

WHO PUBLIC INSPECTION REPORT

(WHOPIR)

Finished Product Manufacturer

Part 1: General information about the inspection

Name of manufacturer	Cipla Ltd
Physical address	Plot No. A - 33, MIDC, Patalganga, Plot I (Unit I), 410 220 Dist. Raigad Maharashtra India
Postal address	As above
Telephone number	+91 2192 250811/250822/304200
Fax number	+91 2192 250819/253536
Summary of all the activities performed by the manufacturer Dosage forms and type of products	Manufacture and distribution of : <ul style="list-style-type: none"> Non-sterile medicinal products: uncoated and film coated tablets, ointments, creams, gels and nasal sprays. Manufacture of <ul style="list-style-type: none"> Active Pharmaceutical Ingredients (APIs) and drug intermediates
Scope and type of inspection	Routine GMP inspection
Pharmaceutical dosage forms	Dispersible tablets, coated and uncoated tablets, creams
Focus of inspection - products in WHO PQ program covered in the scope at the time of inspection with the WHO reference number	Prequalified products: HA40 Aciclovir 200 mg dispersible tablet HA45 Aciclovir 400 mg dispersible tablet HA46 Aciclovir 800 mg dispersible tablet HA48 Aciclovir 5 % cream HA267 Lamivudine/stavudine/nevirapine 150/30/200 mg tablet HA 303 Lamivudine/stavudine 150/30 mg tablet HA 304 Lamivudine/stavudine 150/40 mg tablet 150/40/200 mg tablet HA371

	Abacavir 300 mg tablet MA47 Artesunate/Amodiaquine 50/200 mg tablet MA64 Artemether/Lumefantrine 20/120 mg tablet
Date of inspection:	9 - 12 August 2010
Programme	Prequalification of Medicines Programme

Part 2: Summary

Background information

The manufacturing site of Cipla Ltd, Plot I No A-33 (hereafter referred to as Unit I) located in Patalganga Maharashtra, India was inspected by a WHO prequalification inspection team on the above mentioned dates.

Cipla Ltd is a public limited company, founded in 1935. The company has seven manufacturing sites in India:

- Bangalore - Pharmaceutical formulations and APIs
- Patalganga - Pharmaceutical formulations and APIs
- Kurkumbh - Pharmaceutical formulations and APIs
- Goa - Pharmaceutical formulations
- Baddi - Pharmaceutical formulations
- Sikkim - Pharmaceutical formulations
- Bommasandra - APIs
- Indore - Pharmaceutical formulations

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

Operations at this Patalganga site commenced in 1984. At the time of the inspection Unit I employed approximately 833 employees, approximately 406 of which worked in pharmaceutical manufacturing activities, approximately 174 in QC and approximately 59 in QA.

History of WHO or regulatory agencies inspections

The Patalganga site was previously inspected by WHO on 26, 29, 30 October 2007.

Unit I Formulation facility has been approved by various organizations such as:

- TGA Australia
- ANVISA Brazil
- MCC South Africa
- MHRA UK
- NDA Egypt
- NDA Ethiopia
- Ministry of Health Tanzania)

- NDA Uganda
- NDA Ukraine
- NDA Slovak Republic
- NDA Czech Republic
- NDA Health Canada
- NDA Kingdom of Saudi Arabia
- NDA Sultanate of Oman
- US FDA

Focus of the inspection

The purpose of the inspection was to ascertain the level of GMP compliance for the manufacture of tablets. At the time of the inspection no production of topicals was conducted in Unit I. The emphasis was paid to the products under assessment.

The areas inspected included:

- Receiving areas (raw materials and packaging materials)
- Storage areas for starting and packaging materials
- Sampling and dispensing areas
- Production areas related to WHO products, including areas for sieving, granulation, blending, compression, packaging
- Quality control laboratory (chemical, stability testing, microbiological laboratory)
- Quality assurance and documentation
- HVAC

Documents reviewed included (but not limited to):

- Quality Risk Management
- Batch records
- Deviations
- Complaints
- Product Quality Review
- Training plans and records
- Various SOPs
- Calibration and qualification procedures and records
- Stability testing

General information

Cipla has many corporate documents, for more details see the previous report.

2.1. Quality Assurance (QA)

A quality assurance system generally was implemented and maintained.

