

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

**Part 1: General information**

Name of Manufacturer	Cipla Ltd
Plot number	Unit I & II
Production Block	Plot II
Physical address	Plot No A-33 & A-42 MIDC Patalganga, 410 220 District Raigad, (Maharashtra) India
Contact person and email address.	Mr Anjani Kumar, Site Head, Patalganga E-mail: anjanikumar@cipla.com
Date of inspection	14 - 17 Feb 2011
Type of inspection	Routine inspection
Active Pharmaceutical Ingredient(s) included in the inspection	Lamivudine Artemether Artesunate Moxifloxacin Hydrochloride Lumefantrine
Summary of the activities performed by the manufacturer	Manufacturer of Active Pharmaceutical Ingredients (non-sterile - anti-malaria and anti-viral)

## **Part 2: Summary**

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

Cipla Limited is a public limited company established in 1935 and managed by a professional board of directors. It manufactures and markets a wide range of pharmaceutical formulations and active pharmaceutical ingredients.

The manufacturing facility at Patalganga was commissioned on Plot - I in 1984 and facilities were available for both APIs and Finished Formulations. The facility under the same local management was extended in the year 2006 on Plot - II to have APIs and Formulations manufacturing to meet current production requirements. It was noted that Unit II (or Plot II) was an export oriented unit (EOU) and all WHO APIs products were manufactured at Unit II.

Cipla Ltd has eight manufacturing facilities located at Bangalore, Patalganga, Kurkumbh, Goa, Baddi, Bommasandra, Sikkim and Indore throughout in India.

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

Cipla Limited had been inspected and approved by various regulatory bodies for APIs.

The WHO had inspected this API facility in May 2008.

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

This was a routine inspection of Cipla's API facility located at Patalganga. The inspection focused on the production and control of APIs. The inspection covered most of the sections of WHO Good Manufacturing Practices for Active Pharmaceutical Ingredients, Annex 2 (TRS, 957, 2010) including quality management, personnel, building and facilities, process equipment, documentation and records, materials management, production and in-process controls, storage and distribution, laboratory controls, validation, change control, complaints and recalls.

### ***Inspected Areas***

- Quality management systems including organization chart, job responsibilities, internal audits (self-inspection) and product quality review.
- Production including various process steps and in-process
- Laboratory controls including microbiology lab
- Air handling units
- Water system
- Validation master plan
- Change controls
- Warehouse / store
- Documentation

## 2.1 QUALITY MANAGEMENT

Cipla Ltd had an appropriate quality assurance system in place for the manufacture of active pharmaceutical ingredients (APIs). Cipla Ltd performed manufacturing of APIs and intermediates as per the WHO GMP standard for Active Pharmaceutical Ingredients. The corporate quality assurance department (based in Mumbai) provided support on the quality system and standard operating procedures for all of their manufacturing activities. The SOPs on Self inspection (CQA 54 / 14), Product Quality Review (CQA 97 / 17) and others were reviewed.

## 2.2 PERSONNEL

There were adequate numbers of personnel working on the site. The personnel were appropriately qualified, experienced and trained in their respective areas. The organization chart provided with the site master file was reviewed and found ambiguous. The API production manager directly reported to site manager instead of unit head as currently practiced.

The job descriptions of key personnel were reviewed; however there was some ambiguity noted.

- Job description of Head of Unit II (Formulations) didn't specify responsibility of API operations as presented in the organization chart. As per the job description, Head of unit II was responsible for formulations and not for APIs operations.
- Head Production API reported directly to Facility Manager as per the organization chart instead of Unit Head as currently being practiced by the company.
- The job description of the QA Head for Plot II didn't delegate responsibility to the QC Manager, should QA Head Plot II be away from the office. This was contrary to the job description of the QC Manager which stated that QC Manager was responsible for QA operations in Unit QA Head's absence.

