



**Prequalification Team Inspection services
WHO PUBLIC INSPECTION REPORT
(WHOPIR)**

Finished Product Manufacturer

Part 1: General information

Name of Manufacturer	Cadila Pharmaceuticals Limited, Dholka Site, Ahmedabad, India
Block number	General OSD Block and RIFA Block ONLY
Unit number	N/A
Production Plant	OSD Block for NON-beta lactam products Rifampicin Block
Physical address	Survey No. 1389, Trasad Road, Dholka, Ahmedabad-387810, India
Date of inspection	9 -13 June 2014
Type of inspection	Routine inspection
Dosage forms and type of products	Manufacture of OSDs of NON Beta-Lactam type (Main Pharma Block) Manufacture of Rifampicin Products in a dedicated facility (Rifampicin Block)
Focus of inspection - products in WHO PQ program covered in the scope at the time of inspection with the WHO reference number	Products included in WHO Prequalification Programme: TB008: Ethambutol 400mg Tablets TB009: Ethambutol/Isoniazid 400/150mg Tablets TB015: Pyrazinamide 400mg Tablets TB250: Prothionamide 250mg Tablet TB246: Isoniazid/Rifampicin 75/150mg Tablet TB249: Ethambutol/Isoniazid/Pyrazinamide/Rifampicin 275/75/400/150mg Tablet TB251: Ethambutol/Isoniazid/Rifampicin 275/75/150mg Tablet.
Summary of the activities performed by the manufacturer	Production and quality control of finished dosage forms In addition to the facilities inspected the company has a separate block containing two segregated facilities for the manufacture and testing of betalactam products. In addition there is a dedicated biologicals block. THIS FACILITY WAS NOT INSPECTED

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Part 2: Summary

General information about the company and site

Cadila Pharmaceuticals Limited (Cadila) is one of the oldest pharmaceutical companies in India, having a presence of over 60 years in the Pharmaceutical Market. Company current sphere of activities encompasses formulations; bulk drugs (APIs), hospital products, tissue culture products, diagnostics, veterinary products, biotechnology products, recombinant vaccines, and pharmaceutical machinery manufacturing. Pharmaceutical product portfolio of the Company includes a wide range of cardiovascular, gastrointestinal, analgesics, haematinics, anti-infectives and antibiotics, respiratory agents, antidiabetics and immunologicals.

The company operates several sites for both finished pharmaceutical products and API.

Several of the company's operations and sites are regularly inspected by US FDA, AU TGA, and UK MHRA. The company stated that for its API activities it holds DMFs in USA, CEPs (EDQM), as well as ASMF/DMFs in the EU, Japan and Australia.

The inspected Cadila Pharmaceuticals Limited site is located at Dholka, near Ahmedabad, in Gujarat India. FPP operations are located at the Dholka site, located, relatively close to Ahmedabad. The Dholka site was established in 1998. The total site area is 107,000 sq. m. There are no other industrial premises close to the site.

The Dholka manufacturing facility produces over 350 products, covering 42 therapeutic groups in human & 10 in animal health care. Formulations include tablets, capsules, oral liquids, dry syrups, sachets; sterile products including dry powder injectables, ampoules and vials.

There are several manufacturing blocks located on site including:

Main Pharma block (MPB) - manufacture of tablets, hard capsules, oral liquids, sterile injectables (liquid/lyophilized), 99% of injectable products are manufactured aseptically.

Rifampicin block (RB) - manufacture of tablets and hard capsules;

Cephalosporins block (CB) - manufacture of tablets, hard capsules, dry syrups, sterile injectables (powder);

Penicillins block (PB) - manufacture of tablets, hard capsules,

Products are manufactured for domestic and for export markets (incl. Europe and USA).

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History of WHO and/or regulatory agency inspections

International regulatory inspections of the operations have been conducted by:

- US FDA, UK MHRA, Australian TGA, WHO-PQ
- South African MCC

Both the Main Pharma Block and the RIFA block have been inspected regularly by WHO-PQ and the last inspection covered all the areas covered during this current inspection.

The previous WHO PQ inspection of Main Pharma Block was performed during 20th-23rd November, 2012 jointly by Latvian State Pharmaceutical Inspection, and WHO.

Last inspection of Rifampicin Building was conducted jointly by Latvian State Pharmaceutical Inspection and WHO during 20th-23rd November, 2012
All these inspections passed satisfactorily after CAPA.

The inspection was led by a staff WHO Inspector supported by WHO co-inspectors provided by ANSM France and NDA, Uganda. Prior to the inspection India Ministry of Health was informed and Gujarat State Health of the inspection, and representatives of the Indian Competent Authority were present during the inspection as observers.

Focus of the inspection

The inspection focused on the production and control of Oral Solid Dosage products. The inspection covered all the sections of the WHO GMP texts applicable to OSDs, including premises, equipment, documentation, materials, validation, sanitation and hygiene, production, quality control and utilities.

