

**Prequalification Team
WHO PUBLIC INSPECTION REPORT
(WHOPIR)
Active Pharmaceutical Ingredient (API) Manufacturer**

PART 1: GENERAL INFORMATION

Name of Manufacturer	Cadila Pharmaceuticals Ltd
Unit	Unit I
Production blocks	ETA blocks - Ethambutol hydrochloride API MPP-II blocks - Ondansetron monohydrochloride dihydrate API
Physical address	294 GIDC Industrial Estate, Ankleshwar 393 002, Gujarat, India
Date of inspection	21 – 24 April 2015
Type of inspection	Routine GMP inspection
Active Pharmaceutical Ingredient(s) included in the inspection	Ethambutol API used for: Ondansetron monohydrochloride dihydrate API used for:
Summary of the activities performed by the manufacturer	Production and quality control of intermediates and finished non-sterile APIs. No toxic or hazardous substances were handled or manufactured

PART 2: SUMMARY***General information about the company and site***

Cadila Laboratories Limited was established in 1951. Restructuring of Cadila Laboratories Limited took place in June 1995 and Cadila Pharmaceuticals was formed. The Active Pharmaceutical Ingredients manufacturing facility is located at Ankleshwar, Gujarat, India.

According with the company presentation total number of employees was about 389:

- 25 employees were involved in QA activities
- 61 employees were involved in QC activities
- 195 employees were involved in production activities.

Production activities were carried out in six API manufacturing blocks:

- Alpha block
- Omega block
- ETA block
- MPP-II block
- MPP-III block
- MPP-IV block

Ethambutol hydrochloride API was manufactured at ETA block and Ondansetron monohydrochloride dihydrate API was manufactured at MPP-II block.

The manufacturing site was previously inspected by:

- US FDA – March 2014
- Australia TGA – December 2013 and certified for particular products, including Ondansetron Hydrochloride and Ethambutol Hydrochloride (2013)
- COFEPRIS Mexico (2015)
- KFDA South Korea
- ISO 9001:2008 Quality management System – certificate valid until 22nd April 2016
- ISO Environmental Quality Management System – certificate valid till 17th May 2016
- OHSAS 18001:2007 Health and Safety management System - certificate valid till 23rd July 2017

The site holds a CEP for Ondansetron Hydrochloride.

History of WHO and/or regulatory agency inspections

The site was previously inspected by the WHO team in 26 – 29 November 2012.

Focus of the inspection

The inspection focused on the production and control procedures of Ethambutol API and Ondansetron monohydrochloride dihydrate API.

The inspection covered the following sections of ICH Q7, including premises, equipment, documentation, materials, validation, sanitation and hygiene, production and quality control.

Inspected Areas

- Quality Management
- Personnel
- Buildings and facilities
- Process equipment
- Documentation and records
- Materials management
- Production and in-process controls
- Packaging and identification labelling of APIs and intermediates
- Storage and distribution
- Laboratory controls
- Validation
- Change control
- Rejection and reuse of materials
- Complaints and recalls
- Contracts

PART 3: INSPECTION OUTCOME**3.1 QUALITY MANAGEMENT****Principles**

In general, a system for managing quality was established, documented and implemented. The quality unit was independent of the production department. The person responsible for release of intermediates and APIs was specified. Deviations from established procedures were documented and explained. Materials were released after quality unit satisfactory evaluation.

The organizational chart of the Chemical SBU (Strategic Business Unit) for the manufacturing blocks (Unit I and Unit II) was reviewed. All quality functions of the six blocks in Unit I were reporting to Vice President (VP) of Quality.

The In-process Quality Assurance (IPQA) team was set up recently. The responsibilities of the team included daily plant rounds, review of the ongoing batch records, review of Quality Control (QC) data under analysis as well as compliance and labeling related responsibilities on 'as needed' basis.

Responsibilities of the quality unit(s)

Responsibilities of the Quality units and production units were specified in individual job descriptions.

The following Job descriptions were reviewed:

- Vice President – Quality
- Senior Vice President – Operations
- Vice President – Operations.

