

**WHO PUBLIC INSPECTION REPORT
(WHOPIR)
of the API manufacturer**

Part 1: General information about the inspection

Name of manufacturer	IPCA Laboratories Ltd. Indore, India
Physical address: Manufacturing facility and factory office:	Plot No 89A-B/90/91 Industrial Estate, Pologround, Indore, Madhya Pradesh, India
Physical address: Raw material & packaging material warehouse	Plot No F-10 Industrial Estate, Pologround, Indore, Madhya Pradesh, India
Physical address: Solvent & acid storage / bounded storage room & commercial block	Plot No 78/79 & 80 Industrial Estate, Pologround, Indore, Madhya Pradesh, India
Inspected Unit(s)	Production units: Plant No 5 area for synthesis and controlled/clean area, Plant No 1 micronisation
Summary of activities of manufacturer (e.g. manufacturing, packing).	Manufacturing, quality control and batch release of: • Anti-malarial • Anti-histamine • Anti-inflammatory • Anti-fungal Active Pharmaceutical Ingredients (APIs) and intermediates
Active Pharmaceutical Ingredient(s) included in the inspection	Prequalified API APIMF030 Amodiaquine Hydrochloride
Scope and type of inspection	Routine inspection
Date of inspection:	18 - 20 March 2014
Project (if any):	Prequalification Programme

Part 2: Summary

General information about the company and site

IPCA Laboratories Ltd., India has 7 active pharmaceutical ingredient (API) manufacturing sites in India located at:

- Indore
- Ratlam
- Aurangabad (Unit – I)
- Aurangabad (Unit – II)
- Mahad
- Ankeshwar
- Nandesari

The Indore site is specialized in the manufacturing of anti-malarial APIs and “key starting materials”.

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

- Synthesis workshop in Plant No 5
- Powder Processing Area (PPA) in Plant No 5 (controlled/clean area)
- Micronizing Area in Plant No 1 (controlled/clean area)
- Finished product storage room in Plot 79 (across the road);
finished products warehouse at basement level of Pilot plant was not inspected
- Raw material and packaging material warehouse (RM store);
key starting materials (solids produced on site) were also stored in this warehouse;
RM store had sampling and dispensing units which were not entered during the inspection
- Areas for storage of solvents and acids
- AHU supplying air to the Micronizing Area in Plant No 1
- Demineralized water system (DMW), on top floor of building 67
- Quality Control (QC) laboratory

Background information

The total number of employees engaged on the site for Production, Engineering, QC and Quality Assurance (QA), Stores and Distribution were 275 employees.

The site is operational 24 h, in three shifts.

Amodiaquine Hydrochloride API had been manufactured at the site for 25 years.

Product codes related to specific processes of synthesis; for example different solvents and different in-process controls would result in different API product code.

Starting materials (key starting materials) were synthesized on site and stored in raw material store until further use in API production.

Key starting materials and the synthesis point at which API production begins were defined in documents submitted for the WHO Prequalification Programme.

History of WHO or regulatory agencies inspections

The site was previously inspected by WHO inspection team on 26 to 29 March, 2012 and 14-15, 18, September, 2012. The site was also inspected by Central Drugs Standard Control Organization, Government of India. The site was certified against:

- ISO-9001:2008
- ISO-14001:2004
- OSHAS 18001

Focus of the inspection

The inspection focused on the production and control procedures of

- APIMF030 Amodiaquine Hydrochloride

Inspected Areas

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

- Quality management
- Qualification and validation
- Recalls
- Personnel training
- Premises
- Equipment
- Materials
- Documentation
- Production
- Rejection and reuse of materials
- Quality control

2.1 QUALITY MANAGEMENT

In general, a system for managing quality was established. The Quality Unit was independent of production.

Product quality review (PQR)

The SOP “Product quality review” was spot checked. PQRs were prepared annually.

PQRs for 2012 and 2013 were reviewed for APIMF030 Amodiaquine Hydrochloride.

No out of specification (OOS), out of trend (OOT), critical deviations, complaints were reported in the four PQRs reviewed.

Responsibilities – job descriptions

Not covered during this inspection.

