20, AVENUE APPIA – CH-1211 GENEVA 27 – SWITZERLAND – TEL CENTRAL +41 22 791 2111 – FAX CENTRAL +41 22 791 3111 – WWW.WHO.INT

Prequalification Team Inspection services
WHO PUBLIC INSPECTION REPORT
(WHOPIR)
Finished Product Manufacturer

Part 1	**General information**
Manufacturers details	
Name of manufacturer	Cadila Pharmaceuticals Ltd.
Corporate address of manufacturer	Cadila Corporate Campus, Sarkhej-Dholka Road, Bhat, Ahmedabad, Gujarat, 382 210, India
Inspected site	
Name & address of inspected manufacturing site if different from that given above	Survey No.1389 Trasad Road, Dholka 382 225 Ahmedabad, Gujarat, India
Unit / block / workshop number	Main Pharma Block and Rifampicin Block
Inspection details	
Dates of inspection	25-27 March 2019
Type of inspection	Follow up inspection
Introduction	
Brief description of the manufacturing activities	The Cadila Dholka campus includes several buildings dedicated to different operations including Preclinical, CRO, R&D and Manufacturing. The manufacturing activities took place in separate buildings which are dedicated to Rifa FPPs, Penicillin and Cephalosporin FPPs, Biologicals as well as tablets, capsules, oral liquids, dry syrups sachets and sterile products (Main Pharma Block)
General information about the company and site	Cadila Laboratories Limited was established in 1951 and the Dholka campus became operational in 1995. This manufacturing facility produced over 350 products covering over 45 therapeutic groups of human health care. The campus was located approximately 55Km southwest of Ahmedabad international airport.
History	The previous WHO inspection was performed during 13-16 November 2017.

Brief report of inspection activities undertaken – Scope and limitations	
Areas inspected	**Document reviewed including but not limited** • Organization Chart • Job descriptions for key personnel • Product Quality Review • Quality Risk Management • Management Review • Responsibilities of the quality units and production • Complaints and Recalls • Deviation control and change control • OOS and investigation • CAPA procedure • Material release • Validation and qualification • Equipment calibration • Data integrity • Sampling and testing of materials • Batch processing records • Materials management system • Purified water system **Site visited:** • OSD Main Pharma Block • Rifa Block • QC laboratories including chemical and microbiological • Starting material and finished goods warehouse
Restrictions	The inspection concentrated on the implementation of CAPAs following the observations made during the previous WHO inspection with a special focus on measures to prevent cross-contamination with beta lactams. The inspection scope extended to storage, production, quality control areas where WHO prequalification products were manufactured.
Out of scope	Products not submitted to WHO for Prequalification
WHO products covered by the inspection	TB008 Ethambutol 400mg Tablets TB009 Ethambutol/Isoniazid 400/150mg Tablets TB015 Pyrazinamide 400mg Tablets TB276 Isoniazid Tablet 300mg HA595 Ondansetron (hydrochloride) Tablet, Film-coated 4mg HA596 Ondansetron (hydrochloride) Tablet, Film-coated 8mg

Abbreviations	Meaning
AHU	Air handling unit
ALCOA	Attributable, legible, contemporaneous, original and accurate
API	Active pharmaceutical ingredient
APR	Annual product review
APS	Aseptic process simulation
BMR	Batch manufacturing record
BPR	Batch production record
CC	Change control
CFU	Colony-forming unit
CIP	Cleaning in place
CoA	Certificate of analysis
CpK	Process capability
DQ	Design qualification
EDI	Electronic deionization
EM	Environmental monitoring
FMEA	Failure modes and effects analysis
FPP	Finished pharmaceutical product
FTA	Fault tree analysis
GMP	Good manufacturing practices
GPT	Growth promotion test
HEPA	High efficiency particulate air
HPLC	High performance liquid chromatography (or high performance liquid chromatography equipment)
HVAC	Heating, ventilation and air conditioning
IQ	Installation qualification
LAF	Laminar air flow
LIMS	Laboratory information management system
MB	Microbiology
MBL	Microbiology laboratory
MF	Master formulae
MFT	Media fill Test
MR	Management review
NC	Non conformity
NRA	National regulatory agency
OQ	Operational qualification
PHA	Process hazard analysis
PLC	Programmable logic controller
PM	Preventive maintenance
PQ	Performance qualification
PQR	Product quality review
PQS	Pharmaceutical quality system
PW	Purified water

QA	Quality assurance
QC	Quality control
QCL	Quality control laboratory
QMS	Quality management system
QRM	Quality risk management
RA	Risk assessment
RCA	Root cause analysis
RO	Reverse osmosis
SIP	Sterilization in place
SMF	Site master file
SOP	Standard operating procedure
URS	User requirements specifications
UV	Ultraviolet-visible spectrophotometer
WFI	Water for injection