Product release was the responsibility of the QA manager (Authorized person), hierarchically independent from production. The QC Head was designated to deputize the QA manager for product release. For more details see the previous report.

Change Control

Change control was described in a written SOP and flow chart. Changes were classified. A number of change control cases were reviewed and found to be acceptably managed.

Deviation management

Deviation management was described in a written SOP and flow chart. Deviations were classified. A number of deviations were reviewed and found to be acceptably managed.

Product Quality Review (PQR)

PQRs for two anti-malaria kits were reviewed.

Quality risk management (ORM)

SOP Risk management was reviewed and found to be acceptable.

SOP was applicable to equipment, facilities and manufacturing operations which are likely to affect the product of process and for investigating the root causes of product complaints, OOS, deviations or problems.

QRM approach flow charts for process and equipment were available. QRM was found to be appropriately performed.

2.2. Good manufacturing Practices for Pharmaceutical products

Good manufacturing practices were implemented and generally maintained.

Necessary resources were generally provided, including qualified and trained personnel, adequate premises and space, suitable equipment and services, appropriate materials, containers and labels, approved procedures and instructions, suitable storage, adequate personnel, laboratories and equipment for in-process controls.

Manufacturing steps were recorded in batch manufacturing and packaging records; records were made during manufacture.

Instructions and procedures were generally written in clear and unambiguous language.

Qualification and validation were performed.

2.3 Sanitation and Hygiene

The topic was not specifically covered during the inspection; no notable concerns were identified during the inspection. Production personnel hygiene was monitored by taking swabs from operators' hands.

2.4 Qualification and Validation

The key elements of the qualification and validation program were defined and documented in Validation Master Plan (VMP). Re-validation/re-qualification periods were specified.

Process validation

Process validation report including Batch Manufacturing Records (BMR) and Batch Packaging records (BPR) were available and were inspected in brief. Critical manufacturing steps were defined, analytical raw data was available, was spot-checked and found to be acceptable.

Compressed air validation

Validation studies were performed annually for all user points. Validation report was reviewed and found to be acceptable, raw data was available.

Cleaning validation

The "worst case scenario" and 10 ppm approach was applied for the cleaning validation studies. Swab and rinse samples were collected for the analysis. Equipment drawings indicating the sampling positions were available. All equipment parts which were in direct contact with the product were taken into account for total area calculations. Cleaning verification was carried out annually.

Specific product cleaning validation report was briefly reviewed, attention was paid to the total area calculations. Swab recovery studies were carried out.

Cleaning validation of garments was carried out. Re-validation report was reviewed during the inspection. Swab samples were taken for analysis. Re-validation was performed annually for one garment set.

2.5. Complaints

For general information see the previous report.
Complaints were trended.

2.6 Product Recalls

- Recall procedure was reviewed. Responsible person for the recall was Corporate QA. Corporate QA afterwards informed Unit QA. Recalls were classified. There were several levels of recalls:
 - Wholesaler level
 - Retail level
 - Consumer level

Mock recall was carried out once in two years on the corporate level.

2.7 Contract production and analysis

Manufacturing activities were not contracted out. Based on the contracts, some products were manufactured for other companies.

Some outside analytical laboratories were used for a few specific tests than can not be carried out at the site.

Contract laboratories were audited regularly. Laboratory audit SOP and schedule were available. Laboratories were re-audited after two years.

2.8 Self inspection and Quality Audits

This topic was not covered during the inspection. For general information see the previous report.

Supplier audit and approval. Vendor qualification

SOP + flow chart was available for inspection. SOP was applicable for starting material (raw material, packaging material) manufacturers.

API, sterile packaging material, primary packaging material and printed packaging material manufacturers were to be audited before procurement.

Audits were performed by audit teams, according to the check list format.

Manufacturers of APIs used in WHO products had been audited. Audit and re-audit schedule and audit reports were available. Re-audit was carried out every 3 years.

Audit reports were available for inspection. Reviewed audit report was found to be acceptable.

Approved suppliers lists were available from the Inventory Management System.

2.9 Personnel

In general, the personnel met and interviewed during the inspection were experienced, skilled and conscientious.

2.10 Training

For general information see the previous report.