Change control (CC)

Change control system was applied to situations where change was intended to be permanent; unplanned temporary changes were managed in the system for deviations. The SOP “Procedure for change control proposal for API and intermediates” and flow chart were checked. Changes were categorized as:

- Minor
- Major

According to the SOP, if CC was not approved within 6 months then an interim letter should be issued by the responsible department. Letter shall state the reason for not approving or rejecting the CC. If CC was not implemented within 6 months of its approval it shall be considered as rejected.

Change control logs/registers for 2012 and 2013 were reviewed.

A specific Change control proposal was checked. This CC was classified as major.

The following documents were checked for the CC in Demineralized water system:

- Design Qualification (DQ) protocol “Water loop system”
- Installation Qualification (IQ) protocol “Water loop system”
- Operation Qualification (OQ) protocol “Water loop system”
- Performance Qualification (PQ) protocol “Demineralized water system”

On random checks, the following instrument calibration certificates were attached to the protocols:

- Digital multimeter
- Digital temperature calibrator
- Digital pressure gauge with pressure comparator

Welder’s certificate was available and presented to the inspectors as well as orbital welding test reports for 10% of the welding points.

Deviations

The SOP “Handling of deviation Active pharmaceutical ingredients and intermediates” was checked. This SOP was applicable for unplanned deviations. Deviations were categorized as:

- Minor – brief excursion from the established procedures not affecting product quality, purity, safety etc.
- Critical – deviation from established procedures / process may affect product quality, purity, safety etc.

The SOP “Handling of planned deviation Active pharmaceutical ingredients and intermediates” was checked. Planned deviations were categorized as:

- Minor
- Major

Deviations were recorded in the following separate logs/registers:

- Unplanned minor deviations
- Unplanned critical deviations
- Planned deviations

Critical deviation investigation report was checked

Management review

The SOP “Quality review (QR)” was checked. Quality review was performed by the site Management review committee consisting of members of Technical committee and Change control committee. According to the SOP, QR meetings should be held at least once per year.

Corrective action and preventive action (CAPA)

The SOP GMP/IND/82/2009, “Corrective and Preventive actions (CAPA)” was checked.

The procedure was applicable for:

- Non-conformances
- Deviations
- OOS
- OOT
- Market complaints
- Audit observations

Risk assessment (RA)

The SOP “Guideline for Quality Risk Assessment” (QRA) was checked. The SOP was applicable for:

- Product development
- Facilities
- Process
- Material
- Laboratory control
- Packaging/labelling
- Distribution of drug substances

QRA was categorized as:

- Planned RA
- Unplanned RA

For Failure mode and effects analysis (FMEA) 1-5 scoring system was used to specify severity, occurrence and detection. QRA register for 2013 and 2014 was spot checked.

Responsibilities of the quality and production units

Not covered during this inspection.

Internal audits (self-inspection)

Not covered during this inspection.

In addition to scheduled audits, the Company exercised a system of un-notified visits (“inspections”) to operation areas, “covering activities from receipt of materials to dispatch of finished APIs” - as described in the relevant SOP. Findings from such visits were documented as “non-conformances”. A separate SOP and log was applicable. This topic was discussed briefly and verbally, not going into the content.

Supplier approval

Not covered during this inspection.

Vendors were managed on the corporate level. The site conducted testing of received materials.

2.2 PERSONNEL

Personnel qualifications

There was an adequate number of personnel qualified, trained and experienced to perform and supervise the manufacture of intermediates and APIs.

Training

The SOP “Analyst certification” was checked. Analysts were qualified by analysing a previously tested and known sample. Sample was coded.

The following certifications of specific analysts were checked:

- Chemical analysis (liquid Ammonia for description, solubility, density and assay)
- Physical analysis (Hydroxy Chloroquine Sulfate for residual solvents: toluene, methanol and isopropyl alcohol)
- Impurities and related substances

Personnel hygiene

During the inspection, no special attention was paid to personnel hygiene. Spot checks showed that personnel were wearing adequate protective clothing.