Part 2	Summary of the findings and comments (where applicable)

1. Pharmaceutical quality system

The company had a well-documented pharmaceutical quality system (PQS) with Quality Manual, Policies and written procedures covering essential GMP principles for the site. Quality assurance (QA) function was involved and had oversight of all activities with impact to product quality. The Quality Manual was presented and was briefly reviewed during the inspection. Management review meetings were held monthly, and the relevant procedure was available during the inspection. KPIs were established and trending was performed quarterly. The minutes of the meeting following the previous WHO inspection, were reviewed and inspection observations were included as a point for discussion in the agenda of the meeting. Identified observations were adequately addressed by the company's CAPA plan

Product quality review (PQR)

A PQR procedure was in place describing the steps to verify consistency of existing processes, appropriateness of established specifications for starting materials, in process and finished products as well as monitoring trends. A list of products for which PQRs had to be performed, was presented.

Quality Risk Management (QRM)

The Quality Risk Management procedure was reviewed. The procedure described the required steps for identifying and managing risks while providing information on the use of different risk assessment tools. A cross-functional team with expertise in different areas was responsible for carrying out risk assessments. A risk management plan was available covering all site operations

Change and deviation management

Changes were managed according to a written procedure, describing in detail the steps to be taken and personnel responsibilities. An electronic system was used to record and manage changes. Changes were classified as "minor", "moderate", and "major" based on the impact. Effectiveness of changes was verified 60 days after closure. Review of open changes was performed on a monthly basis.

The procedure for "Handling Deviations" was reviewed. Deviations were registered and managed in an electronic system and the related risk was assessed. QA reviewed the deviation and an id number was assigned. Root cause investigations were carried out in accordance with a documented SOP where the relevant tools (Ishikawa diagrams, FTA etc.) were described in detail. The report was

forwarded to other departments for impact assessment. The final report was approved by Head QA and had to be completed within 30 days. Trend analysis is performed every six months. Records related to handling of deviations were reviewed.

CAPA management

CAPA were handled in accordance with procedure DQA015 and they were registered and managed in LIMS. CAPA relating to deviations were cross-referenced in deviation reports and vice versa. Quality Assurance department was responsible for reviewing CAPA implementation and effectiveness. Trending was performed at the end of the year

Investigation of OOS

The procedure on OOS investigations was reviewed. It adequately covered the principles of reporting, investigating, evaluating and documenting OOS test results as well as decision making on batch release. The investigation was performed in two phases. Relevant records were checked during PQR review and laboratory visit.

2. Good manufacturing practices for pharmaceutical products

Basic principles of good manufacturing practices were described in SOPs. 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. It was noted that the company had taken appropriate organizational and technical measures to avoid the risk of β-lactam cross-contamination. However, for the period of reconstruction of the microbiological lab of the main building, samples were moved to penicillin building for analysis, and the measures taken to avoid cross contamination were not described in detail. Identified observations were adequately addressed by the company's CAPA plan.

3. Sanitation and hygiene

Premises and equipment were generally cleaned according to established procedures and relevant records were kept.

4. Qualification and validation

The key elements of the qualification and validation program were defined and documented in the Validation Master Plan. This was a standalone document containing details on all validation/qualification activities including but not limited to equipment, utilities, processes and cleaning, analytical methodology and computer systems.

Cleaning validation was performed according to a written SOP. The procedure provided guidance on the approach of calculation of MACO and the selection criteria for worst case scenario. The implementation of the procedure was reviewed.

5. Complaints

The company had in place a procedure on registering, investigating and monitoring complaints. CAPA relating to complaints were registered and managed in a database.

6. Product recalls

A procedure on product recall was presented. Head QA was responsible for coordinating recall activities. The most recent mock recall was reviewed

7. Contract production, analysis and other activities

Contract production and analysis were not covered in detail in this inspection. None of the prequalified products manufactured by the company were manufactured or tested by a third party.

8. Self-inspection, quality audits and suppliers' audits and approval

Self-inspection was not covered in detail in this inspection due to time constraints.

9. Personnel

Procedures for creation, revision and maintenance of organization charts and for job descriptions of employees were reviewed. Organization charts for different departments were presented and they were considered acceptable. Job descriptions for key personnel were available. Identified observations were adequately addressed by the company's CAPA plan.

10. Training

Training was performed according to a written SOP and it included induction training, induction program in department, classroom training, on the job training, remedial training and GMP refresher training. A training information management software was used by the company to monitor job assignment and duties. The 2018 and 2019 annual training programs were compiled based on the identified training needs. Identified observations were adequately addressed by the company's CAPA plan.

