



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

**Part 1: General information**

|                                                                |                                                                                                                                                  |
|----------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------|
| Name of Manufacturer                                           | Ipca Laboratories Limited                                                                                                                        |
| Unit number                                                    | Ratlam Unit                                                                                                                                      |
| Production Block                                               | IBD-IX, X, XII                                                                                                                                   |
| Physical address                                               | P.O. Sejavta Dist. Ratlam - 457 002<br>Madhya Pradesh<br>India                                                                                   |
| Contact person and email address.                              | Mr. S. K. Darh<br>Sr. General Manager, Quality Assurance<br>sanjay.darh@ipca.com                                                                 |
| Date of inspection                                             | 10-12 September 2012                                                                                                                             |
| Type of inspection                                             | Routine inspection                                                                                                                               |
| Active Pharmaceutical Ingredient(s) included in the inspection | 1. Artemether [APIMF041]<br>2. Artemether [APIMF163]<br>3. Artesunate [APIMF 081]<br>4. Amodiaquine HCl [APIMF030]<br>5. Lumefantrine [APIMF042] |
| Summary of the activities performed by the manufacturer        | Production and quality control of non-sterile APIs                                                                                               |

## **Part 2: Summary**

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

IPCA Laboratories Limited manufactured APIs and intermediates at Ratlam, Indore, Aurangabad, Mahad, Ankleshwar, and hormones at Nandesari sites. The company's headquarter is situated in Mumbai.

There was no significant change in the function of the API manufacturing and support facilities since the last inspection.

There were 21 API manufacturing blocks at Ratlam site. The Artemether and Artesunate were being manufactured at Block XII, Lumefantrine at Block X and Amodiaquine HCl at Block IX.

Amodiaquine HCL has not been manufactured since 2009 even before the last inspection at IPCA Ratlam site.

Other activities conducted on the site out of the inspection scope include,

- Manufacturing of sterile API's,
- Manufacturing of non-sterile and sterile dosage forms,
- Research and development.

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

Since the last WHO inspection performed in November 2010 at the Ratlam facilities, the API manufacturing has been inspected by various authorities, namely:

- CDSCO, West Zone, Mumbai, India (April 2011)
- USFDA (September 2011)
- LAGESO, Berlin, Germany (April 2012)
- Korean FDA (September 2012)

However, none of the above inspections covered the scope of the WHO inspection except CDSCO which is Indian drug authority.

### **Focus of the inspection**

The purpose of the inspection was to ascertain the level of GMP compliance for the manufacture and control of Artemether, Artesunate, Amodiaquine HCl and Lumefantrine API's used in manufacture of oral solid dosage forms in the WHO pre-qualification programme.

### **Inspection program and the areas inspected**

Introductory Meeting

Overview of activities at site

Personnel

- Organization chart
- Job description
- Staff training programme & records

Quality Assurance and Quality Management System

- Product Quality Reviews (PQR)

- Change Control
- Deviations
- Complaints
- Recalls
- Document control
- Self-inspections
- Retention Samples
- Review of batch documents

#### Inspection of Production Operations & Facilities

- Warehousing and storage
- Production operations
- Packaging and labelling operations

#### Quality Control

- In-process sampling and controls
- QC Labs (physic-chemical and microbiology)
- Sampling
- Testing of APIs, RM's and intermediates (IPC)
- Out of Specification investigations
- Reference substance and working standards
- Stability program

#### Validation

- Process validation
- Validation Master plan, protocols

#### Production facility & equipment management

- Purified Water
- Cleaning and cleaning validation
- Qualification and calibration program
- Maintenance program

#### Material Management

#### Post inspection summary meeting

Amongst buildings with different functions and other facilities at the site the following were inspected:

- Plant for Amodiaquine HCL
- Plant for Lumefantrine
- Plant for Artemether and Artesunate
- Finished API product warehouses
- Raw material and packaging material warehouses
- QC laboratory
- Water plant

The internal material code, starting material, and the batch sizes of the inspected APIs were as follows:

## **2.1 QUALITY MANAGEMENT**

### **General**

Quality management systems were established, documented and implemented in general.

The organizational structure, procedures and resources were provided. The QA/QC department was independent from production.

The production and quality control procedures were defined and were followed in general.

### **Product Quality Review**

The SOP on Annual Product Review (APR) and the API PQRs 2011 of Artemether, Artesunate and Lumefantrine were inspected and found to be acceptable in general. The following APR documents were reviewed:

- Annual product quality review of Artemether for 2011, for Process I, APIMF041
- Annual product quality review of Artemether for 2011, for Process II, APIMF163
- Annual product quality review of Artesunate for 2011
- Annual product quality review of Lumefantrine for 2011

### **Deviations**

SOP on handling of deviation (API and intermediates), SOP on handling of planned deviation proposal for API and intermediates were inspected and found to be acceptable.