## 2.3 BUILDINGS AND FACILITIES

The manufacturing facility was generally found clean and well maintained. The APIs were manufactured based on gravity concept where by starting materials were supplied /dispensed from the top floor (level 3) and final finished product was produced at the ground floor. It was noted that last stages of the manufacturing processes (essentially drying, sieving and milling operations) were carried out in clean areas (class 100,000 or ISO 8) which were supplied with air through an HVAC system that was equipped with terminal HEPA filters (0,3 µm).

There were altogether 12 AHUs installed / in-use for API production. Some of the AHUs were common for few activities such as common AHU for milling and rotacone vacuum dryer (ERCVD) room.

Cleaning of filters was adequate. The pressure differential across filter banks was found satisfactory.

It was noted that buildings used in the manufacture of intermediates and APIs were not properly maintained, repaired and kept in a clean condition in a few places. There were few examples noted during on-site inspection:

- Broken tile was also seen underneath the centrifuge and drain was found unclean.
- Cleaning of compartments in the warehouse was not adequate and dust was seen.

## **2.4 PROCESS EQUIPMENT**

The process equipment was of acceptable construction and design and was found clean and suitably maintained. Also, equipment was adequately identified with unique numbers. Logbooks for each piece of equipment and instruments were maintained.

The calibration range for some of the key process equipment such as thermometers and pressure gauges was not appropriately covered around the target range.

## **2.5 DOCUMENTATION AND RECORDS**

With regards to the management and distribution of documentation and records, no significant issues were noted during the inspection. Cipla Ltd had a reasonably good system of documentation in place and SOPs for production processes, calibration, cleaning, maintenance and laboratory were available and maintained up to date.

The site master file of Cipla Ltd for APIs was found ambiguous; in that it wasn't clear which APIs were manufactured at Unit I or Unit II.

## **2.6 MATERIALS MANAGEMENT**

Material management, in general, was acceptable. Materials were received and checked prior to storage. The sampling plan was based on the statistical method for all materials. The identification test on each container of starting materials was not conducted; instead identification on a composite sample was carried out. The instruction on blending of various containers to form a composite sample was available, however not adequately clear.

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

These activities were found acceptable in general. Production activities were done on a campaign basis followed by a cleaning. For each API, different pieces of equipment that were used were identified. The cleaning procedures were available and were detailed enough. Two levels of cleaning (same product or product change over) for each equipment were available.

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

This area was found to be acceptable although not inspected in detail except for printing of labels and their reconciliation.

## **2.9 STORAGE AND DISTRIBUTION**

The activities were found to be acceptable in general.

## **2.10 LABORATORY CONTROLS**

The laboratory controls performed were acceptable in general. However, calibration was deficient in some areas. Maintenance was adequate in the chemical as well as in microbiological laboratory. In addition, there were some issues noted on the access rights given to reviewer for HPLC analysis.

## **2.11 VALIDATION**

This area appeared to be acceptable in general, with the exception of cleaning method validation which was performed on combination product instead of single API.

## **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**

It was noted that the recovery of solvents for an API was not carried out for those batches which were supplied to WHO. However a column for recording recovered solvents is provided for in the Process data sheet.

## **2.14 COMPLAINTS AND RECALLS**

SOP on Complaints was reviewed and found acceptable in general. However, timeline for handling serious complaints were set to 15 working days which appeared to be more than usual timeline set for serious complaints.

SOP on Recall was reviewed and found acceptable in general. It was noted that the dummy recall though done for FPP was not carried out for APIs to ensure effectiveness of recall procedure and its associated management.

## 2.15 CONTRACT MANUFACTURERS (INCLUDING LABORATORIES)

This area was not covered in great detail during this inspection. However, it was noted that there were no manufacturing activities or process steps contracted out to any other manufacturer. Some of the laboratory tests were outsourced to outside laboratories.

### 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, **Cipla Ltd, Patalganga II (API site)** was considered to be operating at an acceptable level of compliance with WHO GMP guidelines.

The manufacturer responded to all observations listed in the inspection report in a satisfactory manner.