The inspection was system orientated using examples from the products of interest to PQT.

Inspected Areas

- Quality Assurance
- Sanitization and hygiene
- Qualification and validation
- Complaints
- Recalls
- Self-inspection
- Personnel
- Training

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- Personal hygiene
- Premises and production including both the OSD main pharma block and Rifa block,
 - Warehouses for starting materials and packaging materials,
 - Starting materials sampling room,
 - Starting materials dispensing rooms,
 - Purified water (PW), Water for injection (WFI) and Pure steam (PS)
 - production area,
 - HVAC systems oral solid dosage forms,
 - Personnel gowning airlocks,
 - Tablets and capsules manufacturing areas
 - Equipment (OSD)
- Equipment
- Materials
- Documentation
- Quality control laboratory (analytical & microbiology)

Specific documents inspected included inter alia Standard Operating Procedures and records for the following:

- SOP for "Annual Product Review"
- SOP for Handling of market complaints"
 - o Market complaint register 2012 to date
- SOP for "Product recall procedure"
- SOP for "Deviation management"
- SOP for Out of specification and out of trend results
 - o OOS Register 2012 and 2013
 - o "Handling of out of specification laboratory results"
 - o "Handling out of trends results during stability study"
- SOP for "Change control"
- SOP for "Stability testing"
- SOP for "Release/rejection"
- SOP for Product Quality Reviews
- SOP for validation and VMP

Restrictions

This inspection report is focused on Oral Solid Dosage (OSD) manufactured in the Main Pharma Block and Rifampicin Block only.

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Abbreviations

AHU	air handling unit
ALCOA	attributable, legible, contemporaneous, original and accurate
API	active pharmaceutical ingredient
APQR	annual product quality review
BDL	below detection limit
BMR	batch manufacturing record
BPR	batch packaging record
CAPA	corrective actions and preventive actions
CC	change control
CFU	colony-forming unit
CoA	certificate of analysis
CpK	process capability index
DQ	design qualification
EM	environmental monitoring
FAT	factory acceptance test
FBD	fluid bed dryer
FMEA	failure modes and effects analysis
FPP	finished pharmaceutical product
FTA	fault tree analysis
FTIR	Fourier transform infrared spectrometer
GC	gas chromatograph
GMP	good manufacturing practice
HACCP	hazard analysis and critical control points
HPLC	high-performance liquid chromatograph
HVAC	heating, ventilation and air conditioning
IR	infrared spectrophotometer
IQ	installation qualification
KF	Karl Fisher
LAF	laminar air flow
LIMS	laboratory information management system
LoD	limit of detection
LOD	loss on drying
MB	microbiology
MBL	microbiology laboratory
MF	master formulae
MR	management review
NMR	nuclear magnetic resonance spectroscopy
NRA	national regulatory agency
OQ	operational qualification
PHA	process hazard analysis
PM	preventive maintenance
PpK	process performance index

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PQ	performance qualification
PQR	product quality review
PQS	pharmaceutical quality system
QA	quality assurance
QC	quality control
QCL	quality control laboratory
QRM	quality risk management
RA	risk assessment
RCA	root cause analysis
SOP	standard operating procedure
TAMC	total aerobic microbial count
TFC	total fungi count
TLC	thin layer chromatography
URS	user requirements specifications
UV	ultraviolet-visible spectrophotometer

2.1 PHARMACEUTICAL QUALITY SYSTEM

Company has a reasonably well documented and defined quality management system which covering all the main elements of GMP related activities. Quality assurance (QA) function is involved and has oversight of all activities with impact to product quality. QA is responsible for compliance of systems against their SOPs and suggesting the necessary improvements according to GMP and regulatory requirements. The QA and QC units were independent from production.

Deviations and change control activities are also managed through QA. Deviations were classified as planned and unplanned. Deviations were generally closed within 30 days. The systems in place are fairly comprehensive though observations were made concerning detail of these systems and the overall extent of documentation of the detail of investigations. The company has sought to implement the principles of risk management into these activities but this needs further improvement in several areas, to consolidate practices on a day to day basis. Changes and deviations were also listed in the Annual product review.

Deviations were trended monthly and yearly. The system and the registers of deviations were found to be complex. Logs are kept on both an area and market grouping basis meaning that records are dispersed over many logs. This logging process was understood to have certain advantages however the inspectors noted that the approach also presented the risk of desensitizing the system to the risk of failure to detect common root cause or similar issues across product areas.

The classification of the changes in the change control procedure was found to be not well defined. Three levels of changes were classified (Level I II and III or minor,

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moderate and major) but they were not clearly linked to the risk to the product quality. (E.g. Change of API vendor for Isoniazid, CC/RA/ICH/003/14, had been evaluated as minor change). The company provided adequate CAPA and the effectiveness of the revised system will be verified in future inspections.