### **Batch release**

The SOP on batch release were inspected and found to be acceptable.

The manufactured APIs were released by the QA; the records of the batch release were available.

## **2.2 PERSONNEL**

There was adequate number of personnel qualified to perform and supervise the manufacture of intermediates and APIs. The responsibilities of personnel engaged in the manufacture of intermediates and APIs were specified in writing.

The number of personnel working for the site in different areas of the API manufacturing was about 1000.

Training was conducted as per SOPs. Training programme and records were available for inspection.

Job descriptions of following persons were reviewed.

- QA General Manager
- Senior General Manager of API Production
- Assistant General Manager of QA

## **Personnel hygiene**

Sanitation on the site was considered to be acceptable in general. The gowning and changing rules when entering the clean areas were inspected.

## **2.3 BUILDINGS AND FACILITIES**

### **Design and construction**

In general buildings and facilities used in the manufacture of intermediates and APIs were located, designed, and constructed to facilitate appropriate cleaning and maintenance. The manufacturing facilities were not dedicated to the inspected APIs.

The risk of mix-up and cross contamination was mainly mitigated by campaign based manufacturing.

The workshops and the facilities inspected were maintained to be acceptable in general.

### **Containment**

There were no other highly sensitizing materials either produced or handled at this site as far as the inspectors were aware, nor were there any other APIs of high pharmacological activity, such as some steroids or cytotoxic as claimed by the management.

### **HVAC systems**

The environmental conditions in the controlled areas (Centrifuge room, powder processing, micronizing areas) were maintained by means of HVAC (heat, ventilation and air conditioning) and FFAV (filtration and air ventilation without air conditioning) systems. The qualification of the final filters was EU 8.

The following parameters were qualified in the initial qualification protocol and record: pressure difference, air change, air velocity, microbial count (settle plate), and non-viable particles.

The areas were regularly re-qualified (pressure difference: annually, air change: annually, air velocity: annually, microbial count: monthly, non-viable particles: 6 monthly) and monitored (pressure difference). The re-qualification and monitoring records were available. The SOP on re-qualification was reviewed.

Addition to the re-qualification procedure, the air change and particulate test measurements were detailed in specific SOPs.

The system was equipped with different type and function air filters. The filters were regularly cleaned and replaced.

Apart from the periodic filter maintenance, the filters were cleaned at product changeover. The system breakdown during the filter cleaning was recorded in the "Pressure Differential Record".

### **Water system**

The DM water system was inspected and found to be acceptable in general. The DM water was used in the final crystallisation stages of Artemether and for cleaning of the equipment.

## **2.4 PROCESS EQUIPMENT**

The process equipment was of acceptable construction and design. The annual maintenance program was available.

The calibration, qualification and maintenance documents of the reactor SR04 were discussed.

The measuring devices (temperature probe, pressure gauges) connected to the reactor were regularly calibrated according to the annual calibration program.

The temperature probe was calibrated quarterly according to the specified procedure. The calibration records were available.

## **2.5 DOCUMENTATION AND RECORDS**

Documents related to the manufacture of intermediates and APIs were prepared, reviewed, approved and distributed according to SOP on documentation control.

The issued procedures (SOPs) and their IDs were recorded in a logbook, named: “Issue Record of GMP Manual”. The SOPs were distributed for the departments concerned.

Production, control and distribution records were retained for at least one year after expiry date of the batch. Specifications were established and documented for raw material, intermediates, APIs, labelling and packaging materials.

## **2.6 MATERIALS MANAGEMENT**

### **General controls**

The SOP details the raw material receipt and handling procedures.

According to the SOP every incoming batch should be recorded in the GIM (Goods Inward Memo), entered in the SCM (Supply Chain Management) system, sampled, identified by an analytical (AR) number then qualified before usage.

The materials first enter the “Under test/Quarantine” area and will only be transferred to the “Released” or “Rejected” area according to the QC test result.

### **Vendor qualification**

The suppliers/manufacturers of the “active substance starting materials” were qualified, listed and their performance monitored according to SOPs.

The approved supplier list is updated in the IT system (available for the interested staff, like the warehouse supervisor) but the list was printed out only annually.

The qualification and re-qualification documents (“Vendor Approval Docket” and “Vendor Certification”) of the supplier and manufacturer of Artemisinin starting material were discussed.

## 2.7 PRODUCTION AND IN-PROCESS CONTROLS

### Production operations

Production processes were described and recorded by means of master production control records (MPCR).

During the visit in the manufacturing workshops,

- the production operations were in accordance with the manufacturing program provided by the Company at the beginning of the inspection
- the records (filled in MPCR) of the activity performed were available in the workshops.

The MPCR of the Artemether, Artesunate and Lumefantrine were reviewed.

