

WHO PUBLIC INSPECTION REPORT Finished Product Manufacturer

**WHO PUBLIC INSPECTION REPORT
(WHOPIR)
Finished Product Manufacturer**

Part 1: General information

Name of Manufacturer	Cipla Ltd
Unit number	Unit I & IV
Production Block	General tablet block (Unit IV) and oral liquids (Unit I)
Physical address	Plot No 9, 10 & 15, Pharma Zone, Phase II, Sector III, Indore Special Economic Zone, Pithampur, Dist: Dhar, Madhya Pradesh – 454 775, India
Contact address	Mr Davinder Singh, Technical Director dsingh@cipla.com Mr Sanjay Gorana, Site Head, Cipla Pithampur sanjaygorana@cipla.com
Date of inspection	13, 14, 15 and 16 October 2014
Type of inspection	Routine GMP inspection
Dosage forms(s) included in the inspection	Solid and liquid dosage forms (tablets, oral liquids- solutions and suspensions)
WHO product categories covered by the inspection	<u>Prequalified products</u> 1. HA053: Lamivudine 50mg/5ml oral solution 2. HA200: Nevirapine oral suspension 50mg/5ml 3. HA382: Abacavir oral solution 20mg/ml 4. HA365: Lamivudine/Nevirapine/Zidovudine tablets 150/200/300mg 5. MA064: Artemether/Lumefantrine tablets 20/120mg 6. HA060: Lamivudine/Zidovudine tablets 150/300mg 7. HA052: Zidovudine capsules 100mg 8. HA054: Zidovudine oral solution 50mg/5ml <u>Under Assessment:</u> Artemether /Lumefantrine Dispersible Tablet (20mg/120mg)
Summary of the activities performed by the manufacturer	Production and control of finished pharmaceutical products

Part 2: Summary

General information about the company and site

Cipla Ltd 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 (APIs). The corporate headquarters including corporate quality assurance (CQA) is located in Mumbai.

The company has eight manufacturing sites in India:

- Bangalore - Pharmaceutical formulations , APIs and Natural Products
- Patalganga - Pharmaceutical formulations and APIs
- Kurkumbh - Pharmaceutical formulations and APIs
- Goa - Pharmaceutical formulations
- Baddi - Pharmaceutical formulations
- Sikkim - Pharmaceutical formulations
- Bommasandra - APIs
- **Indore SEZ- Pithampur - Pharmaceutical formulations**

The manufacturing site of **Cipla Ltd, Indore SEZ** located in **Pithampur**, District Dhar, India, was inspected by the WHO prequalification inspection team on the above mentioned dates. Cipla Ltd, India, Indore SEZ is located on Plot 9, 10 and 15 of the Indore SEZ Phase II, Pithampur District Dhar in Madhya Pradesh (MP), India. The operations were commenced from April 2010. The site had four units which manufactures following dosage forms/products:

- Unit I: Form Filled and Sealed (FFS) Eye Drops, Liquid Orals, Large Volume Parenteral (LVP), Respiratory solution / suspension, Unit dose ophthalmic products
- Unit II: Aerosol--Metered Dose Inhalers
- Unit III: Pre-filled syringes (PFS), Nasal Sprays, 3 Piece Eye Drops
- Unit IV: Coated /Uncoated tablets, effervescent tablets, hard gelatin capsules, powders / granules and pellets

According to the presentation, the site employees approximately 1583 staff, and the operations are mainly carried out in two shifts, if required then operations are extended to third shift.

History of WHO and/or regulatory agency inspections

This was the third WHO inspection of Cipla Pithampur site. The site had been previously inspected by WHO in year 2010 and 2011. From the opening meeting presentation, it was noted that the site is being inspected regularly by the USFDA, UKMHRA, CDSCO India, TGA Australia, MCC South Africa etc.

Focus of the inspection

The inspection focused on the production and control of prequalified products listed under Part 1. The inspection covered most of the sections of the WHO GMP text, including premises, equipment, documentation, materials, validation, sanitation and hygiene, production, quality control and utilities.