Decisions of batch release were based on the evaluation of relevant production, QC and other related data. This activity is performed by the QA group which has the requisite independence from other functions within the company.

There was a system in place for the assessment and audit of the suppliers of key raw materials (APIs and excipients) and these were evaluated according to the SOP on vendor approval of raw materials. New suppliers of raw materials and packaging materials are assessed by suitable questionnaires. There is a system of onsite audit in place.

Quality reviews were available and these contained detailed and comprehensive data, although there was a lack of robust critique and assessment of the data beyond a basic review against specification. Specifically the reviews inspected recorded specific critical in-process controls and parameters and whilst most of the parameters selected appeared reasonable (in the experience of the inspectors) there was no documented rationale or discussion in the PQR of why in fact a specific variable or attribute was critical to process and end product quality nor were there relevant references or linkages to other documents such as Risk Management plans, validations or product development reports where specific parameters studied might have been identified as critical. Better review and discussion of trends is necessary if the full value of this data for quality improvement purposes is to be realised. The company provided adequate CAPA and has undertaken to utilise tools for more comprehensive statistical analysis and process capability assessment and the implementation of the revised system will be verified in future inspections.

2.2 GOOD MANUFACTURING PRACTICES FOR PHARMACEUTICAL PRODUCTS

Manufacturing processes were generally 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 in general 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 generally found to be sufficient to assure the prevention of contamination of the premises and product, however it was found that greater attention needs to be given to the maintenance of the RIFA block. The company provided adequate CAPA and the effectiveness of the revised system will be verified in future inspections.

2.4 QUALIFICATION AND VALIDATION

The key elements of a qualification and validation program were defined and documented in a VMP. In general Significant changes to the premises, facilities, equipment or processes were qualified and validated.

An ongoing validation program was available. The responsibility of performing validation was clearly defined.

2.5 COMPLAINTS

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

In case of quality complaints other batches were checked in order to determine whether they are also affected. The records reviewed were generally satisfactory.

2.6 PRODUCT RECALLS

Recalls were handled in accordance with written procedure. The recall procedure was regularly reviewed and updated. Recalls were classified in 3 categories and 3 recall levels. Trial recalls are performed periodically to test the system where necessary.

2.7 CONTRACT PRODUCTION AND ANALYSIS

Manufacture of pre-qualified products was not contracted out. Contract laboratories were not used.

2.8 SELF INSPECTION AND QUALITY AUDIT

Self-inspection was performed in accordance with written procedure. Procedure included questionnaires on GMP requirements and main GMP items were covered. After

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completion of self-inspection, self-inspection report was drawn up and necessary CAPA's were initiated. Implementation of CAPA's was monitored. A self-inspection schedule was available for inspection.

2.9 PERSONNEL AND TRAINING

There generally appeared to be a sufficient number of qualified and experienced personnel available in the company. Organizational charts of the site as well as for inspected blocks were available during inspection. In general the management team is competent and experienced, their duties and responsibilities clearly stated and described in relevant SOPs and job descriptions reviewed.

Company provided training for all personnel involved into production, quality assurance and quality control, and for other personnel whose activities could affect the quality of product (engineering/maintenance, cleaning personnel, etc. as well as visitors.

It was stated that basic Quality Assurance and GMP was provided for all personnel annually. There was an SOP on training and appropriate records were available where requested.

In the review of training SOPs it was generally noted that the effective date for implementation of new procedures was very close to the last approval and the time elapsed between the last signatures. The inspectors expressed the concern that the approach could mean that in the case of the implementation of more complex changes this may not allow sufficient time for full understanding of the procedure and training of staff.

In production the manufacturing personnel wore garments appropriate to the operations carried out in production and quality control areas. Garments for the different manufacturing blocks garments are colour-coded. Each of the areas had it's their own laundry facilities.

The cephalosporin and penicillin were well segregated from the general block. There were appropriate controls in place restricting the movement of both operators and management and supervisory staff between beta-lactam blacks and the general blocks. These included for example engineering staff. See below.

2.10 PERSONAL HYGIENE

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

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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.

2.11 PREMISES AND EQUIPMENT

Manufacturing facilities at Dholka site in the inspected blocks were laid out in a logical order according to flow from receipt of materials to dispatch of products. Personnel and material flows are generally well designed and separated correspond to a logical sequence of operations. Factory layout is based on modular design and built according to GMP standards. There was sufficient space for the movement of materials and personnel. There were separate personnel and material entrances.

Manufacturing areas construction and finishes were appropriate in the general OSD area for particular products manufactured. Inspected facilities were found to be generally adequately maintained however several observations were made concerning detailed maintenance issues to which the company provided adequate CAPA.

Manufacturing equipment was generally installed in a way that minimized risk of error or of contamination. A preventative Maintenance program was in place however observations were made.