The following manufacturing activities were performed during the inspection at the inspected facilities.

|                    |                                                                 |
|--------------------|-----------------------------------------------------------------|
| Artemether         | milling, drying, reaction, purification, packing                |
| Dihydroartemisinin | reaction, distillation, isolation                               |
| Lumefantrine crude | drying, condensation and centrifuge, distillation and isolation |
| Lumefantrine pure  | drying, distillation and isolation                              |

## 2.8 PACKAGING AND IDENTIFICATION LABELLING OF APIs AND INTERMEDIATES

The procedures for packaging and labelling have not been changed since the last inspection. The practice was inspected during the tour at the manufacturing workshops and the warehouses.

## 2.9 STORAGE AND DISTRIBUTION

The materials were stored in different areas of warehouses.

Underground tank-park: methanol, n-hexane, acetone, cyclohexene, isopropyl-alcohol, toluene.

The solvents were generally transferred from the tank park to the workshops in SS barrels. The exceptions were the methanol and acetone, transferred through fixed pipelines.

Raw materials and packaging materials were stored in the ambient storage room and no control of temperature and/or humidity.

Artemether and its raw material Artemisinin stored in the temperature controlled warehouse to which the temperature was controlled and was recorded daily.

Lumefantrine finished API product was stored in the warehouse with temperature controlled below 25 °C and recorded daily.

## 2.10 LABORATORY CONTROLS

The Quality Control Department was responsible for the chemical, physical and microbiology testing of raw materials, intermediates and APIs as required. The IPC laboratory was located in the separate area with QC department which was also belonging to the QC Department.

The department consisted of 7 laboratories performing chemical and instrumental tests.

The main instruments of the laboratories: HPLC, UV-VIS spectrophotometer, analytical balance, KF titrator, FTIR spectrophotometer, GC, Particle size analyser, Polari meter, pH meter.

The analytical instruments were regularly qualified and maintained by an external partner or a full-time internal expert (engineer) following to written protocols. The qualification and maintenance records of the HPLC were reviewed.

The specifications and analytical test methods for the raw materials, intermediates and APIs were reviewed.

The samples were taken by the QC personnel according to the sampling procedure and recorded in the “API Inward Register” or the “Bulk Drug and RM Inward Register” as applicable.

The sampling, sample distribution records, test records and COAs (certificate of analysis) for the inspected raw materials and solvents e.g. Artemisinin, methanol from the tanker, methanol blended, intermediate (Dihydroartemisinin) and the inspected APIs (Artemether [APIMF041, APIMF163], Artesunate [APIMF 081], Lumefantrine [APIMF042]) were available.

There were CRS and working standard reference materials used. The working standards (from a released commercial batch) were qualified against CRS. The reference materials were stored in a designated refrigerator. The inventory (including usage record) was available.

### Stability monitoring of APIs

A documented, ongoing stability study SOP and register of the stability batches were available for inspection. Stability study was conducted at the conditions:

- Artemether: 25°C±2°C , RH 60% ± 5%
- Artesunate: 25°C±2°C, RH 60% ± 5%.
- Lumefantrine: 30°C±2°C, RH 65% ± 5%.

### Reserve/retention samples

The retention samples were stored in the same packaging as the commercial API batches.

### Handling of out of specification (OOS) results

OOS handling procedure and the investigation of OOS test result was found to be acceptable in general. The OOS register of 2012 was reviewed.

## **2.11 VALIDATION**

The company's validation policy was documented in different corporate and local SOPs and documents:

- Validation Master Plan
- Validation policy
- process validation
- Equipment qualification
- Cleaning validation
- Change control
- Analytical method validation

### **Validation documentation**

The manufacturing process validation documents of the inspected products (Artemether, Artesunate and Lumefantrine) were reviewed and compared to the existing MPCR (master production and batch control records).

### **Cleaning validation**

Cleaning validation was regulated per SOP. The cleaning validation protocol of a reactor and a dryer as well as product change over cleaning validation reports were reviewed.

Cleaning procedure per SOP on complete cleaning of equipment used for processing of active APIs was available for inspection.

### **Change control**

There was a procedure for change control in place (Change control proposal for API and intermediates).

The change control register and records were maintained which have been reviewed.

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

### **Reprocessing and Reworking**

Reprocessing and reworking were performed per SOP.

### **Recovery of materials and solvents**

The company claimed that recovered solvents were used in the same process only.

## **2.13 COMPLAINTS AND RECALLS**

Complaints and recall were recorded and investigated according to a written procedure.

According to the PQR of Artemether there were two product returns recorded in year 2011 and discussed.

The procedure and practice was considered to be acceptable in general.

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

There was no manufacturing or quality control outsourced for third party.

### **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, APIs manufactured at IPCA Laboratories Limited, P.O. Sejavta Dist. Ratlam – 457 002 Madhya Pradesh, 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 3 years, provided that the outcome of any inspection conducted during this period is positive.