Internal audits (self-inspection)

Regular internal audits were performed in accordance with approved SOP “Internal audit (self-inspection)”. Quality Assurance (QA) personnel were responsible for preparation of the audit plan and audit check list and conducting the audit. Internal audits were carried out by a cross functional team that consisted of personnel from different departments. Auditors were trained in-house. A list of internal auditors and auditors training records were presented to inspectors. During inspection training of internal auditors was discussed. It was advised to follow international guidelines for internal auditors training.

Audits were carried out once every three months (except QC which was audited every month), using department based check lists. After audit the non-conformance report (NCR) was written.

NCR was approved by the Head – QA. The CAPAs were verified by the auditor and Head of the QA.

Product quality review (PQR)

The SOP “Product Quality review” was reviewed. In accordance with the SOP, PQRs should be prepared annually for the complete range of products manufactured. The responsibility was assigned to Quality Assurance along with a time limit (May) for completion. Regular quality reviews of APIs were conducted and included quality and yield parameters as:

- General product information
- Process flow diagram
- List of key starting materials and its quality attributes
- Review of batch wise results of quality attributes and yield of the product
- Review of in-process controls
- Review of Out of Trend (OOT) recorded for the product
- Review of Out of Specification (OOS) recorded for the product
- Failures recorded during the manufacturing process
- Review of reprocessing and reworking for the product
- Review of deviations recorded during manufacturing process
- Review of new documents initiation, temporary change controls and change control details in manufacturing process
- Review of new documents initiation, temporary change controls and change control details in the specifications and analytical methods of intermediates and finished drug substance specifications
- Review of market complaints, recalls and sales returns
- Review of packaging and labelling materials
- Review of microbial study of the finished product
- Review of purified water (PW) analysis and environmental monitoring

- Review of qualification of equipment, analytical method validation, process validation and revalidation
- Review of vendor qualification
- Review of on-going stability studies
- Review of corrective and preventive actions (CAPA) for the product
- Review of previous year recommendations & actions taken in the current year and recommendations for next year and suggested revalidation, if required.

The results of PQR were evaluated and an assessment was made of whether corrective action or any revalidation should be undertaken.

Ethambutol hydrochloride PQR for 2014 and Ondansetron HCl PQR for years 2013 and 2014 were reviewed.

Deviations

The SOP “Deviation Management system” was reviewed.

The process of initiation of deviations included a QA review of information and issuance of a deviation number. QA made the decision on initiating an investigation as minor deviations did not require investigation.

Root cause investigation techniques were used by the investigation teams.

Quality risk management (QRM)

The SOP “Risk” was reviewed. Based on the SOP, the QRM for 30 products (including Ethambutol HCl and Ondansetron HCl) was completed with the conclusion that all processes were in state of control with no quality risk to patients.

Management review

The SOP “Information to management” was spot checked. Management meetings were carried out monthly. Department heads were participating in the management review meetings.

3.2 PERSONNEL

Personnel qualifications

There were an adequate number of personnel qualified to perform and supervise the manufacture of intermediates and APIs. The responsibilities of personnel engaged in the manufacture of intermediates and APIs were specified in writing.

Personnel hygiene

Acceptable sanitation habits were observed on site. Direct contact with intermediates or APIs was avoided. Personnel were wearing clean clothing suitable for the manufacturing activity in which they were involved.

Training

SOP “Training” was spot checked. The following training modules were used:

- Induction training program for new employees
- On-job training program
- GMP training for all employees/class room training
- External training

Training attendance sheet for the topic “Cross contamination in API manufacturing industries” along with training assessment report were spot checked. Training records were maintained in the HR department. Training was carried out on different topics every month. Training schedule January 2015 – June 2015 was presented to the inspectors.

The SOP “Competency qualification of analyst” was reviewed. According with the SOP before assigning the independent work, the new analyst should be validated.

A specific training record for analyst working with HPLC was checked. Analysts training records were maintained in the QC laboratory.

Individual analyst qualification records and specimen signature lists were available and presented to the inspectors.

