

## WHO PUBLIC INSPECTION REPORT

### (WHOPIR)

#### Finished Product Manufacturer

#### Part 1: General information about the inspection

Name of manufacturer	Cipla Ltd
Physical address	Plot D7, D-22, MIDC Industrial Area, Kurkumbh 413 802, District Pune, Maharashtra, India
Postal address	Mumbai Central Mumbai 400 008 India P.O. Box India
Telephone number	+(91 2117) 235231/235234/235381/235383
Fax number	+(91 2117) 235232
Summary of all the activities performed by the manufacturer (e.g. manufacturing, packing).  Indicate dosage forms and type of products (e.g. tablets; penicillin or cephalosporin containing products)	Manufacture and distribution of : - non-sterile medicinal products (solid dosage forms: tablets (uncoated, film-coated, enteric coated, chewable, effervescent), hard and soft gelatin capsules, suppositories and enteric coated pellets, effervescent granules. - Active Pharmaceutical Ingredients (APIs)
Scope of inspection	Routine GMP inspection
Date of inspection	16 - 19 September 2009
Programme	Prequalification of Medicines Programme

## **Part 2: Summary**

The manufacturing site of Cipla Ltd. located in Kurkumbh, Maharashtra, India, was inspected by a WHO prequalification inspection team on 16 - 19 September 2009.

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

The Cipla Ltd Corporate headquarters are located at Mumbai Central. Senior qualified corporate personnel from Mumbai were available for providing support to the manufacturing plants in the areas of Technology, Research & Development, Production, Quality Control and Quality Assurance.

Cipla Ltd is a public limited company which was founded in 1935. The company has seven manufacturing facilities in India.

- Patalganga
- Kurkumbh
- Bangalore
- Goa
- Baddi
- Sikkim
- Bommasandra

First three sites produces pharmaceutical formulations and Active Pharmaceutical Ingredients (APIs), next three sites produces only pharmaceutical formulations and last site produce only APIs.

The Kurkumbh site is located in an industrial park at distance of 250 km from Mumbai and 70 km from Pune. The total area of the site is 160.000 m<sup>2</sup>. There are separate blocks for manufacture of pharmaceutical formulations and Active Pharmaceutical Ingredients.

The Kurkumbh site commenced operations in 1994. At the time of the inspection the Kurkumbh site employed approximately 1130 employees, approximately 573 of which worked in pharmaceutical manufacturing activities, approximately 238 worked in QC and approximately 89 worked in QA.

### *History of WHO or regulatory agencies inspections*

The Kurkumbh site was previously inspected by WHO (Geneva - prequalification programme) in October 2007.

The site has also been inspected by MHRA in January 2008, TGA in March 2008 and US FDA in March 2009.

### *Focus of the inspection*

The purpose of the inspection was to ascertain the level of GMP compliance for the manufacture of tablets, hard gelatine and soft gelatine capsules in the company's Pharma I and Pharma II manufacturing facilities. Tablets, hard gelatine capsules and soft gelatine capsules manufactured at the site are provided for the treatment of HIV/AIDS and are in the WHO prequalification list.

### *Areas inspected*

Areas listed below, and associated documents (SOP's, log books, batch records, validation and qualification protocols and reports) were inspected as follows:

- **Day 1 :**

The inspection started with the opening meeting with the company executives in the conference room. Following self introductions and exchange of business cards, the inspectors explained the objectives of the inspection, procedures for WHO Prequalification Programme, the procedures and standards used for inspection. The tentative inspection plan was discussed and confirmed. The company made a presentation about Cipla and the site to be inspected. The presentation highlighted the capacities, Quality Management System, inspection history of the site and highlighted the changes made since the previous inspection.

Various documents were reviewed such as:

- Layout of the site
- Organigram
- Quality Manual
- Change control SOP
- Different change control forms
- Lists of all products manufactured, with their marketing destination
- SOP for Annual Report
- Annual report for Forcan-150 (year 2008)
- Stability studies for particular product

After lunch, the inspectors reviewed several documents e.g.:

- SOP for Out Of Specification results ("OOS")
- Laboratory Investigation report, related to an OOS result on HPLC testing for particular product

During the afternoon, the inspectors started the Plant tour, going first to Building Pharma I, which was dedicated to Formulation, Quality Control, Sampling, Dispensing, Tablets and capsules manufacturing and Warehouse. They went to:

- Receiving zone for Raw Materials



- Rejected Material Store
- Quarantine Storage Room
- Cold Storage Room
- Sampling Rooms for excipients, and for active ingredients
- Dispensing Rooms
- Primary Packaging Components Storage Room
- Rejected Packaging Materials Storage Room
- Labels and Leaflets Storage Room
- Packaging Material testing Lab

- **Day 2 :**

The inspectors started with a summary of the previous day's observations. Then the inspectors reviewed various documents, such as:

- Item Codes Lists for the APIs used in all the Cipla Plants

Then the inspectors made the tour to the manufacturing facilities, including:

- Dispensing Material Store
- Hoist for Dispensed Material
- Sifting Area
- Spare Part Rooms (for punches and dyes)
- Granulation Room
- Blending Room
- Tablet Press Room
- IPQC Room
- Wash Room
- Capsules Filling Room
- Coating Room
- Packing Hall

In the afternoon, the inspectors made the tour of Building Pharma II, which was dedicated to Soft Gelatine Capsules manufacturing, including:

- Shell Manufacturing
- Blend Manufacturing
- IPQC Room
- Drying Area
- Degreasing Area
- Inspection Area
- Packaging Hall
- Suppository Filling Area

Then the inspectors reviewed various documents, such as:

- Design Qualification, Installation/Operational/Performances Qualifications for specific AHU, dedicated to the ventilation of the dispensing of active ingredients



- SOP for Sanitation and Upkeep of premises
- Validation Reports for HVACs located in Building Pharma I
- SOP for Preventive Maintenance of specific AHU "
- SOP "Purified Water Generation, Storage and Distribution System of Pharma I"
- Water Sampling and Analysis Schedule
- SOP for Water Sampling
- SOP "Equipment Operation of Purified Water Generation, storage and distribution loop System"
- Change Control Form, related to the installation of the distribution loop in Building Pharma I
- IQ, OQ and PQ for the re-qualification of the Purified Water Storage Tank and the Distribution Loop System
- IQ, OQ and PQ for the re-qualification of the SEPTRON System
- IQ, OQ and PQ for the re-qualification of the Ultra-filtration System
  
- The last part of for Granulation Room
- Purified Water Plant Room

- **Day 3 :**

The inspectors started with a summary of the previous day's observations.

Then the inspectors made the tour of the Quality Control Laboratory, including chemical, microbiological areas, as well as stability chambers. This tour took the whole morning.

After lunch, the inspectors reviewed various documents, such as:

- Trend Analysis for the quality of Purified Water, in Building Pharma I and Building Pharma II (covering years 2008 and 2009)
- General SOP for Cleaning of Glassware
- Cleaning Validation Protocol (for cleaning of Glassware in the washing machine) Cleaning Validation Report (for the cleaning of the Glassware in the washing machine)
- Cleaning Validation Protocol (for manual cleaning of the Glassware)
- Cleaning Validation Report (for manual cleaning of the Glassware)
- Batch Manufacturing Record for specific product
- Analytical Test Report for the Batch of specific product
- SOP "Equipment Operation Metal Detector"
- Batch Manufacturing Record for specific product
- Batch Packaging Record for the same Batch of specific product.

- **Day 4:**

The inspectors started with a summary of the previous day's observations.

Then the inspectors the inspectors reviewed various documents, such as:

- TSE Certificate for sourcing of Gelatine used in the manufacturing of Soft Gelatine Capsules
- List of personnel authorized to accept/reject and release the batches of Raw Materials, Bulks, Packaging Components and Finished Products
- Validation Master Plan for 2009
- Validation Protocol and Report for Compression of specific Tablets
- Validation Protocol and Report for Lubrication of Granules
- Validation Protocol and Report for Coating of Tablets
- Validation Report for Lubrication of Tablets
- Validation Protocols and Reports for the Manufacturing Process of specific products

At the end of the day closing meeting with company representatives was held and inspection observations were presented.

## 2.1. QUALITY ASSURANCE

A Quality Management System was in place and appeared correctly maintained. The quality assurance system of Cipla Kurkumbh covered all the manufacturing activities on site. The quality assurance system implemented and met, in general, the requirements of WHO GMP. The quality assurance system covers all the relevant activities performed in the site. 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 risks of mix-ups and cross-contamination.

