

WHO PUBLIC INSPECTION REPORT (WHOPIR)

Finished Product Manufacturer

Part 1: General information

Name of Manufacturer	Cipla Ltd
Plot number	A-42
Production Block	Unit II
Physical address	MIDC Patalganga 410 220 District Raigad, Maharashtra, India
Contact address	Mr Anjani Kumar, Site Head E-mail: anjanikumar@cipla.com
Date of inspection	21 - 24 February 2011
Type of inspection	Routine GMP inspection
Dosage forms(s) included in the inspection	Tablets
WHO product categories covered by the inspection	<ul style="list-style-type: none"> ○ TB 224 & TB 225 (Ofloxacin Tablets) ○ HA 488(Abacavir sulfate 60mg) ○ HA267 Triomune 30 (Lamivudine, Stavudine and Nevirapine) Tablets ○ HA303 (Lamivudine/stavudine 150/30mg tablet) ○ MA064 (Lumartem: Artemether and Lumefantrine tablets 20/120mg) ○ HA371 (Abacavir Sulfate Tablets 300mg)
Summary of the activities performed by the manufacturer	Manufacturer of Finished product formulations

Part 2: Summary

General information about the company and site

Cipla Limited is a public limited company established in 1935 and managed by a 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.

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

The Patalganga site is located in an industrial park at a distance of 80 km from Mumbai. There are separate blocks for manufacture of pharmaceutical formulations and Active Pharmaceutical Ingredients.

The following products were manufactured on site:

- Uncoated and film coated tablets
- Non-sterile ointments, creams and gels
- Nasal sprays
- APIs and drug intermediates

History of WHO and/or regulatory agency inspections

The Patalganga site was previously inspected by WHO on 9 - 12 August 2010.

Focus of the inspection

The inspection focused on the production and control of finished pharmaceutical products including bio-waiver applications (TB 224 and TB 225) for Ofloxacin 200mg and 400mg tablets. The inspection plan for the four day inspection was as followed:

Day 1	
Morning	<p>Opening meeting</p> <ul style="list-style-type: none"> • Introductions • Attendance Record • Confirmation of scope of inspection and inspection plan • Company overview and presentation (about 15 minutes) • Summary of manufacturing processes and product range • Changes since last inspection and proposed changes.
	<p>Personnel</p> <ul style="list-style-type: none"> • Organization Chart

	<ul style="list-style-type: none"> • Job descriptions for key personnel • Training procedures and records
Afternoon	<p>Quality Management</p> <ul style="list-style-type: none"> • Product Quality Review • Quality Risk Management • Complaints • Recalls • Deviation control • Change control • Contract agreements • Supplier approval • Document Control • Self inspection
	Summary of the observations of the day

Day 2		
Morning	<p>Quality Control Laboratory</p> <p>Organization and management</p> <ul style="list-style-type: none"> • Quality management system • Personnel, training and assessment • Premises • Sampling and sample handling • Work allocation <p>Documentation:</p> <ul style="list-style-type: none"> • Specifications and test methods • SOPs, logbooks, records • Worksheets and test reports • Contract testing • Stability program • OOS results • Analytical method validation • Evaluation of results, release and rejection procedures • Trending of results • Traceability <p>Materials:</p> <ul style="list-style-type: none"> • Chemicals and reagents • Reference standards • Retention samples <p>Equipment, instruments and devices</p> <ul style="list-style-type: none"> • Operation and maintenance • Calibration and qualification 	
	Lunch	
Afternoon	<p>Microbiology Laboratory</p> <ul style="list-style-type: none"> • Personnel • Premises, environment • Equipment • Reagents and culture media, preparation and control • Reference materials and reference cultures 	

	<ul style="list-style-type: none"> • Sample handling • Purified Water monitoring • Environmental monitoring • Testing of materials and finished product • Disposal of waste 	
	Summary of observations for the day	

Day 3		
Morning	<p>Quality Control Continued</p> <ul style="list-style-type: none"> • Dissolution data including comparative dissolution <p>Engineering & Services and utilities such as HVAC and water:</p> <ul style="list-style-type: none"> • Preventive Maintenance • Calibration 	
Afternoon	<p>Buildings and Facilities</p> <ul style="list-style-type: none"> • Design and construction • Site layout • Personnel and material flow <p>Warehouse(s)</p> <ul style="list-style-type: none"> • Storage – quarantine, release, reject • Materials • Receipt, handling and storage • Identification • Sampling • Status Control • Weighing/dispensing/issuing • Temperature (and humidity) monitoring • Packaging materials • Finished Products and distribution 	
	Summary of observations for the day	