Consultants

Four consultants were used on site. Consultants CVs were presented to the inspectors and spot checked. Spot checks showed that consultants had sufficient education, training, and experience.

3.3 BUILDINGS AND FACILITIES

Design and construction

In general buildings and facilities used in the manufacture of intermediates and APIs were located, designed, and constructed to facilitate cleaning, maintenance and operations as appropriate to the type and stage of manufacture. Buildings and facilities had adequate space for the orderly placement of equipment and materials. Laboratory areas and operations were separated from production areas.

Utilities

Not covered during this inspection.

Water

Not covered during this inspection.

Containment

Highly sensitizing materials were not manufactured on site.

Lighting

Adequate lighting was provided in to facilitate cleaning, maintenance and proper operations.

Sewage and refuse

Not covered during this inspection.

Sanitation and maintenance

In general buildings used in the manufacture of intermediates and APIs were properly maintained and repaired and kept in a clean condition. Written procedures were established for sanitation and describing the cleaning schedules methods, equipment and materials to be used.

The equipment cleaning was performed as Type-I and Type II cleaning. Type I cleaning was batch to batch cleaning and Type-II cleaning was complete cleaning after changeover or between the batches of the campaign production.

Contamination control

The SOP “Environmental monitoring (EM) in powder processing area” was checked. Powder processing area EM was carried out every month. EM was performed using settle plates containing soybean casein digest agar medium. Settle plate location positions were attached to the SOP for each manufacturing block. Alert and action limits were defined.

EM trends for 2014 were reviewed. All results were less than alert limit. It was said that alert limit was never reached through the entire site.

3.4 PROCESS EQUIPMENT

Design and construction

In general equipment used in the manufacture of intermediates and APIs was of appropriate design and adequate size, and suitably located for its intended use. Major equipment such as reactors and centrifuges, and permanently installed processing lines used during the production of an intermediate or API were appropriately identified.

Equipment maintenance and cleaning

Schedules and procedures were established for the preventive maintenance of equipment. In general leaning procedures contained sufficient details to enable operators to clean each type of equipment. Acceptance criteria for residues and the choice of cleaning procedures and cleaning agents were defined. Equipment was identified as to its contents and its cleanliness status.

Preventive maintenance

The SOP “Preventive maintenance” was presented during inspection along with Planner prepared for the calendar year.

Maintenance records were verified for SS reactor maintenance and centrifuge maintenance.

Overall maintenance was performed during shutdown (once/year).

Calibration and qualification

Control, weighing, measuring, monitoring and test equipment that was critical for assuring the quality of intermediates or APIs were calibrated according to written procedures and an established schedule. Records of calibrations were maintained. The current calibration status of critical equipment was known and verifiable.

Two SOPs were in place for calibration practices. The SOP “Calibration scheduling” and the SOP “External Calibrations” were spot checked.

Critical and non-critical equipment was differentiated by different color tags. Calibration schedule was prepared for every block each year.

Instruments calibrated by external party are: thermometers, pressure gauges, digital temperature indicators, temperature sensor elements, differential pressure gauges, vacuum gauges.

Computerized systems

GMP-related computerized systems in Quality Control laboratory (QCL) were validated upon installation by the service provider. Validation protocols/reports were not checked during the inspection. Computerized systems were not used in production.

Laboratory computerized systems (HPLC, GC and FTIR – were checked) had sufficient controls to prevent unauthorized access or changes to data. There were controls in place to prevent omissions in data (e.g. the system being turned off and data not captured).

The records were available of data change made, the previous entry, the person who made the change and when the change was made. Back-up system was provided.

Electronic data back-up was performed on weekly basis on tapes.

In the warehouse, materials were managed using the SAP system. It was explained that the system had been re-validated in March 2014 by external company. Validation documents had not been reviewed.

3.5 DOCUMENTATION AND RECORDS

Documentation system and specifications

In general documents related to the manufacture of intermediates and APIs were prepared, reviewed, and approved. Specifications were established and documented for raw material, intermediates and finished API. Acceptance criteria were established and documented for in-process controls. Production, control and distribution records were retained for at least one year after the expiry date of the batch.