Inspected Areas

Day 1, 13th October 2014

- Introductions
- Site presentation
- Update on WHO inspection process
- Product quality review (PQR) procedure
- PQR of Artemether and Lumefantrine tablets (Lumartem)
- Complaints
- Product recalls
- Quality risk management
- The site organogram and organograms for Units I and IV
- Job descriptions of Key personnel for both Unit I and IV
- Training
- Sanitation and Personal Hygiene and Medical Checks
- Batch release

Day 2, 14th October 2014

- Feedback on day 1 observations
- Review of floor plan of Unit IV for ground floor
- Review of floor layout of ground floor and mezzanine and first floor of Unit I manufacturing area for the oral liquids
- Inspection of Raw material receiving area Units I and IV
- Inspection of inventory management system (IMS) for inventory of incoming materials
- CQA/S-17 SOP on receipt of materials
- Raw material creation application (RMCA) for creation of new material code and supplier list
- Feedback provided on day 2 observations

Day 3, 15th October 2014

After giving a summary of the observations seen and areas inspected during day 2, inspectors inspected production and the quality control laboratory in parallel.

- Clarification provided on outstanding issues from Unit I and Unit IV

- Inspectors proceeded to Unit I & IV for the inspection of production and laboratory sections

Day 4, 16th October 2014

- Feedback provided on day 3 observations
- Inspection of Building Management System (BMS)
- Inspection of laboratory
- Review of cleaning validation
- Review of validation and verification of analytical methods
- Review of computerised system validation
- Inspection of the water system
- Review of Deviation and Change Control
- Review of Preventive maintenance
- Review of vendor evaluation and qualification
- Meeting among inspectors
- Exit meeting with the site management

2.1 QUALITY ASSURANCE

The quality management system was generally well established and an adequate organizational structure, standard operating procedures and related resources. Quality assurance was independent from production and adequately fulfilled its functions in the most part. Managerial responsibilities were well defined and specified in signed job descriptions.

The observations raised from this section have been satisfactorily addressed, and it will be verified during future inspections.

2.2 GOOD MANUFACTURING PRACTICES (GMPs) FOR PHARMACEUTICAL PRODUCTS

Good manufacturing practices were adequately implemented in general. The necessary resources were provided. Manufacturing processes were defined and reviewed. Qualification and validation was performed. Operators were trained to adequately carry out the prescribed procedures, and generally adequate records were made during manufacture.

The manufacturing facility of Unit I and Unit IV was found to be clean, tidy and spacious.

The observations raised from this section have been satisfactorily addressed, and it will be verified during future inspections.

2.3 SANITATION AND HYGIENE

Adequate procedures and facilities were established for sanitation and hygiene. There were cleaning SOPs for different areas and equipment, and access to production and quality control areas were restricted. There were gowning procedures available upon entry and exit from controlled areas.

The observations raised from this section have been satisfactorily addressed, and it will be verified during future inspections.

2.4 QUALIFICATION AND VALIDATION

Protocols and reports were in place for qualification and validation. A Validation Master Plan existed. Protocols and reports pertaining to cleaning validation and computer system validation inspected were generally acceptable and evidence of improvement over the years was evident.

The company identified what qualification and validation work was required. Documentary evidence was available that the premises, supporting utilities, equipment and processes have been designed, installed, operated in accordance with their design specifications.

2.5 COMPLAINTS

The procedure for handling product complaints was available for inspection. One of the complaints was reviewed and investigation was done in accordance with their procedure. A six monthly trend was prepared and found to satisfactory.

2.6 PRODUCT RECALLS

The written procedure to recall products from the market was available for inspection. There was no recall reported for the products inspected.

2.7 CONTRACT PRODUCTION AND ANALYSIS

This area was not inspected due to time constraints.

2.8 SELF INSPECTION AND QUALITY AUDIT

Self-inspection was carried out in accordance to their procedure once every six month. A schedule for year 2014 was available. In general, this area was found to be adequate.

2.9 PERSONNEL

The manufacturer had an adequate number of personnel with the necessary qualifications and practical experience. Responsible staffs, specific duties were recorded in written job descriptions. Personnel were aware of the principles of GMP and received initial and continuing training, including hygiene instructions, relevant to their needs. An organization chart was available - and was appropriate.

Job descriptions for selected positions as well as training records were reviewed. A large number of key people had extensive experience and had been working at the company for a long time. They had appropriate qualifications.

