



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

Part 1: General information

Name of Manufacturer	Ipca Laboratories Limited
Unit number	Sejavta, Ratlam, API
Production Block	IBD-IX, X, XII
Physical address	P.O. Sejavta Dist. Ratlam - 457 002 Madhya Pradesh India
Contact person and email address.	Mr. S. K. Darh General Manager, Quality Assurance +91 93032 77658 skdarh@ipca.co.in
Date of inspection	30 November – 03 December 2010
Type of inspection	Routine inspection
Active Pharmaceutical Ingredient(s) included in the inspection	1. Artemether [APIMF041] 2. Artesunate [new APIMF 081 - old APIMF009] 3. Amodiaquine HCl [APIMF 030] 4. Lumefantrine [APIMF042]
Summary of the activities performed by the manufacturer	Manufacturing of non sterile API's Other activities (not covered during this inspection): -Manufacturing of sterile APIs. -Manufacturing of non sterile and sterile dosage forms.

Part 2: Summary

General information about the company and site

Ipca manufactures API's and intermediates at Ratlam, Indore, Mahad, Aurangabad, Dombivli, Nandesari and Ankleshwar sites.

The site located at Sejavta Ratlam houses about 18 blocks which are involved in the production of several API's and intermediates. It was originally opened in 1985 and additional units, such as the injectables unit were opened later on.

The company declared that artemether and artesunate were being manufactured at Building XII, lumefantrine at Building X and amodiaquine HCl at Building IX hence the inspection covered only these blocks.

History of WHO and/or regulatory agency inspections

Since 2003, the Ratlam facility has been inspected by various authorities for the manufacturing of API's, namely:

- WHO (Artemether and Artesunate, August 2003)
- USFDA (23 APIs, April 2008)
- EDQM (1 API, Nov. 2004)
- WHO (Artesunate, Artemether and Amodiaquine HCl, Sept. 2006)
- Danish Medicines Agency (30 APIs including Lumefantrine, Apr. 2007)
- Korean FDA (4 APIs, Nov. 2007)
- WHO (Lumefantrine August 2008)
- Lageso, Berlin (Germany) [For Various APIs in Nov. 2010]

Other inspections have also been performed for the manufacturing of finished products (not listed here).

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 tablets and parenteral products that have already been accepted or that are still under assessment in the WHO prequalification programme.

The inspection covered all the sections of WHO GMP guidelines for active pharmaceutical ingredients, including premises, equipment, documentation, materials, validation, sanitation and hygiene, production, quality control and utilities.

Inspected Areas

Day 1

After arrival, inspectors introduced themselves and explained the procedure for inspection in line with the WHO Prequalification Programme, and the tentative inspection plan. Afterwards the company gave a presentation about the company. Inspectors then proceeded to the review of the following documents:

- Annual product quality reviews of artesunate for year 2009, for 2 different grades being manufactured at this site.
- Annual product quality review of artemether for year 2009 (1 grade).
- Annual product quality review of lumefantrine for year 2009 (1 grade).
- Annual product quality review of amodiaquine HCl for year 2009 (1 grade).
- Procedure for "Change Control".
- Summary of returned goods for artesunate, year 2009.
- Procedure for "Deviations".
- Register for critical deviations for 2009 and 2010.
- Procedure for "Out-of-Specifications".
- Procedure for "Recalls".
- Mock recall of 2006.
- Procedure for "Internal audit".
- Internal audit plan for 2009.
- Validation master plan.

Inspectors then proceeded to the visit of the warehouse for storage of raw materials and intermediates, which also included the refrigerated storage rooms for storage of artemisinin, sampling rooms and receiving bays.

Note: several grades of API's were being manufactured at the facility. Recovery of mother liquors was performed on certain grades only of artesunate, which were not being supplied for the manufacturing of WHO prequalified products. This was confirmed through the random selection and examination of batch records as well as recent batch distribution records.

Day 2

After presenting the observations from the previous day, inspectors visited the finished API storage warehouse. The distribution management system was audited. The solvent tank farm was then visited. Various solvent and API (artemether) recovery tanks were also visited.

Inspectors then entered Building XII and examined equipments used for synthesis of artemether, which was being manufactured at the time of inspection. The same reactors/equipment were also used for artesunate (but not being manufactured at the time of inspection). All of the areas, from the preliminary steps to the finishing areas in the adjacent building (PP04 area of Building XII) were inspected.

