

Prequalification of Medicines Programme

WHO PUBLIC INSPECTION REPORT
(WHOPIR)

of

Finished Pharmaceutical Product Manufacturer

The report is the property of the organization responsible for performing the inspection.

Part 1: General information

| | |
|---------------------------------------|--|
| Name of manufacturer | Cadila Pharmaceuticals Ltd |
| Physical address | 1389 Trasad Road, 387 810 Dholka Ahmadabad, Gujarat India |
| Postal address | Corporate Office Cadila corporate Campus Sarkhej / Dholka Road, Bhat 382210 Ahmadabad, Gujarat India |
| Telephone number | +91 2714-221481/83/84 |
| Fax number | +91 2714-221848 |
| Summary of activities of manufacturer | Manufacturing of finished products, packaging of finished products, batch control and batch release: tablets, capsules, liquids, dry syrups, injections, including penicillin's and cephalosporin's. |
| Scope of inspection | Routine inspection - 13 - 17 March 2008 Follow up inspection. 20 - 22 August 2008 Tablets and capsules manufacturing within Main Pharma Building and Rifampicin Building. |
| Program | Prequalification Programme: Priority Essential Medicines. |

Part 2: Summary

The Cadila Pharmaceuticals Limited site was located at Dholka, near Ahmadabad, India. This manufacturing facility produces over 350 products, covering 42 therapeutic groups in human & 10 in animal health care. The formulations include tablets, capsules, oral liquids, dry syrups, sachets; sterile products viz. dry powder injections, ampoules and vials.

Focus of the inspection

The purpose of the routine inspection was to follow up on corrective actions taken by the company since the last inspection and to ascertain the level of GMP compliance for the manufacture of tablets which are provided for the treatment of Tuberculosis.

The purpose of the follow up inspection was to verify the implementation of the corrective actions of the deficiencies detected in previous visits, and to verify GMP compliance of the Main Pharma building as well as the Rifampicin building. The inspection focused on the ventilation system of Main Pharma building and Rifampicin building.

History of WHO or regulatory agencies inspections

Since 2002, this plant has been periodically inspected by WHO inspection teams. The latest of these inspections was done in March 2008.

The facility was approved by various regulatory agencies including the UK-MHRA, TGA-Australia and African regulatory agencies like MCC-South Africa and NDA-Uganda. The site was ISO 9001 and 14001 certified.

Inspected Areas

Areas listed below, and associated documents (Sop's, log books, batch records, validation and qualification protocols and reports) were inspected.

2.1. Quality Assurance (QA)

Product release was the responsibility of the General Manager, Quality Assurance (QA) who was also authorized person, hierarchically independent from production. The General Manager, Quality Assurance was also responsible for dealing with other QA related activities, such as handling of complaints, change control and out-of-specification (OOS) result investigations, internal and external audits. QA personnel were involved in all the production and quality control activities.

Managerial responsibilities were specified in job descriptions.

Changes were grouped as temporary (time bond) and permanent. If changes were related to the Marketing Authorization, Regulatory Authorities (RA) were informed and implemented after RA approval. In year 2006 Main Pharma building HVAC system was re-designed and re-installed.

Deviations were classified as planned and unplanned. Deviations were closed within 30 days. Deviations were trended monthly and yearly.

Changes and deviations were listed in the Annual product review.

Annual product review (APR) was performed for all pre-qualified products manufactured. APR in general was detailed, trends were part of APR.

2.2. Good Manufacturing Practices for Pharmaceutical products

Manufacturing processes were clearly defined and reviewed. Manufacturing steps were recorded in Batch Manufacturing Documentation. The storage and distribution of products ensured batch traceability. Records were made during manufacture.

Qualification and validation were performed and all necessary resources were provided.

Instructions and procedures are written in clear and unambiguous language.

2.3 Sanitation and Hygiene

The site's hygiene program covered personnel, equipment, materials and premises. The hygiene measures in place at the time of the inspection were found to be sufficient to assure the prevention of contamination of the premises and product.

2.4 Qualification and Validation

The key elements of a qualification and validation program were defined and documented in a VMP.