Equipment cleaning and use record

Records of major equipment use, cleaning, sanitization and maintenance showed the date, time, product and batch number of each batch processed in the equipment, and the person who performed the cleaning and maintenance.

Records of raw materials, intermediates, API labeling and packaging materials
Some records were spot-checked.

Master production instructions

Master production instructions had been established and appropriately approved.

Batch production records (BPR)

The BPR for Ethambutol HCL and related batches of all intermediates were checked against Master Formula. BPR batch and process operations were traceable.

The company assigned a batch number for the intermediate gained from every stage during the manufacturing process. For every batch of the intermediate used for finished API, both Production and QA Department reviewed the BPR for release and a release note signed by QA was included to BPR. Batches and process operations were traceable. BPR contained all critical steps, which were printed in bold letters, and detail records of all critical process parameters.

Laboratory control records

Some laboratory records were spot checked.

3.6 MATERIALS MANAGEMENT

General controls

In the warehouse, materials were managed using the SAP system. Raw Material Store, Packaging Material Store, Finished Goods Store, Hazardous Material Store, Reject/Return Goods, Acid Yard, Plastic Waste, Solvents Tanks were inspected.

Receipt and quarantine

Receiving area in Raw Material Store was inspected and the SOP “Receipt and storage of Raw Material, Packaging Material” was reviewed. Receiving area was equipped with de-duster, conveyor rollers and two scales (600 Kg, 300 Kg capacity). Materials were held under quarantine until they were sampled, tested and released for use.

Sampling and testing of incoming production materials

Containers from which samples were withdrawn were marked to indicate that a sample has been taken. Sampling and dispensing of key starting materials and primary packing materials were carried out in the warehouse in separate room, protected from environment.

Before sampling of solvents delivered in road tankers, tanker cleaning certificate was checked, then sampling was carried out. Samples were taken from the top, middle and bottom of the tanker.

The SOP “Sampling, testing and release of raw materials and packaging materials” was spot checked.

Storage

Storage of specific starting materials was spot-checked. The manufacturers of these two starting materials used for Ethambutol HCL were consistent to the List of Approved Vendor for Key Starting Materials.

Temperature mapping protocol/report AC storage room was checked. T mapping was performed seasonal based:

- Summer
- Winter
- Rainy season
- Autumn

Storage areas for primary packaging materials, secondary packaging materials and finished products were also inspected. Finished products were stored in temperature controlled area.

Sales return products were segregated.

There was a designated area for solvent dispensing. Solvents were also stored in above- and underground tanks.

Re-evaluation – retest of raw materials

Follow up of re-tests dates were generated by SAP system. Some exemptions were allowed if re-test was not carried out on specified time. In this case re-testing was carried out before products were taken to the production.

Vendor qualification

The SOP “Vendor qualification” was reviewed. Responsibilities related to vendor qualification were assigned to supply chain management, quality assurance, regulatory affairs, process excellence lab, warehouse and QC.

A vendor list was issued for:

- Starting materials
- Key materials
- Advanced intermediates
- Critical raw materials
- Other raw materials
- Packaging materials

Purified water (PW)

The specification for Purified Water USP and the SOP “Monitoring program Sampling and Analysis of Purified Water” were reviewed.

3.7 PRODUCTION AND IN-PROCESS CONTROLS

In general raw materials for manufacturing of intermediates and APIs were dispensed and measured under appropriate conditions that did not affect their suitability for use, except solvents and acids what were store outside without any protection from weather. Actual yields were compared with expected yields at designated steps in the production process. Deviations were documented and explained. In general processing status of major units of equipment was labelled with product names and batch numbers.

Production operations

Ondansetron HCl was manufactured in MPP-II (Module I) block and Ethambutol HCl was manufactured in the ETA block respectively. Both products were manufactured in non-dedicated facilities on campaign based production along with low, medium and high complexity processes in the same block.

MPP-II production block was inspected. During inspection, manufacturing process and in-process control were checked step by step.