The demineralized water plant was inspected, then the HVAC of the PP04 powder processing area and the solvent recovery farm. The area for production of compressed air and nitrogen was visited.

The following documents were also reviewed at different times during the day:

- Batch record for dihydroartemisinin synthesis.
- Logbook for reactor SR-09.
- Batch record review for the cleaning of reactor lines.
- Procedure for cleaning of reactors.
- Procedure for gowning to enter centrifuge area for finished product.
- Batch records for a selected batch of artemether.
- Procedure entitled "Cleaning procedure for air filters used in forced filtered air ventilation (FFAV)".
- Procedure for "Bubble point test of vent filter of the water tank".
- Procedure for filter maintenance and use of the vent filters.
- Data in clarification of a deviation that was described to the company in the morning session, regarding an out of specification results observed during stability studies.

Day 3

After presenting the observations from the previous day, inspectors proceeded to the review of the following documents:

- The environmental trend analysis for PPA04 (including particle counts and microbial counts).
- Procedure for "Complete cleaning of equipments used for lumefantrine (pure) at IBD-X".
- Procedure for performing particle counts.
- Procedure for performing microbial counts.
- Certificate of calibration for the particle counter used for environmental analyses.
- Report for the stability of crude lumefantrine.
- Maintenance records for the filter cloth for the agitated nutsch filters 1 and 2.
- Procedure for partial cleaning and complete cleaning of an agitated nutsch filter.
- Procedure for "Vendor qualification approval and certification system for raw materials to be used in the manufacturing of API and intermediates".
- Approved vendor list for raw materials used in the production of artemether, artesunate and lumefantrine.
- Study performed and submitted in the CAPAs for the 2008 inspection, regarding the justification of the exposure time for microbial limits testing plates.
- Training records for 2 members of the staff, one working as an operator in IBD-XII and another one in IBD-IX.

- Maintenance records for the glass-lined reactors and the relevant SOP for the spark test.
- Electronic attendance record for the operator which had filled the pressure differential reading record for IBD-IX.
- Records of maintenance of the tray drier used for lumefantrine.

The following areas were inspected:

- Lumefantrine production building (IBD-X).
- Building for cleaning and storage of HVAC filters.
- HVAC technical floor area for IBD-X.
- HVAC for the lumefantrine process area.
- Amodiaquine HCl production building (IBD-IX).
- Primary packaging material storage area.

Day 4

On arrival, inspectors delivered observations from the previous day and inspected the QC laboratory (chemical and microbiological analyses). This included the following areas:

-Chemical analyses:

- Instrumentation for chemical analyses: HPLC, GC, IR, UV, particle size analyser, balances and associated documents.
- Reference standards and associated documents.
- Analyses for related substances for artemether and loss on drying for lumefantrine.

-Microbiological analyses:

- Instrumentation and micropipettes of the LAL test and associated bench/dedicated room;
- Refrigerator for storage of the standard microbial strains; storage area for glassware; incubators, as well as the relevant associated documents.
- The plates for lots of DM water were verified to be incubated as expected. The registrations of the growth promotion test of the media and test for sensitivity of the LAL reagent and the associated SOPs were verified with their logbooks.
- The washing area of the QC laboratory, which was being used to clean glassware.
- Stability chambers
- Retention sample chamber.

Inspectors then reviewed the following documents and inspected the following areas:

- Calibrations records for selected instruments, such as the 33-35°C incubator and its associated thermometer, the 5µL-50µL micropipette, the thermometer of the drier of lumefantrine, the temperature sensor



for the stability chamber as well as the hygrometer/thermometer which was used to calibrate it.

- The cleaning procedure and controls of its efficacy for the recovery-system tanks for isopropanol and the relevant qualification of the analytical methods which were used for two different APIs.
- Verification of the efficacy of the manual cleaning of the rotacone vacuum dryer.
- Trend of the demineralised water analyses over a period of 6 months for 2 sampling points (the main DM water storage tank and Point No. 10 in the lumefantrine manufacturing area in IBD-X).
- Distribution records for the different grades of amodiaquine, artemether and artesunate which were sold between April 2009 and November 2010.
- Executed batch records for artemether, artesunate (APIMF081 grade) and lumefantrine.
- The current specifications being used by the company were compared to those which have been submitted to the WHO in the APIMF.