11. Personal hygiene

The procedure on health and hygiene was reviewed. It included the principles of hygiene applied on site. Instructions and pictorials to be followed were sufficiently clear when it came to personal hygiene. Personnel gowning procedure was appropriate and was generally followed though an operator was seen wearing dirty and worn out production garments. For new personnel medical examinations were foreseen before joining the company and relevant records were checked. Identified observations were adequately addressed by the company's CAPA plan.

12. Premises

Storage areas for the warehousing of raw materials and finished products were of sufficient capacity. Production and QC were located in separate areas. The Main Pharma Block was appropriately designed but required maintenance. Turnstile Access Control System and Biometric Access Control System were introduced both at the Main Pharma Block and The Rifa block as a result of the observations made during the last WHO inspection. The Rifa Block had a separate warehouse for APIs and both production and warehousing areas were adequately maintained. Identified observations were adequately addressed by the company's CAPA plan

13. Equipment

Manufacturing equipment was generally appropriately installed. Preventive maintenance was performed according to a written SOP. An annual maintenance program was issued at the begging of each year. Engineering department was responsible for monitoring its implementation. Maintenance of the manufacturing equipment had to be performed within a month of the target date. The maintenance program for granulation, compression and packaging equipment were reviewed and were found adequate. Maintenance of AHUs and air filters were also performed based on an annual program.

The Purified Water generation and distribution system was reviewed, 45 user points were included in the Main Production building. Different PW generation systems and storage tanks were available for the Main Production Building and the Rifa Block. For Main Production Building, water was coming from bore well and initially was stored in raw water storage tank. The water was chlorinated and dechlorinated, pH was corrected, passed from 5 RO columns and finally stored in a potable water tank. Then water was passing through 2 RO columns and EDI and stored in the purified water tank. Conductivity was measured on line with calibrated conductivity meters. Performance of RO was monitored and documented on a daily basis (i.e. in and out pressure, flow rate, quantity produced and rejected). Pre-treatment sampling points were monitored once a month (chemical and microbiological testing). End user sampling points were monitored rotationally on a monthly basis (chemical testing). The return on the storage tank was monitored daily (microbiological and chemical testing). Water system was sanitized according to a written SOP.

14. Materials

There was a procedure in place describing receipt and storage of raw materials. Materials were registered and managed in awarehouse management system in accordance with a written procedure. A check list was used for receipt of raw materials. Four sampling rooms and 5 dispensing rooms (one dedicated to liquids) were available in the Main Pharma Block. Excipients used in Rifa building were sampled, stored and dispensed from the main warehouse. Rifa APIs were stored in a storage area in the Rifa Block. There was sampling equipment dedicated to APIs. Cleaning of sampling equipment was performed according to documented SOP and the effectiveness of cleaning procedure was validated. Sampling of packaging materials was performed according to a written procedure.

15. Documentation

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

16. Good practices in production

Main Production Building and the Rifa Block were visited. Areas inspected included the dispensing areas, granulation, compression rooms, coating rooms and primary and secondary packaging areas. BMRs and BPRs of batches being manufactured during the tour were spot checked as well as maintenance and calibration of equipment. Identified observations were adequately addressed by the company's CAPA plan.

17. Good practices in quality control

Entry to Quality Control laboratories was done through change rooms. There were separate rooms for instruments, chemical analysis and washing/cleaning. Samples were received and kept in a separate room. Records of chemical analysis were reviewed. Analytical testing records were maintained and there was traceability to reagents that were used. Data integrity, electronic data access and privileges, back up and restoration were reviewed. Identified observations were adequately addressed by the company's CAPA plan.

A separate entrance was used for Microbiological laboratory. The premises included the preparation area and the testing area. Records for performance of microbiological testing were reviewed and traceability was appropriate and adequately documented. Culture media were prepared according to relevant SOP and growth promotion was performed. Microorganisms were stored and used according to the written procedures.

Part 3	Conclusion – Inspection outcome

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, ***Cadila Pharmaceuticals Ltd. (Main Pharma Block and Rifa Block)*** located at ***Survey No.1389 Trasad Road, Dholka 382 225 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.