Ethambutol HCL production block was inspected. During inspection, manufacturing process and in-process control were checked step by step.

Time limits

Time limits were specified in BMRs.

In-process sampling and controls

In-process sampling was done by the operators; controls were carried-out in the Quality control laboratory.

Blending batches of intermediates or APIs

Blending of batches was carried out according to the written SOP “Blending of intermediates/active pharmaceutical ingredients”. After blending the new batch number was assigned. According to the SOP OOS batches should not be blended with other batches. Blending of batches was allowed:

- To increase the batch size
- Blending of tailings from batches to form a single lot.

The expiry or retest date of the blended batch was based on the manufacturing date of the oldest tailings or batch in the blend. Blending operations were carried out as per blending BPR. The blending BPR for Ethambutol was reviewed.

After blending the batch was tested as per established specifications. Finished product work sheet and Certificate of Analysis for the blended batch was spot checked. Analytical work sheet every page was checked and signed by QC assistant manager/deputy manager.

3.8 PACKAGING AND IDENTIFICATION LABELLING OF APIs AND INTERMEDIATES

Primary packaging materials were stored in the warehouse in plastic drums.

Finished product labels were generated by computer system in QA department. Issuance and reconciliation of labels were QA responsibility. The finished API labels contained the following information:

- Mfg. Lic. No
- Lot No.
- Mfg. Date
- Expiry Date
- Gross Wt
- Tare Wt
- Net Wt
- Storage conditions
- Phone and fax numbers
- Manufacturer name and address

During the inspection packaging and labelling operations were not carried out.

3.9 STORAGE AND DISTRIBUTION

Warehousing procedures

Inspectors made an inspection tour to the warehouses – main warehouse, finished product warehoused and solvent farm. Facilities were provided for the storage of all materials, except solvents in drums. Released and rejected materials were stored separately. Quarantine areas were identified.

Distribution procedures

APIs were released for sale after QA approval. According to the company, records for dispatch of batches (linked to the release of batches, as well as issuing of the BPRs) were kept by QA.

3.10 LABORATORY CONTROLS

Physical/Chemical Laboratory was inspected, including HPLC Room, Gas Chromatography Room, IR Room, Retain Sample Room, Stability Chamber Room, and Service Room.

The laboratory operated in 3 shifts. Samples were received and assigned by laboratory supervisor to chemists using LIMS. Sample preparations were recorded on protocols issued by lab supervisor. Completed protocols were returned to supervisor for review.

The laboratory was equipped with a number of HPLC systems, all connected with Empower Software. Empower 3 software was used for electronic data processing from all HPLC systems. In addition, there were a number of Gas Chromatographs, all connected with server

to Quality Control Management System (QCMS). Other equipment used in the QC lab was: UV, FT-IR, Particle Size Analyzer etc.

LIMS was used for data storage and it had interface with SAP.
The software access privileges were defined.

General controls

Quality unit had adequate laboratory facilities – instrumental, chemical, stability and microbiology laboratories. Documented procedures describing sampling, testing, approval or rejection of materials and recording and storage of laboratory data were available. Laboratory records were maintained for 6 years in the document archive. OOS results obtained were investigated and documented. Primary and secondary (working standards) were available to perform analysis.

HPLC columns were stored in a dedicated cabinet. Usage was verified in the logbook for the column C₁₈.

Testing of intermediates and APIs

Testing of intermediates and APIs was carried out in accordance with approved methods of analysis and specifications.

SOP “Testing procedure for in-process samples” was reviewed. Production provided Test Information Report (TIR) and sample for testing. Test results were recorded on TIR. Result pass/fail was entered in the register. One copy of TIR was received by QA with analytical report and the original was sent to Production (BPR).

Batch release

SOP “Finished drug substance release” was reviewed. Check lists were used for controlling BMR and analytical raw data. Analytical raw data review check list did not require reviewing electronic raw data e.g. HPLC, GC chromatograms, UV and FTIR spectrograms and respective audit trails.

Validation of analytical procedures

Not covered during this inspection.