The 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 → Unit QA Manager reports → Corporate QA Manager reports → 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.

A formal system for deviation management was described in a written procedure.

A formal system for change control was described in a written procedure. Some examples of changes were reviewed.

The manufacturing and laboratory equipment were suited for their intended purpose.

Annual product review was done for all products.

## 2.2 GOOD MANUFACTURING PRACTICES FOR PHARMACEUTICAL PRODUCTS

There were no systematic problems seen in relation to GMP. Manufacturing processes were clearly defined and reviewed. Qualification and validation was performed. Products were stored and distributed in a traceable way.

## 2.3 SANITATION AND HYGIENE

A hygiene program covered personnel, premises, equipment, materials and premises.

It was noted that the company demonstrated re-training logs, with the date of the inspection day, for a number of people regarding hygiene and handling of cleaning aids.

## 2.4 QUALIFICATION AND VALIDATION

The Validation Master Plan presented was a comprehensive corporate document. Re-validation periods for HVAC, water systems, compressed air, cleaning, process, analytical methods, and equipment were defined and followed. Several validation reports, as mentioned above, were reviewed during inspection and validations were considered to be appropriately performed.

## 2.5 COMPLAINTS

Complaints were handled by QA head. Complaint records were regularly reviewed. Complaints trend analyses were performed every 6 months

## 2.6 PRODUCT RECALLS

A system for product recall was in place. Recalls were handled by corporate QA head. The recall SOP was reviewed and considered to be very comprehensive. The SOP described procedure how to inform competent authorities of all countries where product has been distributed. Recalled products could be stored in a segregated secure area.

## 2.7 CONTRACT PRODUCTION AND ANALYSIS

No manufacturing was contracted out. Contract laboratories were used for some tests. Contract laboratories were scheduled to be audited once per year by corporate QA staff. Audit reports were maintained.

## 2.8 SELF INSPECTION AND QUALITY AUDIT

A self inspection program for 2009 was available. Self inspection was performed routinely, twice per year according to SOP. Reports were prepared and corrective actions were required. Proposed corrective actions were reviewed and approved. Implementation of corrective actions was controlled. Self inspection covered GMP related items.

## 2.9 PERSONNEL

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

An organization chart was available. Key personnel responsibilities were specified in job descriptions. Head of production and quality control responsibilities were in line with GMP requirements.

## 2.10 TRAINING

All staff, including new staff and operating staff, was given basic training in GMP during induction and at regular intervals subsequently. The training programs were periodically updated. During training, emphasis was put on regulatory requirements of health, hygiene and safety. Employees were also kept updated on new developments in technology.

Training involves in-house and external faculty. All employees were provided with training in conformity with their needs.

Training evaluation was carried out by questionnaires, oral and written examinations and detailed audits of work performance.

Retraining needs were identified through performance evaluation. Records of both training as well as retraining were maintained.

## 2.11 PERSONAL HYGIENE

Employees were regularly subjected to medical examination by a qualified medical practitioner. Medical examinations were conducted annually.

Personnel suffering from illness such as skin rashes, colds, communicable diseases, cuts and open lesion to the body were required to report the same and were excluded from working in the clean and critical areas.

## 2.12 PREMISES

Buildings and facilities used for manufacture and quality control were located, designed, and constructed to facilitate proper cleaning, maintenance, and production operations. Facilities were designed to minimize potential contamination and had

adequate space for the placement of equipment and materials to prevent mix-ups and contamination. Premises were protected from entrance by insects, birds or animals.

The cleaning SOP was common for warehouses and production cubicles, cleaning records were maintained.

There were separate personnel and materials air locks and material pass –through cubicles. Temperature, relative humidity and pressure differentials were regularly monitored and recorded.

The buildings were well maintained and clean.

#### *Storage areas*

There were sufficient storage areas for starting and packaging materials, intermediates, bulk products and finished products. Released finished products – soft gelatine capsules were stored in the manufacturing department.

Receiving and dispatch areas protected materials and products from weather. Special storage conditions were provided for storage of products in cold temperature.

Under quarantine and rejected materials and products were stored separately. Separate sampling areas were designed for sampling of API and excipients.

#### *Weighing areas*

Separate areas were designed for weighing of API and excipients.

#### *Production areas*

The facilities were designed and maintained to minimize the risk of cross-contamination and contamination. Production areas were effectively ventilated. Separate AHUs were provided for each manufacturing, sampling and weighing cubicles.