Consultants

N/A

2.3 BUILDINGS AND FACILITIES

Design and construction

“Controlled rooms” / “powder processing areas” (clean areas with associated heating, ventilation and air conditioning (HVAC) systems and filtered air supply) used in the final stages of production and in finishing of APIs were located, designed, and constructed to facilitate cleaning, maintenance and operations as appropriate to the type and stage of manufacture. “Controlled rooms” had adequate space for the orderly placement of equipment and materials. Pressure differentials between different production rooms were monitored. Change room doors were interlocked.

Utilities

HVAC

Air to the “controlled areas” was supplied via several AHUs. The company stated that air in the controlled areas was not recirculated. This was evidenced when inspecting AHU supplying air to the micronising area.

Air was supplied via filter cascade.

Pressure differentials were monitored between EU6 and EU7 filters (in AHU). Filters were cleaned once in two weeks and changed upon requirement. Filtered compressed air and potable and DM water were used for filter cleaning; cleaning was carried out in a separate room.

Dust collectors were used (not inspected).

Demineralized (DM) Water system

Over the last two years, the proposed changes had been implemented in the DM Water system. Related qualifications and validations had been completed with positive conclusions.

DM Water trends for the sampling point located at the beginning of the loop were checked. Action and alert limits were established.

Sanitization procedures for the DM Water generation system were checked.

Gases

The site produced Nitrogen and compressed air; these operations were not inspected.

Containment

As stated by the company, highly active or sensitizing materials were not manufactured on site.

Lighting

On spot checks lighting was adequate.

Sewage and refuse

Not covered during this inspection.

Sanitation and maintenance

During the inspection, no special attention was paid to sanitization and maintenance of the premises. On spot checks sanitization and maintenance of “Controlled areas” was found to be adequate.

2.4 PROCESS EQUIPMENT

Design and construction

Equipment used in the manufacture of finished APIs was of adequate size, and suitably located for its intended use. Major equipment such as reactors and centrifuges used during

the production of an intermediate or API were appropriately identified. All equipment was multipurpose. In Plant 5, within current production arrangements, this actually meant that two APIs were produced using Plant 5 equipment – Amodiaquine HCl.

Preventive maintenance

Not covered during this inspection.

Cleaning

Not covered during this inspection.

Calibration

Not covered during this inspection.

Equipment qualification

Not covered during this inspection.

Laboratory equipment calibration

The following analytical instruments were checked regarding usage and calibration:

- Karl Fisher titrator
- Analytical balances
- High-performance liquid chromatography (HPLC)
- Gas chromatography (GC)
- Infrared spectroscopy (IR)
- Melting point

Standards, standard solutions, chemical reference standards (RS) used for calibration of the mentioned equipment were traceable.

Laboratory equipment maintenance was carried out yearly by contractors.

2.5 DOCUMENTATION AND RECORDS

Documentation system and specifications

Documents related to the manufacture of intermediates and APIs were prepared, reviewed, and approved. Specifications were established and documented for raw materials, key starting materials, intermediates and finished API. Acceptance criteria were established and documented for in-process controls.

Equipment cleaning and use records

Spot checked records were adequate.

Records of raw materials, intermediates, API labeling and packaging materials

The SOP “Receipt, storage and issue of material at plot 80 Godown” was checked.

Master production instructions (MPI)

Master production instructions had been established and appropriately approved.

Batch numbering system

The SOP “Batch numbering of products (Active pharmaceutical ingredients and intermediates)” was checked.

Batch production records

Batch production and packaging records were called “Batch production and control record” (BPCR).

Laboratory records

The handling of dry chemicals and reference standards as well as the preparation of solutions and working standards was done according to approved procedures.

Control of laboratory test results

A check list for the verification of the QC reports was used. The QC report verification was done by QA.

Batch production record review/batch release procedure

The SOP “Batch release (Active pharmaceutical ingredients and intermediates)” was checked. The following documents were audited before the batch release:

- Batch production and control records (BPCR)
- Analytical records

The SOP “Batch record audit (Active pharmaceutical ingredients and intermediates)” was spot checked. Quality Assurance Executive / Quality Assurance officer or the authorized nominees were responsible for BPCRs audit. Audit was carried out using check list.