Significant changes to the premises, facilities, equipment or processes were qualified and validated.

An ongoing validation program was available.

The responsibility of performing validation should be clearly defined.

All products production procedures were validated every 2 years.

2.5. Complaints

Complaints and other information concerning potentially defective products were reviewed according to written procedure and the corrective actions were taken.

QA head or his authorized persons were responsible for complaints' investigations. Complaints were classified as product quality complaints, product packaging complaints and medical complaints. Complaints were categorized as category I, II and III. Complaints were reviewed every 3 months.

In case of the quality complaints other batches were checked in order to determine whether they are also affected.

If necessary product recall, should be initiated after investigation and evaluation of the complaint.

The decisions made and measures taken were recorded.

2.6 Product Recalls

Recalls were handled in accordance with the written procedure. Recall procedure was regularly reviewed and updated.

Recalls were classified in 3 categories and 3 levels. According to the recall SOP dummy recalls should be performed once per year.

2.7 Contract production and analysis

Manufacturing operations were contracted out to 10 companies. Manufacture of pre-qualified products was not contracted out.

The contracts were available. The contracts permitted to the contract giver to audit the facilities of the contract acceptor. The responsibilities of contract giver and contract acceptor were defined.

Contract laboratories were not used.

2.8 Self inspection and Quality Audits

Self-inspection was performed in accordance with written procedure. Procedure included questionnaires on GMP requirements and main GMP items were covered. After completion of self inspection, self inspection report was drawn up and necessary Corrective and preventive actions (CAPA's) were initiated. Implementation of CAPA's was monitored. Self inspection schedule was available for inspection. Self inspection was carried out every 6 months. Self inspection team was properly trained. Self inspection observations were classified as critical, major and minor.

2.9 Personnel

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

An organization chart was available. Key personnel responsibilities were specified in job descriptions. The production and quality control responsibilities were independent, in line with the cGMP requirements.

2.10 Training

Training issues were covered in written SOP. Company provided initial training at the time of recruitment and regular continuous SOP training. Comprehension of training content was assessed by discussions and written questionnaires. The training plan and program for the year 2008 was availed to the inspectors. Training records were maintained.

2.11 Personal Hygiene

All personnel prior and during employment passed medical examinations. Persons with illness and open lesions were not allowed to work in areas where open products were exposed to the environment.

The level of hygiene observed and the measures taken to manage were considered sufficient.

All changing rooms were provided with photos describing the gowning procedures.

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. There was sufficient space for the movement of materials and personnel. There were separate personnel and material entrances. Temperature, relative humidity and pressure differentials were regularly monitored and recorded.

Storage areas

Storage areas ensured good storage conditions. Storage areas were clean, dry, sufficiently lit and maintained within acceptable temperature limits. Special storage conditions were provided. Temperature, relative humidity was controlled and monitored.

The receiving and dispatch areas protected materials and products from the weather. Quarantined, rejected, recalled and returned materials and products were stored separately and secured.

Temperature mapping of storage areas was done and reports were available for inspection.

Solvents were stored in the separate building.

Sampling areas

There were 4 sampling rooms in the Main Pharma building. 2 separate rooms were dedicated for sampling of APIs, 2 rooms were dedicated for sampling of other starting

materials. Sampling was done under reverse laminar air flow (RLAF). Primary packaging materials were sampled in separate room under RLAF.

In Rifampicin building there was common sampling/dispensing room. Sampling was done under RLAF.

Weighing and dispensing areas

There were 4 dispensing rooms in the Main Pharma building. 2 dispensing rooms were dedicated for the APIs and 2 rooms were dedicated for other starting materials. Solvents were dispensed in a separate room.

Production spare parts room

Punches, dies and other production equipment spare parts were stored in the separate room in stainless steel cabinets.

Production areas

Main Pharma building

In general Main Pharma building facility was designed to minimize the risk of cross-contamination and mechanical contamination. Production areas were ventilated with supply air grills located higher than return air grills, such that there was a downward flow of clean air from above and exhausted lower down.

Rifampicin Building

In general Rifampicin building facility was designed to minimize the risk of cross-contamination and mechanical contamination.