#### *Quality control areas*

QC laboratories were separated from production areas. Adequate storage space was provided for storage of samples, laboratory reagents and reference standards, solvents, reagents and records. Separate rooms were provided for instruments such as analytical balances, HPLC, IR and GC.

## 2.13 EQUIPMENT

The process equipment were located, designed and maintained to suit the operations to be carried out.

Generally, the equipment was well maintained. A preventive maintenance program was in place and was followed. Preventive Maintenance performed was recorded in check lists.

Balances with appropriate range and precision were used in production and quality control operations.

Cleaning SOP and records were available for all equipments. Equipment was identified as to its contents and cleanliness status by appropriate labels.

Equipment calibration schedule was established and followed for each department. The system to verify and control the calibration status of critical equipment was in place.

Food grade lubricants were used to lubricate production equipments. QA approved lubricant's list was available.

## 2.14 MATERIALS

Procedures describing the receipt, identification, quarantine, storage, handling, sampling, testing and approval or rejection of materials were available. Sampling and dispensing were carried out in separate sampling and dispensing rooms.

Incoming goods and finished products were quarantined until release. Rejected and returned materials were stored separately. Materials and products were stored in a proper manner.

Materials were transported from warehouse to production departments in locked stainless steel trolleys.

Samples of starting materials were taken from each container in dedicated sampling rooms. Materials were stored in quarantine areas until approval by the quality control.

Lists of approved suppliers of raw materials and packaging materials were available.

Primary packaging materials were sampled in a controlled environment. Specific reference numbers were assigned to each delivery of packaging materials.

SOP on reprocessing and rework was reviewed.

Purified water (for Pharma I and II) was produced by reverse osmosis. A new distribution loop for the water treatment system has been installed.

Sampling of water was done based on a weekly schedule. The use of water for production was documented.

Trend analysis on the quality of the water (Pharma I and Pharma II) was reviewed, without any remarkable findings.

Sampling plan was established for routine monitoring of purified water; final user points were monitored with suitable frequency.

Water for the quality control laboratory was made in the laboratory. The quality of the water for laboratory use was defined and controlled on weekly basis.

Nitrogen, used in contact with the product was filtered through 0.01 $\mu$  filters.

Oil free compressed air, used in production with direct contact to the product, was made by a centralized compressor plant, situated separate utility building. The quality of the compressed air was defined; qualification of the equipment and the filters used was performed. Microbiological monitoring programme covered compressed air.

Materials which were in contact with product, such as lubricants, oils, textile for removal of oil from capsules, were approved by QA.

Laboratory reagents and culture media were prepared and controlled according to written procedures and were appropriately labelled. Positive and negative controls were applied to control the suitability of culture media.

Official reference standards were used, except for APIs where no official standards were available. Working standards were standardized against the official reference standards and were labelled and stored properly. Log books of usage of standards were maintained.

## 2.15 DOCUMENTATION

In general the documentation system was correctly established and maintained. Documents were approved, signed and regularly reviewed. Specifications, testing procedures, master formulas, instructions and batch records were in place.

## 2.16 GOOD PRACTICES IN PRODUCTION

Production processes appeared generally under control.

Deviations were recorded and approved. Some deviation files were reviewed.

In-process controls were correctly organised.

Holding time in between blending and compression was defined.

Yield calculations for bulk products and reconciliation calculations for finished products appeared correctly carried out.

## 2.17 GOOD PRACTICES IN QUALITY CONTROL

Analytical methods were used on the basis of Ph. Eur, BP, USP and Indian Pharmacopoeia. Pharmacopoeia methods as well as in house methods were validated.

The use of HPLCs was recorded in column log books. Column washing and preparation of mobile phase were done in according with written procedures. Columns were stored appropriately.

Some out-of-specification result investigations were reviewed, and did not give rise to major comments

The microbiological laboratory was acceptable for the purpose it was used for. General procedures were in place, including handling and control of media. Autoclave and incubators were maintained and qualified according to programmes.

Stability studies were inspected for specific product. The company had collected data on bulk and finished product. Data collection and stability results appeared to be correctly handled, and did not give rise to major comments.

### **Part 3: Conclusion**

The manufacturer Cipla Limited, located in Kurkumbh, District of Pune, Maharashtra, India, was found to be operating to a good level of compliance with the 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.