Personnel access to manufacturing, QC and other related areas were controlled, since the last inspection the company has introduced a control system using biometric data.

Each manufacturing block is designed and built to be self-sufficient. Blocks CB and PB where beta-lactam products are manufactured, as well as RB are fully separated and dedicated to the manufacture of respective products only (incl. warehouses, personnel, and laundry and canteen facilities). Completed records and retention samples of products were stored locally in CB and PB respectively. Personnel movement between P-lactam blocks and MPB as well as between RB and MPB is segregated in time (cannot visit both the same day). Each block uses different color-coded garments. The exhaust air is HEPA-filtered in CB and PB. Effluent water from beta-lactam production is treated with caustic soda before being sent to the waste water treatment plant.

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

Equipment calibration schedule was established and followed for each department.

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All equipment inspected was within their calibration intervals.

Rifampicin Building

In general Rifampicin building facility was designed to minimize the risk of cross-contamination and mechanical contamination. The facilities for the Rifa products are now rather old and the equipment nearing the end of its useful life. Although in general the Rifampicin facility was satisfactory there were several areas where cleaning and maintenance of facilities and equipment were found to be deficient. A number of poor practices concerning the design and maintenance of items in this area were made to which the company has provided adequate CAPA. The company is expected to maintain the enhanced maintenance plans and this will be verified in future inspections.

The HVAC systems

The HVAC systems in the Main Pharma building were installed, commissioned and qualified in the year 2007. That in the Rifampicin blocks in the year 2006

The HVAC system has discrete Air Handling Units (AHU's) in both the Main Pharma building and Rifampicin building. The HVAC system was designed in a way that production corridors were positive pressurized in relation to the production rooms. The HVAC system in the main building was controlled and monitored by a BMS system. In the MPB there are separate HVAC systems for each of the tablet areas. HEPA filters were installed in plenum and additionally terminally in cleanroom ceilings (HEPA EU13). Supply air was RH controlled; systems were qualified initially and thereafter every 6 months.

Purified water system

There is a centralized water pre-treatment plant built for the entire Dholka site. Artesian water is drawn from 3 artesian wells located on site, and is pumped to a storage tank - all wells and tank were found to be tested monthly according to drinking water specifications. Water then was pre-treated through multi-graded filters, an activated carbon filter, ion exchange (softener), cartridge filters and a finally reverse osmosis (RO-I) system.

Process purified water is then produced from the pre-treated water by a second reverse osmosis system (RO-II). The RO-I (pretreatment plant) was located in the utility block, RO-II was located in the Main Pharma building. Where required 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.

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2.12 MATERIALS

There was a copy of the QA issued Approved Vendor list for raw materials and packaging materials available in the warehouse.

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.

A NIR instrument was used for the ID tests of every container before sampling. Starting materials were 100 % sampled for identity 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.

2.13 DOCUMENTATION

Whilst a number of comments were made concerning the detailed content of certain SOPs (which the company has addressed in CAPA), in general, the documentation system was well established and maintained. Documents are prepared, reviewed, approved and revised according to established written procedures. The documents reviewed during the inspection were generally found to be designed, prepared, reviewed and distributed with care. Documents were approved, signed and dated by the appropriate responsible persons.

Documents generally had unambiguous contents were laid out in an orderly fashion. There was a system to ensure that they were regularly reviewed and kept up to date. Majority of documents has been updated during the current year. Appropriate procedures, specifications, methods, protocols and records were available.

2.14 GOOD PRACTICES IN PRODUCTION

Production operations were performed following clearly defined procedures. The 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 labelled 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, however it was noted that the company OOS procedure did not specifically include IPC checks and appeared to apply to the QC laboratory operation only.

2.15 GOOD PRACTICES IN QUALITY CONTROL

In general Good Practice in Quality Control was implemented and maintained. The quality control and quality assurance release processes and functions were independent of other departments.

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

Specifications for starting materials, intermediate and finished product were available in the laboratory. Only starting materials released by QC were used in production.

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. Analyst competency lists and training files were available.

Out of Specification SOPs were available. OOS was evaluated and investigated in accordance with written procedure. OOS was trended quarterly. OOS was closed within 30 days.

Dry chemicals and solutions expiry dates were set up. No examples of expired reagents were observed during the inspection.

Analytical equipment and apparatus was qualified and regularly calibrated. An annual calibration plan and list of equipment were available during the inspection.

It was the working practice for reference standards to be opened and sealed several times during their entire usage. The company had insufficient validation to show their quality

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was not impacted by this practice.

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, the **Oral Solid Dosage form facilities (for non-beta-lactam products and rifampicin products only) at Cadila Pharmaceuticals Limited, Survey No. 1389, Trasad Road, Dholka, Ahmedabad-387810, India** was considered to be operating at an acceptable level of 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.