Certificates of analysis (CoA)

Certificates of Analysis were issued, verified and approved in QC. Certificates of Analysis along with analytical raw data were forwarded to QA for final release and “approved” label issuance. CoA`s were issued, checked and approved for finished APIs.

Analytical test reports (ATR) were issued, checked and approved for all intermediates tested. CoA`s and ATRs listed each test performed.

Stability monitoring of API's

The SOP “Stability Study” was reviewed. Product specific stability study protocol for API's was required to be pre-approved before execution.

Stability study for the reprocessed batch of Ethambutol HCl was spot-checked to evaluate if the SOP of Stability Study was followed properly.

Ethambutol Hydrochloride Stability Study Protocol which was used for process validation batches was reviewed.

Access to stability sample storage was controlled. Stability Chamber Room was inspected. 5 chambers and 1 walk-in chamber were used to keep the samples for stability study in different conditions. One of the chambers was on “stand.by”. Alarm systems were installed on the chambers to inform QC person once the temperature/RH was out of the limit. The temperature and RH of the chambers were recorded automatically once an hour. The samples for long-term stability study of Ethambutol HCl were checked.

The following conditions were provided in individual stability chambers:

Temperature: $25^{\circ}\text{C} \pm 2^{\circ}\text{C}$ and Relative Humidity: $60\% \pm 5\%$

Temperature: $40^{\circ}\text{C} \pm 2^{\circ}\text{C}$ and Relative Humidity: $75\% \pm 5\%$

Temperature: $30^{\circ}\text{C} \pm 2^{\circ}\text{C}$ and Relative Humidity: $65\% \pm 5\%$

Temperature: $30^{\circ}\text{C} \pm 2^{\circ}\text{C}$ and Relative Humidity: $75\% \pm 5\%$

Expiry and retest dating

Expiry dates assigned to the products were based on stability studies. In case stability studies had not been finalized re-test date was assigned based on information provided from R&D department.

Reserve/retention samples

SOP “Storage and control of retain sample” was checked. Appropriately identified reserve samples of each batch of API were retained for one year after the expiry date. In case of APIs with re-test date the SOP did not specify retention time. The reserve samples were stored in the same packaging system in which the API was stored. Sufficient quantities were retained to conduct at least two full analyses.

Access to retained sample storage was controlled. Storage of retained samples was verified by locating batch numbers. Storage and record keeping of 2013 retained samples was checked. Temperature and RH meter was checked and related record was reviewed. Register and retain samples for Ethambutol HCl and Ondansetron HCl since 2013 were spot-checked.

Reference standards

All reference standards used for physical/chemical laboratory were stored in the refrigerator. Caffeine standard which was used as a reference standard for HPLC calibration and supplied by Sigma-Aldrich, use log and COA were spot-checked. The SOP “Usage and Storage of

Reagents & Chemicals” was reviewed. Storage (temp 2-8 °C) and record keeping of primary standards was checked.

The SOP “Preparation and qualification of working standard and reference standard” was reviewed

Out of specification investigations (OOS)

The SOP “Investigation out of specification results” referred to Laboratory investigation (phase I) for raw materials, intermediates, finished products and stability testing. LIMS was in process of development with respect to record keeping of OOS.

The process of issuance of OOS investigation started with the analyst informing the supervisor about the non-conformance, all sample preparations were retained, available for further analysis. QA issued OOS. If laboratory phase investigation did not identify the root cause the investigation would be extended to other areas. Re-sampling had to be approved by QA manager. The time frame for QC investigation was limited to 10 days.

OOS Phase II investigation procedure was explained in the separate SOP “Failure Investigation”. This SOP was linked to the deviation procedure, as above.

A specific OOS investigations were reviewed.

The document “Comprehensive review report out of specification” – 2014 was checked.

3.11 VALIDATION

Validation policy (Validation Master Plan) VMP

The VMP was reviewed. According to the procedure, the VMP was revised when changes occurred to the production processes.

Approaches to process validation

Guidelines on the content of validation protocol were based on various processing steps and they were included in the VMP. Validation protocol and report formats were included in Process Validation SOP.