Part 4	List of WHO Guidelines referenced in the inspection report

1. WHO good manufacturing practices for pharmaceutical products: main principles. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Eighth Report Geneva, World Health Organization, 2014 (WHO Technical Report Series, No. 986), Annex 2. ***Short name: WHO TRS No. 986, Annex 2***
   http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_986/en/
2. WHO good manufacturing practices for active pharmaceutical ingredients. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957), Annex 2. ***Short name: WHO GMP for APIs*** or ***TRS No. 957, Annex 2***
   http://www.who.int/medicines/publications/44threport/en/

3. WHO good manufacturing practices: water for pharmaceutical use. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fourth-Sixth Report. Geneva, World Health Organization, 2012 (WHO Technical Report Series, No. 970), Annex 2
   Short name: WHO TRS No. 970, Annex 2
   http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_970/en/

4. WHO guidelines for sampling of pharmaceutical products and related materials. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-Ninth Report. Geneva, World Health Organization, 2005 (WHO Technical Report Series, No. 929), Annex 4
   Short name: WHO TRS No. 929, Annex 4
   http://whqlibdoc.who.int/trs/WHO_TRS_929_eng.pdf?ua=1

5. Guidelines on heating, ventilation and air-conditioning systems for non-sterile pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-Second Report Geneva, World Health Organization, 2018 (WHO Technical Report Series, No. 1010), Annex 8. **Short name: WHO TRS No. 1010, Annex 8**
   http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_1010/en/

6. Supplementary guidelines on good manufacturing practices: validation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fortieth Report. Geneva, World Health Organization, 2006 (WHO Technical Report Series, No. 937), Annex 4
   Short name: WHO TRS No. 937, Annex 4
   http://whqlibdoc.who.int/trs/WHO_TRS_937_eng.pdf?ua=1

7. WHO Good Practices for Pharmaceutical Quality Control Laboratories. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957, Annex 1
   Short name: WHO GPPQCL Guidelines or ***TRS No. 957, Annex 1***
   http://www.who.int/medicines/publications/44threport/en/

8. WHO Good Practices for Pharmaceutical Products Containing Hazardous Substances. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957), Annex 2
   Short name: WHO TRS No. 957, Annex 2
   http://www.who.int/medicines/publications/44threport/en/

9. WHO good manufacturing practices for sterile pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 6
   Short name: WHO TRS No. 961, Annex 6
   http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

10. WHO guidelines on transfer of technology in pharmaceutical manufacturing WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 7
    Short name: WHO TRS No. 961, Annex 7
    http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

11. Model guidance for the storage and transport of time-and temperature-sensitive pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 9. ***Short name: WHO TRS No. 961, Annex 9***
    http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

12. General guidelines for the establishment maintenance and distribution of chemical reference substances. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-First Report Geneva, World Health Organization 2007 (WHO Technical Report Series, No.943) Annex 3
    Short name: WHO TRS No. 943, Annex 3
    http://whqlibdoc.who.int/trs/WHO_TRS_943_eng.pdf?ua=1

13. WHO good practices for pharmaceutical microbiology laboratories. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 2
    Short name: WHO TRS No. 961, Annex 2
    http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

14. WHO guidelines on quality risk management. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Seventh Report Geneva, World Health Organization, 2013 (WHO Technical Report Series, No. 981), Annex 2. ***Short name: WHO TRS No. 981, Annex 2***
    http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_981/en/

15. WHO guidelines on variation to a prequalified product. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Seventh Report Geneva, World Health Organization, 2013 (WHO Technical Report Series, No. 981), Annex 3. ***Short name: WHO TRS No. 981, Annex 3***
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_981/en/

16. WHO guidelines for drafting a site master file. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 14. ***Short name: WHO TRS No. 961, Annex 14***
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

17. WHO Guidelines on good manufacturing practices: validation, Appendix 7: non-sterile process validation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 3. ***Short name: WHO TRS No. 992, Annex 3***
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

18. WHO General guidance on hold-time studies WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 4. ***Short name: WHO TRS No. 992, Annex 4***
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

19. WHO Technical supplements to Model Guidance for storage and transport of time – and temperature – sensitive pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 5. ***Short name: WHO TRS No. 992, Annex 5***
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

20. WHO Recommendations for quality requirements when plant – derived artemisin is used as a starting material in the production of antimalarial active pharmaceutical ingredients. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 6
Short name: WHO TRS No. 992, Annex 6
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

21. Guidance on good data and record management practices. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fiftieth Report Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 5
Short name: WHO GDRMP or ***WHO TRS No. 996, Annex 5***
http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex05.pdf

22. WHO general guidance on variations to multisource pharmaceutical products. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fiftieth Report* Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 10
Short name: WHO TRS No. 996, Annex 10
http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex10.pdf

23. Stability testing of active pharmaceutical ingredients and finished pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-Second Report Geneva, World Health Organization, 2018 (WHO Technical Report Series, No. 1010), Annex 10.
Short name: WHO TRS No. 1010, Annex 10
http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex10.pdf