In production rooms air supply grills were located higher than return air grills.

Quality control (QC) areas

Quality control laboratory was separated from the 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. Microbiological laboratory was separated from chemical laboratory.

Equipment

Manufacturing equipment was installed in a way that minimizes risk of error or of contamination.

Preventive Maintenance program was in place and were followed.

Cleaning Sop's and records were available for all equipment. Production and quality control equipments were identified as to content and cleanliness status and appropriately indicated by labels.

Equipment calibration schedule was established and followed for each department.

All equipment inspected was within their calibration intervals.

Materials

General procedures describing the receipt, identification, quarantine, storage, handling, sampling, testing and approval or rejection of materials were available for inspection and evaluated.

Incoming goods and finished products were quarantined until tested and released by QA. Materials and products were stored in a proper manner.

Damage of containers was reported to QC. Containers under quarantine and approved containers were appropriately indicated.

Approved vendor list for raw materials and packaging materials were available in the warehouse.

Near infra red instrument was used for the identity tests (ID) tests of every container before sampling. Starting materials were 100 % sampled for ID test. After sampling chemical ID tests were performed on each container.

Usage of reference and working standards was recorded; standards usage log books were available for inspection.

Lubricants and disinfectants were approved by QA.

Overprinting of labels and cartoons were done in two rooms.

Documentation

In general documentation system was well established and maintained.

Documents were designed, prepared, reviewed and distributed with care. Documents were approved, signed and dated by the appropriate responsible persons.

Documents had unambiguous contents were laid out in an orderly fashion and were easy to check.

Documents were regularly reviewed and kept up to date.

Good practices in production

Production operations were done following clearly defined procedures.

Necessary checks on yields and reconciliation of quantities were carried out.

During processing, materials, bulk containers, major items of equipment, and the rooms and used packaging lines were labeled and indicated the products being processed, its strength and the batch number.

Access to production premises was restricted. Unauthorized person was not allowed to enter

Line clearance was performed and recorded before processing operations were started.

Necessary in-process controls were carried out and recorded.

Good practice in Quality Control

In general Good Practice in Quality Control was implemented and maintained.

The quality control functions were independent of other departments.

Adequate facilities, trained personnel and approved procedures were available for all relevant activities.

Batches of products were released for sale or supply only after certification by the authorized person or designated persons.

Sufficient samples of starting materials and products were retained to permit future examination of the product.

Quality control personnel had access to production areas.
An analyst competency list and training files were available.

OOS results were evaluated and investigated in accordance with written procedure. OOS was closed within 30 days.

Dry chemicals and solutions expiry dates were set up.

Utilities

The HVAC system

The new HVAC system was installed in the Main Pharma building. The system was commissioned and qualified in the year 2007.

3 new additional AHU were installed in the Rifampicin block in the year 2006.

The HVAC system has 22 Air Handling Units (AHU's) for Main Pharma building and of 8 AHU for Rifampicin building.

The inspection of the air handling system entailed a visual inspection of the equipment in the plantroom, measurement of room pressure differentials, checking some return air velocities, airflow patterns, qualification documents and drawings. In general the air handling equipment appeared to be in good condition and well maintained.

AHU's recovery time was established during validation studies. Recovery time was 20 minutes.

Purified water system

The Purified water system underwent a cursory inspection following the process through from the raw water input into the system, through to the purified water loop serving the general block. The PW was produced by 2 reverse osmosis systems. RO-I (pre treatment plant) was located in the utility block. RO-II was located in the Main Pharma building. Components were made of 316L SS material. In the main building water was circulated continuously at 80 °C. PW system was sanitized regularly; filters were changed every 6 months.

Compressed air

Compressed air receiver was located in the utility block. Air dryer was located on the technical floor of Main Pharma building. Incoming air was filtered via several pre-filters and dried. 0.01 µm filters were installed at the used points. Compressed air samples were taken and analyzed on regular basis.

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 together with the corrective actions taken and planned, Cadila Pharmaceuticals, Ltd. Dholka-Trasad site, was considered to be operating at an acceptable level of compliance with WHO GMP guidelines.