Electronic data

On random checks on HPLC programmes, audit trail functions were activated; date and time functions were locked. The company stated that manual integration was not used; on random checks manual integrations had not been used. The company stated that integration parameters were entered into HPLC projects by “method developer” and that analysts did not have access rights to change the parameters. The latter was confirmed for a test which was presently running on one of the HPLCs.

Computerized systems

Processes were controlled manually.

The “Analytical data backup of HPLC” was checked. The similar SOPs were available for the following equipment:

- UV spectrometer
- IR
- GC
- Total organic carbon analyser (TOC)
- Particle size analyser

The specified back-up frequency was once a day and once in six months back up for retrieval of data. Back-up data was saved in the same server where original data was stored. The company explained that in near future a separate server with Chromaline software will be purchased.

2.6 MATERIALS MANAGEMENT

Materials were categorised as following:

- Starting material / key starting material
- Critical raw material
- Other material
- Solvents

A common warehouse was used for storage of raw materials, starting materials and primary packaging materials.

Solvents were stored in over ground tanks (located in the main area) or underground tanks (across the road).

Toluene and methanol were dispensed for Plants 3 and 5 by volume, pumped from underground tanks into drums and transported to the Plants.

Acids Hydrochloric acid and Phosphoric acid were handled in the similar manner, pumped from tanks (across the road) into drums. Acids were charged into Plant 5 reactors by pumps located outside of the building.

Supply Chain Management system (SCM) was used for materials management and inventory control. SCM was managed and maintained on the corporate level. There were separate sampling and dispensing rooms in the RM warehouse. Rejected materials were stored separately in a locked location. Products under quarantine were stored separately in a marked area.

2.7 PRODUCTION AND IN-PROCESS CONTROLS

Production operations

Stainless steel (SS) and glass lined (GSL) reactors were used for production. The production process mainly was carried out in closed systems.

Some operations required handling of valves located in different areas; as understood by inspectors, valves did not have unique identification numbers. This topic was not followed further during the inspection. Critical process parameters were marked in BPCRs, yields were established.

In-process sampling (IPC) and controls

IPC tests were carried out in the quality control laboratory. IPC samples were taken by production personnel.

Blending batches of intermediates or APIs

The SOP “Blending of Active pharmaceutical ingredients” was checked.

2.8 PACKAGING AND IDENTIFICATION LABELLING OF APIs AND INTERMEDIATES

Not covered during this inspection.

2.9 STORAGE AND DISTRIBUTION

Warehousing procedures

As stated by the company, solvents were delivered in dedicated transport tankers. Samples of solvents were taken from transport tankers and released for filling into storage tanks after QC release. After mixing fresh solvent with the remaining solvents in the storage tanks samples were taken, analyzed and released by QC

Receipt and quarantine

Materials were held under quarantine until they were sampled, tested and released for use. Separate room was provided for storage of rejected starting materials.

Sampling and testing of incoming production materials

Containers from which samples were withdrawn were marked to indicate that a sample has been taken.

Distribution procedures

APIs were released for sale after QA approval.

2.10 LABORATORY CONTROLS

Procedures describing sampling, testing, approval or rejection of materials and recording and storage of laboratory data were available. Laboratory records were maintained. Specifications were established for APIs and intermediates.

Specifications included testing of impurities - organic impurities and residual solvents.

Reference standards

Working Standards (WS) and Reference Standards (RS) were available. WS were qualified against chemical RS if existing. If chemical RS were not available WS were prepared from selected API batches. WS were dispensed under LAF which was located the microbiological laboratory and used for microbial tests (MB). WS were dispensed in amber glass bottles. One bottle of WS was intended for use within 2 months. Usage of standards was documented.

Traceability of standards was ensured.

Out of specification (OOS) results, out of trend results (OOT), Incidents

Separate procedures had been written for OOS and for OOT. Both were applicable also to stability studies. OOT concept was only applied to finish APIs which were considered as produced by validated processes or which were established in a pharmacopoeia.

Separate procedure was applicable to microbiology testing, out-of-alert and out-of-action limits were established.

Several separate OOS logs were kept; 2013 logs for:

- API
 - Stability
 - Intermediate and in-process
- were spot checked.

Incident logs from 2013 and 2014 were reviewed. 2013 logbooks (two for the full year) included all incidents.