After review of the above-mentioned documents, inspectors presented observations and closing meeting conclusions.

2.1 QUALITY MANAGEMENT

The quality management system was satisfactory overall. However, observations were made with regards to the product quality reviews such as the absence of critical raw material trending. Furthermore the management of OOS results was not always accomplished in a satisfactory manner according to one example which had been consulted during this inspection. These issues have been satisfactorily resolved through the company's corrective and preventive actions (CAPAs).

2.2 PERSONNEL

Personnel met during the audit were experienced, skilful, conscientious and wore clothing suitable for manufacturing activities.

2.3 BUILDINGS AND FACILITIES

The design and construction of buildings and facilities was adequate in general except that changeover areas were rather tight and the area for storage and cleaning of the filters required many improvements. Surfaces were not always smooth, with some cracks which did not always permit effective cleaning of the PPA04 powder processing area. The hermiticity of doors also needed improvements as gaps and torn linings had been noted. Repair work was required in the centrifugation room of the artemether / artesunate areas due to leakages observed from the ceiling and the floor which was uneven and damaged. These issues have been satisfactorily addressed by the company's CAPAs.

UTILITIES

HVAC system

Concerns were raised with regards to the degree of environmental control that was provided by the HVAC systems in the final powder processing areas for all APIs which were the subject of this inspection. Namely, active ingredients to be used in the manufacture of dosage forms for parenteral administration should be produced in a manner which ensure minimal presence of endotoxins. Major issues were noted in this regard and have been satisfactorily addressed in the company's CAPAs.

Demineralised and purified water system

The maintenance and general structure and procedures were acceptable, but issues were raised regarding the water tests being performed. These issues have been satisfactorily addressed in the company's CAPAs.

2.4 PROCESS EQUIPMENT

The process equipment was of acceptable construction and design. Its maintenance was found acceptable, apart from the grade of the oil (not a food grade oil) which was being used to lubricate the gears directly in contact with the shafts. The company has explained that there were measures in place in order to prevent contamination with gear oil.

2.5 DOCUMENTATION AND RECORDS

With regards to management and distribution of documentation and records, no significant issues were noted, with the exception of the documentation related to filters and the HVAC system.

2.6 MATERIALS MANAGEMENT

This area was acceptable in general, with the exception of the building for the storage of filters which was deficient. Corrective actions have been brought by the company.

2.7 PRODUCTION AND IN-PROCESS CONTROLS

These activities were found acceptable in general except that cross-contamination and contamination risks were present in some areas (e.g., in the fluconazole powder processing area of building IX, where the door was slightly open while production was ongoing). This issue was corrected in the company's CAPAs.

2.8 PACKAGING AND IDENTIFICATION LABELLING OF APIs AND INTERMEDIATES

This area was found to be acceptable although not inspected in detail with regards to printed label reconciliation.

2.9 STORAGE AND DISTRIBUTION

The activities were found to be acceptable in general with the exception of the area used for storing filters. This issue was corrected by the company.

2.10 LABORATORY CONTROLS

The laboratory controls performed were acceptable overall. Issues were noted with calibration in the chemical laboratory and maintenance in the microbiological laboratory. These were corrected in the company's CAPAs.

2.11 VALIDATION

This area appeared to be acceptable in its most part, with the exception of cleaning validation which was not sufficiently comprehensive in some areas. The company has addressed these issues in their CAPAs.

2.12 CHANGE CONTROL

This area appeared to be acceptable from the perspective of the SOPs being used and the records which were presented.

2.13 REJECTION AND RE-USE OF MATERIALS

The recovery of solvents installations needed maintenance as many pipelines and tanks were rusty, especially the first stage reactors for isopropanol recovery in which the solvent was brown from rust saturation.

2.14 COMPLAINTS AND RECALLS

No complaints had been filled; hence this point could not be assessed. Issues were noted with regards to the follow-up of the recalls procedure.

2.15 CONTRACT MANUFACTURERS (INCLUDING LABORATORIES)

This area was not examined during this inspection.



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, **Ipca Laboratories Limited, Ratlam, Sejavta, India (Production blocks IX, X and XII)** was considered to be operating at an acceptable level of compliance with WHO GMP guidelines for active pharmaceutical ingredients.

All of 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.