

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

Part 1: General information

Name of Manufacturer	CADILA PHARMACEUTICALS LTD
Unit number	N/A
Production Block	MAIN PHARMA BLOCK (MPB)
Physical address	1389, Trasad Road, Dholka – 387810 Dist.: Ahmedabad, Gujarat India.
Contact address	As above
Date of inspection	11 to 14 April, 2011
Type of inspection	Routine GMP inspection
Dosage forms(s) included in the inspection	Tablets
WHO product categories covered by the inspection	TB Tablets
Summary of the activities performed by the manufacturer	Production and quality control and release of tablets, capsules, oral liquids, dry syrups, sachets; sterile products viz. dry powder injections, ampoules and vials



Part 2: Summary

General information about the company and site

The Cadila Pharmaceuticals Limited site is located at Dholka, near Ahmadabad, India.

The formulations manufactured at this site include tablets, capsules, oral liquids, dry syrups, sachets; sterile products viz. dry powder injections, ampoules and vials. The company manufactured products for human and veterinary use.

History of WHO and/or regulatory agency inspections

Since 2002, this plant has been periodically inspected by WHO inspection teams. The last routine inspection was performed in August 2008; an inspection of data verification was performed in December, 2010. The facility has been inspected by various regulatory agencies including the MHRA, TGA, MCC, NDA and other agencies.

Focus of the inspection

The inspection focused on the production and quality control of oral solid dosage forms, in particular tablets and on the assessment of compliance with WHO Good Manufacturing Practices specifically. 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. Various documents were reviewed. These included inter alia Standard Operating Procedures and records for the following:

- Product quality review (PQR)
- Material code allocation and changes
- Complaints
- Recalls
- Deviations
- Change control
- Approved suppliers list
- Quality control
- Cleaning validation
- Source data for process validation, stability testing etc
- Batch Manufacturing Records
- Specifications

Inspected Areas

During the opening meeting, the scope of the inspection was clarified e.g. that the inspection will be conducted according to WHO GMP guidelines. The newly published GMP CD-ROM was provided to the company. The activities and scope of PQ programme was explained including the procedures for the publication of WHO Public Inspection Reports (WHOPIRs) and Notices of Concern (NOC). The inspectors explained that the inspection would focus on the production and control of the prequalified products and the inspection plan that had been communicated with the company.

All the company representatives present in the opening meeting signed the attendance sheet. The company made a brief presentation of the site.



In the Dholka plant, there was a Main Pharma Block (MPB), a Cephalosporin Block (CEPHA Block), a Penicillin block, Rifampicin Block, as well as R&D and utility blocks etc.

The inspection focused on the MPB and utility block.

After the opening meeting, the inspectors started the inspection by reviewing the organization chart and job descriptions. They reviewed various job descriptions, section organization charts and training records for selected persons, including General Manager of Main Pharma Block, QC manager and other persons in relation to key responsibilities and delegations.

Selected log books, raw data and reports were reviewed. The following documents were further reviewed.

- SOP of producing and handling the different products in the block.
- SOPs of complaints
- SOP of deviation
- SOP of PQR
- SOP of change control

Complaints of 2008, 2009 and 2010 were reviewed by inspectors. There were no complaints for the WHO PQ products.

On the second day, the inspectors gave feedback on the observations made on the first day of the inspection and sought clarification.

The inspectors proceeded by inspecting the warehouses - receiving of materials, storage and sampling areas. Selected SOPs and records were inspected including check lists for materials received, approved vendor list, temperature monitoring, sampling and cleaning (starting materials) and sampling of packaging materials, as well as leaflet checking. Material codes in the SAP, in terms of receiving material list, were checked in the computer.

FTNIR was used for ID testing of several materials.

The schematic drawing for the production block and air handling system were reviewed. The pressure differential was discussed and questions regarding the range and monitoring of the system was discussed. Selected aspects and components were checked in the records including but not limited to installed filter testing, cleaning, monitoring and maintenance records.

The remaining SOPs and selected records scheduled for inspection during the previous day were then reviewed.

On the third day, feed back was given on the observations of the previous day and inspectors sought clarification.

Production areas inspected included the dispensing area, tools storage (including punches and dies), FBD bags, in process storage, blender and granulation areas, compression areas, coating areas, tablet inspection and primary packaging areas. Sampling tools, vacuum cleaner, and sifter were inspected and the metal detectors were checked.



Inspectors reviewed the following documents:

- Batch document preparation
- SOP of dispensing and cleaning
- SOP of clean log book and batch records
- SOP and batch records
- SOP for dispensing and issuing raw materials,
- SOP for cleaning of equipment, area and utensils and handling and storage of work in process.
- SOP for in-process control of tablet compression,
- SOP for washing and cleaning of the bins
- SOP for handling of raw materials.
- SOP for handling any new API introduction, including the technology transfer check list
- SOP and cleaning validation matrix were reviewed, worst case was selected in terms of toxicity, solubility and maximum carryover (MACO).
- SOP for change control of Software upgrade for FTNIR
- The validation document of FTNIR and the challenged study

On the fourth day, the inspectors gave feedback on the observations made on the previous day of the inspection.