2.10 TRAINING

Training was provided in accordance with a written programme for all personnel whose duties take them into manufacturing areas or into control laboratories. Training records were kept. Records for Analyst qualification and verification were in place for review.

The observations raised from this section have been satisfactorily addressed, and it will be verified during future inspections.

2.11 PERSONAL HYGIENE

Entry changing and washing/hand sanitization followed a written procedure. Direct contact was avoided between the operator's hands and starting materials, primary packaging materials and intermediate or bulk product.

2.12 PREMISES

The premises were clean and well maintained. There was general uni-directional flow of man and materials. The floors and walls were smooth and in good condition. The floors were curved and had trolley guards in the production areas. All electrical fixtures, supply grills and return risers were flush with the walls. The production area was kept such that there was minimal exposure of product to the environment as it was essentially a closed system.

The toilets and canteen areas were separate from the production and quality control areas. The change rooms for gowning were adequate and had the relevant gowning procedures available and gowning material.

The sampling and dispensary areas had the necessary reverse laminar airflow (RLAF) booths. There was a separate dispensing booth for API and excipients and a separate area which had an LAF for the dispensing of sugar. The environmental conditions were monitored by Building Management System.

The observations raised from this section have been satisfactorily addressed, and it will be verified during future inspections.

2.13 EQUIPMENT

Process equipment was installed and maintained in a way that minimizes risk of contamination and cross contamination. Production equipment was identified as to its content or purpose and cleanliness status by label.

A qualification/calibration and preventive maintenance program as well as cleaning procedures for critical manufacturing equipment were in place and followed.

Water system was qualified and monitored according the written procedure.

Preventive maintenance of equipment in Unit I was done according to a schedule. There was a master schedule which was developed yearly in December for the upcoming year. This schedule was based on monthly, quarterly and six monthly schedules of preventive maintenance and each equipment had a corresponding log where the maintenance exercise was recorded. This was also reviewed by QA monthly.

2.14 MATERIALS

Incoming materials were purchased from approved suppliers, sampled and tested according to specifications and testing procedure. Printed packaging materials were stored in secured conditions.

2.15 DOCUMENTATION

In general documents were well designed, comprehensive, and prepared, reviewed and distributed with care. Documents were approved, signed and dated by the appropriate responsible persons. Documents were regularly reviewed and kept up to date. Records were made or completed when any action was taken. Many procedures are corporate with others being based upon a corporate template with local implementation criteria included.

2.16 GOOD PRACTICES IN PRODUCTION

The inspected finished dosage form facilities Unit I and IV are multi-product facilities. Good practices were followed in all areas of production. Production operations followed clearly defined procedures in accordance with manufacturing and marketing authorizations, with the objective of obtaining products of the requisite quality.

Deviation instructions and procedures were comprehensive and the examples chosen for review by the inspectors adequately handled and had been performed in accordance with the approved procedure.

Validated manufacturing procedures were followed in general. The temperature, relative humidity and air pressure differentials were monitored according to written procedures.

Before packaging operations begun, steps were taken to ensure that the work area, packaging line, printing machine and other equipment were clean and free from any products, materials or documents used previously according to the procedure. The line clearance was performed and recorded in BPR. Production records were reviewed as part of the approval process of batch release.

The observations raised from this section have been satisfactorily addressed, and it will be verified during future inspections.

2.17 GOOD PRACTICES IN QUALITY CONTROL

The QC function was independent of other departments. Adequate resources were available to ensure that all the QC arrangements are effectively and reliably carried out. Samples of starting materials, packaging materials, intermediate products, bulk products and finished products were taken by approved methods.

Tests followed the instructions given in the relevant written test procedure. The result was checked by the QC supervisor before the material or product was released. Out-of-specification results and out of trend results obtained during testing of materials or products were investigated in accordance with an approved procedure. Records were maintained.

The quality and stability of finished pharmaceutical product were evaluated. Expiry dates and shelf-life specifications were established on the basis of stability tests related to storage conditions. A written programme for ongoing stability determination was developed and implemented.

The observations raised from this section have been satisfactorily addressed, and it will be verified during future inspections.

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, **Cipla Limited, Unit I & IV, Plot No 9, 10 & 15, Pithampur, India** was considered to be operating at an acceptable level of compliance with WHO GMP guidelines.

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.