Microbiological Testing

Not covered during this inspection.

Testing of intermediates and APIs

Laboratory tests were performed for intermediates in the QCL.

Certificates of analysis

Certificates of analysis (CoA) were issued for each batch of API.

Stability monitoring of APIs

Not inspected in detail during this inspection.

Samples for stability testing were adequately packed and stored.

Expiry and retest dating

The SOP “Assignment of expiry date / retest date of Active pharmaceutical ingredients and intermediates” was checked.

The SOP “Manufacturing dates for Active pharmaceutical ingredients and intermediates” was checked. For regular API batch or intermediate the month and year in which the final stage of purification was commenced was considered as Mfg date. For blended batches the month and year in which the oldest batch was manufactured was considered as Mfd date.

Reserve/retention samples

Retention samples were stored under lock and key. Access to the storage room was controlled. Temperature (T) was recorded once per day.

2.11 VALIDATION

Validation Master Plan

Validation Master Plan was checked. According to the VMP.

Qualification

Not covered during this inspection.

Cleaning validation

The SOP “Cleaning validation Active Pharmaceutical Ingredients” was checked. Cleaning validation was carried out starting from the final stage (purification stage).

Two types of cleaning were applied:

- Batch to batch
- Product to product cleaning

Monitoring for product to product cleaning (campaign production, at the end of campaign) was carried out as:

- Visually clean
- Chemical rinse (residue of active substance; the company stated that specifications were available for each product and each equipment)

Established acceptance criteria was based on maximum allowable carryover (MACO) calculations which was the maximum quantity of previous drug substance allowed in the next drug substance. The following criteria were used for MACO calculations:

- 10 ppm
- Therapeutic Daily Dose (TDD)

Swab and rinse samples were collected for cleaning validation. Chemical and microbiological analysis was undertaken for 3 continuous batches. Swab recovery studies were carried out (80 - 120%).

Validation of analytical methods

“Analytical method validation data part for Amodiaquine HCl” protocol and report were spot checked.

1.12 REJECTION AND RE-USE OF MATERIALS

Rejection

Intermediates and APIs failing to meet established specifications were rejected. Reprocessing and reworking were applied.

Reprocessing and reworking

The SOP “Reprocessing / reworking policy (Active pharmaceutical ingredients and intermediates)” was checked. Reprocessing and reworking register for 2013 and 2014 was checked. 2 batches had been reprocessed in 2013 and 1 in 2014 till the date of inspection.

Recovery of materials and solvents

The SOP “Movement of fresh and distilled solvents in Plant No 05” was checked. According to the SOP mother liquor shall be distilled as per BPCR. Distilled solvent shall be used in the next batch of the same product & stage. E.g. toluene and methanol were recovered „during processes” as stated by the company.

Returns and rejects

Not covered during this inspection.

Waste management

Not covered during this inspection.

1.13 COMPLAINTS AND RECALLS

The SOP “Recall of API and Intermediaries” was spot checked. This was corporate level SOP and was applicable for all IPCA manufacturing sites. Recalls were classified as:

- Class – I
- Class – II
- Class – III

According to the SOP the effectiveness of the system of recall should be evaluated at least once in 5 years. Last Mock recall was carried out on August 2011 from Ratlam site. APIs and intermediates from all IPCA manufacturing sites were transferred to the central warehouse, located in Mumbai.

1.14 CONTRACT MANUFACTURERS (INCLUDING LABORATORIES)

Production activities were not contracted out. Inspectors were told that analytical testing was not contracted out for WHO products.

Part 3: Conclusion

Based on the areas inspected, the people met and the documents reviewed, and considering the findings of the inspection listed in the Inspection Report IPCA Laboratories Ltd. Indore, India, Plant No 5 located at 89A-B/90/91, Pologround, Indore, Madhya Pradesh, India was considered to be compliant with WHO GMPs for Active Pharmaceutical Ingredients published by WHO for the scope of activities listed below:

Manufacture and packaging of Active Pharmaceutical Ingredient

- APIMF030 Amodiaquine Hydrochloride

All the non-compliances observed during the inspection that were listed in the full report 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.