Several training files were reviewed and found to be comprehensive. Training effectiveness was evaluated by objective and subjective questions.

SOPs, training files and records, as well as classroom training files and records were stored in the QA department.

2.11 Personal Hygiene

Direct contact was avoided between operators' hands and starting materials, primary packaging materials and intermediate or bulk product. All changing rooms were provided with photographs which described the gowning procedures.

2.12 Premises

For general information see the previous report.

"Painting" SOP and schedule was reviewed and found to be acceptable. The SOP was applicable for the buildings.

Separate SOP "PM of building" and schedule also was reviewed and found to be acceptable. On spot checks schedule was followed.

Ventilation

According to the company, there had been no changes in the ventilation system design since the previous inspection. Latest re-qualifications of AHU (sifting) and AHU (compression II) were spot-checked. No remarks.

2.13 Equipment

For general information see the previous report.

Production equipment was in good condition.

SOP Preventive Maintenance (PM) + schedule was available for inspections. This SOP was also applicable to production equipment. On spot checks the PM schedule was followed.

PM performance SOPs and checklists were available for all equipment.

2.14 Materials

For general information see the previous report

Materials were managed in the electronic Inventory Management System IMS.

API suppliers used in the manufacture of WHO products were according to the submitted dossiers.

Temperature (T) mapping and RH distribution study for packing material stores, was reviewed. T mapping and RH distribution study was found to be acceptable.

Upon receipt, materials were checked against purchase orders. Starting materials were sampled 100% for identity tests and labeled with "sampled" labels.

Packaging materials sampling was carried out in accordance with Acceptable Quality Level (AQL). Pharmacodes were provided for printed paper/carton materials and were used for on-line identity checking during packaging runs, except for materials intended for manual packaging.

2.15 Documentation

In general, the documentation system was established and maintained; documents were approved, signed and dated by appropriate responsible persons, regularly reviewed and kept up to date. Alterations made to documents were signed and dated. Specifications and testing procedures were available.

Specific product BMR and BPR were reviewed. On spot-checks process parameters were in correlation with validation data.

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.

Punches and dies, sieves and finger bags were properly managed. FBD finger bags were dedicated for each product.

In-process products holding times were specified.

IPQC room was provided with instruments for controlling compression parameters such as thickness and hardness, disintegration and friability.

Primary and secondary packaging

Tablet packaging activities were inspected and in general found to be satisfactory.

2.17 Good practice in Quality Control

Adequate facilities, personnel and approved procedures were available. Records of analysis were checked. During inspection particular attention was paid to the Dissolution apparatus and HPLC apparatus, analyst training and qualification and Out of Specification (OOS) investigations.

Latest calibration of a dissolution apparatus was inspected and found to correspond to the established calibration procedures.

HPLC

Mobile phases were freshly prepared and not reused. Mobile phase was sonicated for 2-3 minutes. Columns were dedicated for each product/material and for each different type of test. Columns were not regenerated. Disposable vials were used for analysis.

Latest calibration of an HPLC apparatus was inspected and found to correspond to the established calibration procedures.

Reagents and mobile phases were appropriately labeled and stored. Expiry dates were specified for reagents.

KBr used for identity tests was dried before use.

OOS

A number of OOS investigation reports were reviewed. OOS investigations were found to be comprehensive.

Analyst certification and qualification

Analysts competency list was available.

A number of analyst certification and validation records were reviewed and found to be comprehensive. Analyst qualification involved practical evaluation where comparative tests on the same sample were conducted by the new analyst and an experienced analyst.

Stability studies

A number of on stability and going stability studies were reviewed.

Analytical raw data used for stability studies (HPLC) were spot-checked and found to be acceptable.

Reference substances

Reference and working standards were managed appropriately and stored under controlled conditions.

Microbiology

Application of the harmonized method for total viable counts, non sterile products was checked. According to the company explanation, validation had been performed for new products and was in progress for old products.

Media sterilization, growth promotion checks, water monitoring and microorganism identification was inspected. No remarks.

Part 3: Conclusion

Based on the areas inspected, the people met and the documents reviewed, and considering the findings of the inspection, reflected in the observations listed in the

inspection report, Cipla Ltd, located in Patalganga, District-Raigad Maharashtra India, Unit I, was considered to be operating in compliance with WHO GMP.

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.