Process validation programme

Process validation protocol for the manufacturing of Ondansetron HCl was reviewed during the inspection.

Equipment qualification list, raw materials for each stage of processing, recovered solvent checklist, critical process parameters, in process checks, analysis requirements, cleaning requirements and recording sheets were included in the process validation protocol.

Cleaning validation

The cleaning validation master plan was reviewed during the inspection

Ethambutol HCl cleaning validation protocol/report were reviewed.

The company defined two types of cleaning procedure:

Type I:

- same product: between two successive batches

Type II:

- Same product: after 20 +/-2 batches
- Changeover from one stage to another stage of the same product
- After maintenance
- Product changeover

Cleaning procedures described three types of evaluation: visual, swab and rinse samples.

The limit for maximum allowable carryover (MACO) of previous product in the next product was described to be established on therapeutic dose based criteria or a limit of 10 ppm was applied.

3.12 CHANGE CONTROL (CC)

A formal CC system was established to evaluate changes that may affect the production and control of the intermediate or API. The potential impact of the proposed change on the quality of the intermediate or API was evaluated.

The SOP “Change Control System” was reviewed. A flowchart and change control form was included in the procedure. Changes were classified as:

- Minor
- Moderate
- Major

According to the current procedure change classification was taken into consideration by QA during change control management.

A specific CC reports were reviewed.

3.13 REJECTION AND RE-USE OF MATERIALS

Rejection

The SOP “Rejection and re-use of material” and register from 2013 were reviewed along with the SOPs “Sampling, Testing and Release of Raw Materials (RM) and Packaging Material (PM)”, Raw Material and Packaging Material NCR Inward Register 2013, 2014 and 2015.

Reprocessing and reworking

The SOP “Reprocessing and reworking of Active Pharmaceutical Ingredients and intermediates”) was reviewed.

Recovery of materials and solvents

The SOP “Receipt, dispensing & Issuance of Solvents”, the SOP “Preparation and Filling of Solvent Distillation Record”) and the SOP “Testing Procedure for Recovered Solvents” were reviewed.

3.14 COMPLAINTS AND RECALLS

The SOP “Handling of market complaints” was reviewed. Complaints were categorized as:

- Critical complaints
- Other complaints.

The responsible person for dealing with complaints was specified and was the site Head QA. The Head of QA was responsible for the investigation of the complaint, monitoring the CAPAs and closing out of complaint. According to the SOP “previous” and “after” batches should be investigated. If required decision of the recall was considered by the Head QA and Factory Head. It was discussed that investigation of possibly affected other product batches manufactured using the same premises and equipment also should be taken into account.

Complaint registers 2013 and 2014 were checked.

The document “Comprehensive review report market complaints – 2014” was reviewed.

The SOP product recall procedure was reviewed. According to the SOP, a recalls can be voluntary or it can be initiated based on instruction from any legal, regulatory authority.

The responsible person for dealing with recalls was specified and was site Head QA. In case of recall from overseas respective regulatory authority should be informed.

There were no recalls initiated until the inspection. According to the SOP Mock recalls should be performed annually. Till the date of inspection one mock recall was performed.

3.15 CONTRACT MANUFACTURERS (INCLUDING LABORATORIES)

Production operations were not contracted out.

Two contract laboratories were used for two tests according with customer specific requirements.

Technical agreement (service agreement) with contract laboratory was spot checked and was found acceptable. Parties (contract giver and contract acceptor) responsibilities were clearly specified.

“Qualification of contract analytical laboratory” audit report was spot checked.

PART 4: CONCLUSION

Based on the areas inspected, the people met and the documents reviewed, and considering the findings of the inspection, including the deficiencies listed in the Inspection Report, as well as corrective actions taken and planned, APIs (Ethambutol and Ondansetron) manufactured at Cadila Pharmaceuticals Ltd, located at 294 GIDC Industrial Estate, Ankleshwar 393 002, Gujarat, India, were considered to be manufactured in compliance with WHO GMP for Active Pharmaceutical Ingredients.

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.