The inspectors proceeded to inspect the quality control laboratories which included:

- Testing documentation of a selected batch
- Equipment qualification
- Reference and working standards handling
- Purified water sampling, testing and trend monitoring
- Culture media preparation and testing including growth promotion testing.

2.1 GOOD MANUFACTURING PRACTICES (GMPs) FOR PHARMACEUTICAL PRODUCTS

The company had an organization chart and job descriptions specifying the responsibilities and reporting relationships of the various staff. The quality assurance systems were supported by documented and approved procedures to guide routine operations and activities. There were systems for control and approval by QC/QA of starting materials, intermediate products, finished goods for use or distribution. Policies and procedures were in place for qualification and validation of equipment and systems, change control and deviation management, self inspection and product quality review.

2.2 SANITATION AND HYGIENE

An acceptable level of sanitation and hygiene was practised on site. The scope of sanitation and hygiene covered personnel, premises, equipment and apparatus, production materials and containers, products for cleaning and disinfection, and anything that could become a source of contamination to the product.



2.3 QUALIFICATION AND VALIDATION

Qualification of equipment and validation of systems and processes was guided by a Validation Master Plan which outlined policies and approaches to qualification, validation and calibration. Validation and qualification activities were guided by approved protocols. Equipment underwent initial qualification and requalification was planned. The principles for cleaning validation were established plus the policies on number of cleaning cycles, discussion of worst case, setting of limits, justification of the limits and analytical methods used and general documentation was held.

There was a summary of qualification status and due date for routine requalification for major production, packaging and QC equipment and utilities.

2.4 COMPLAINTS

The SOP dealing with complaints was in place.

2.5 PRODUCT RECALLS

There was no product recall recorded.

2.6 CONTRACT PRODUCTION AND ANALYSIS

The company acted as a contract giver as well as a contract acceptor.

2.7 SELF-INSPECTION AND QUALITY AUDIT

This chapter was not examined during this mission.

2.8 PERSONNEL

There were sufficient numbers of personnel to carry out all the tasks for which the manufacturer was responsible. Individual responsibilities were defined. Delegated duties were not always clearly defined. Organization charts and job descriptions were in place.

2.9 TRAINING

Training was provided - training records were generally kept.

2.10 PERSONAL HYGIENE

An acceptable level of personal hygiene was observed. Direct contact was avoided between the operator's hands and starting materials, primary packaging materials and intermediate or bulk product. Personnel were wearing clean body coverings appropriate to the duties they performed.

Personal hygiene procedures included the use of protective clothing for all persons entering warehouse and production areas.



2.11 PREMISES

The premises were located, designed, constructed, adapted, and maintained to suit the operations carried out. The layout and design of the premises aimed to minimize the risk of errors and permit effective cleaning and maintenance in order to avoid cross-contamination, build-up of dust or dirt, and, in general, any adverse effect on the quality of products.

In areas where dust was generated (e.g. during sampling, weighing, mixing and processing operations, packaging of powder), appropriate measures were taken to avoid cross-contamination and facilitate cleaning.

2.12 EQUIPMENT

Equipment was located, designed, constructed, adapted, qualified and maintained to suit the operations to be carried out. The layout and design of equipment also aimed to minimize the risk of errors and permitted effective cleaning and maintenance in order to avoid cross-contamination, build-up of dust or dirt, and, in general, any adverse effect on the quality of products.

2.13 MATERIALS

Materials were mainly sourced from approved suppliers. All incoming materials and finished products were quarantined immediately after receipt until they were released for use or distribution.

2.14 DOCUMENTATION

Documents were designed, prepared, reviewed and distributed. Documents were approved, signed and dated by the appropriate responsible persons. Documents were laid out in an orderly fashion and were easy to check. Reproduced documents were clear and legible.

2.15 GOOD PRACTICES IN PRODUCTION

Production operations followed defined procedures. In process control were carried out. Materials, bulk containers, major items of equipment, and where appropriate, the rooms used were labelled with an indication of the product or material being processed. Access to production premises were restricted to authorized personnel.

2.16 GOOD PRACTICES IN QUALITY CONTROL

There was a quality control and assurance department whose functions were independent of production. The laboratories generally had adequate facilities in form of space, working environment, equipment, chemicals, reagents, personnel and approved procedures for sampling and testing starting materials, packaging materials and finished goods. The equipment evaluated had been qualified and/or calibrated and the procedures were validated.

Samples of starting materials and finished products were retained for future analysis.



The hold time for intermediates and bulk products had been scientifically established and was in the process of being put in place. This should be completed.

The inspection of the microbiology laboratory focused on the preparation of culture media and the sampling, testing and monitoring of pharmaceutical water.

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, CADILA PHARMACEUTICALS LTD, 1389, Trasad Road, Dholka – 387810 Dist. Ahmedabad, Gujarat, 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.