Day 4		
Morning	<p>Production</p> <ul style="list-style-type: none"> • Batch document preparation • Production area • Packaging • Cleaning • Finished product release • Batch record review 	
Afternoon	<p>Validation and qualification:</p> <ul style="list-style-type: none"> • Validation Master Plan • Validation and qualification status (matrix) and schedule • Equipment qualification • Process validation • Cleaning validation • Computer validation 	
	Summary of observations for the day	
	Summary by inspectors (closed meeting)	
	Closing meeting with company representatives	

Inspected Areas

- Organization chart
- Training
- Product quality review
- Complaints
- Recalls
- Deviation control
- Change control
- Supplier qualification
- Self inspection
- Document control
- Laboratory controls
- Production controls
- HVAC system
- Water system

2.1 QUALITY ASSURANCE

Quality management systems were generally well implemented and maintained.

The quality assurance system of Cipla Patalganga covered all the manufacturing activities on site. The quality assurance system implemented and met, in general, the requirements of WHO GMP. QA personnel were strongly involved in all the production and quality control activities. The company had a good line clearance system for different production steps. The quality system was designed to reduce the risk of mix-ups and cross-contamination.

QA department and QC laboratory were independent from production and both reported to the management of the company. Reporting system was following QC Manager reports to the Unit QA Manager who reports to the Corporate QA Manager who in turn reports to the Joint Managing Director.

The production and quality control procedures were clearly specified, different procedures (SOPs) were described in detail and were followed by personnel.

Managerial responsibilities were specified in job descriptions. Necessary controls and calibrations were carried out. Products were released for sale after certification by QA head. Batch release procedure required checks of batch manufacturing and packaging protocols and laboratory records.

2.2 GOOD MANUFACTURING PRACTICES (GMPs) FOR PHARMACEUTICAL PRODUCTS

There were no systematic problems seen in relation to GMP. For detailed observations in this area see below. Manufacturing processes were clearly defined and reviewed.

Qualification and validation was performed. Products were stored and distributed in traceable way.

2.3 SANITATION AND HYGIENE

Hygiene program covered personnel, equipment, materials and premises. During the inspection, major problems in relation to sanitation and hygiene at the site were not observed, however some observations were made.

2.4 QUALIFICATION AND VALIDATION

Few aspects were verified and generally found acceptable.

2.5 COMPLAINTS

Complaints were handled properly.

2.6 PRODUCT RECALLS

SOP on recalls was in place. No recalls had taken place.

2.7 CONTRACT PRODUCTION AND ANALYSIS

Contract production and analysis were not reviewed during the inspection.

2.8 SELF INSPECTION AND QUALITY AUDIT

Self inspection was performed routinely, twice per year according to a written procedure. Reports were prepared and corrective actions were required. Proposed corrective actions were reviewed and approved. Implementation of corrective actions was controlled.

2.9 PERSONNEL

The personnel met during the audit were experienced, skillful and conscientious.

Personnel were adequate in number and well trained to carry out the task assigned. However, personnel receiving training should be supervised until they were trained in their respective areas.

2.10 TRAINING

Training was done according to an annual schedule.

Persons engaged in manufacturing and QC operations had received comprehensive initial training (induction programme) and “on the job” training covering their operational

duties and GMP. Effectiveness of training was examined by written exam, but there was need to effectively monitor compliance with the policy on pass mark and retraining.

2.11 PERSONAL HYGIENE

Personnel hygiene was found to be satisfactory.

2.12 PREMISES

Premises were generally well designed and well maintained.

2.13 EQUIPMENT

Equipment were well designed, installed and well maintained. Maintenance of use logbooks should be tightened.

2.14 MATERIALS

The flow of materials and movements were found generally adequate.

Materials were managed in the electronic Inventory Management System IMS.

2.15 DOCUMENTATION

Cipla has many corporate documents in place.

Generally, documentation system was found adequate. However, specifications needs to be adequately controlled.

2.16 GOOD PRACTICES IN PRODUCTION

Temperature and relative humidity in the production rooms were manually controlled.

The general design of the facilities was appropriate.

Processes were generally under control. Tablet manufacturing activities were inspected and in general found to be satisfactory.

The production practices were generally acceptable, however operators were required to update the logbooks at the time of operation.

2.17 GOOD PRACTICES IN QUALITY CONTROL

Adequate facilities, personnel and approved procedures were available. Records of analysis were checked during the 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, Cipla Ltd, Patalganga II (FPP) 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.