workup. Cleaning procedures were generally validated. Pressure cascades were in place and the AHUs were designed and fitted with H13 filters for supply air. The inspected AHUs were designed with re-circulation of air (85% recycled with 15% fresh air). Some observations were made as to the maintenance of the different AHUs but these were addressed in the company's CAPAs.

## **2.8 PACKAGING AND IDENTIFICATION LABELLING OF APIs AND INTERMEDIATES**

Packaging and labelling operations were conducted as per standard operating procedures. After batch release, the QC person affixed approved labels and handed over the release

intimation to production department. The production department then transferred the material to the warehouse along with a transfer note and the finished product was then dispatched from the warehouse.

## **2.9 STORAGE AND DISTRIBUTION**

Appropriate and separate storage warehouses and areas for starting materials, packaging materials, solvents, intermediates, and finished APIs were available. Conditions of storage were monitored in the appropriate areas. Appropriate records for stock and distribution were maintained.

## **2.10 LABORATORY CONTROLS**

Analytical control records (results) for raw materials were available and were presented for inspection. Source data were verified for testing included test procedures, use logs and instrument registers (e.g., HPLC and Gas chromatography). The thermal chambers and the list of samples in the chambers were verified.

## **2.11 VALIDATION**

The Validation Master Plan, process validation protocols and reports were examined. Validations of processes, analytical methods and equipment qualification were found to be appropriately managed in general except for an issue regarding the validation of the manufacturing process for amodiaquine HCl. The company committed to perform validation of the up-scaled process for amodiaquine HCl on 3 consecutive commercial batches of the same size in their CAPAs.

Major pieces of equipment were qualified as per the written installation and operational qualification protocols. In general, qualification reports were available.

A presentation of the approach to cleaning validation was given by the company and was found to be adequate in general.

Analytical method validation was examined and considered to be acceptable in general.

## **2.12 CHANGE CONTROL**

The procedure for change control was found to be acceptable overall.

## **2.13 REJECTION AND RE-USE OF MATERIALS**

Recovery of solvents and materials at different stages of synthesis was done according to documented instructions and procedures. Solvent recovery was performed on site. The in house recovery processes were validated as part of the process validation. Recovered ethyl acetate was used at final purification of lumefantrine. Ethyl acetate solvent was recovered from mother liquor by reflux and followed by a distillation. Issues were raised recording the

testing of recovered solvents during the inspection. They have been addressed by the company after the inspection.

## **2.14 COMPLAINTS AND RECALLS**

The standard operating procedures for the handling of market complaints and of product recalls, as well as the complaint logbook were verified and found to be acceptable.

## **2.15 CONTRACT MANUFACTURERS (INCLUDING LABORATORIES)**

Deficiencies were raised with regards to the qualification of contract laboratories and manufacturers. The conditions for maintenance of a particular company on the approved vendor list and the approved contract testers list were clarified further to the inspection.

### **Part 3: Conclusion**

Based on the facilities inspected, the personnel 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, Lumefantrine (APIMF100), artemether (APIMF101, APIMF138), artesunate (APIMF135), amodiaquine HCl (APIMF134) APIs manufactured at *Mangalam Drugs & Organics Ltd.* were considered to be manufactured in compliance with WHO Good Manufacturing Practiced 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

The WHOPIR will remain valid for 3 years, provided that the outcome of any inspection conducted during this period is positive.