

**WHO PUBLIC INSPECTION REPORT
(WHOPIR)
API Manufacturer**

Part 1: General information

Name of manufacturer	Cadila Pharmaceuticals Ltd
Unit	Unit I
Production block	ETA block
Physical address	294 GIDC Industrial Estate, Ankleshwar 393 002, Gujarat, India
Date of inspection	26 - 29 November 2012
Type of inspection	Routine GMP inspection
Active Pharmaceutical Ingredient(s) included in the inspection	Ethambutol <u>Hydrochloride (HCL)</u>
Summary of the activities performed by the manufacturer	Production and quality control of intermediates and finished APIs

Part 2: Summary

Background information

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.

The total number of employees was about 265. Nine employees were involved in QA activities, 35 in QC activities and 116 in production activities.

Production activities were carried out in seven API manufacturing blocks and eight powder processing blocks.

The manufacturing site was previously inspected by the following authorities:

- US FDA
- Australia TGA (certified for particular products)

The following methods of syntheses were used at the site:

- Alkylation
- Halogenations(Cl, Br)
- Condensation
- Methylation
- Friedel-Crafts reaction
- Idol Condensation
- Cyanation
- Darzen's Condensation
- Loop Chlorination
- Sandmeyer reaction
- Trans – Esterification
- Catalytic reduction
- Oxidation
- Knoevenagel Condensation
- Catalytic Hydrogenation up to 12 kg/Cm²
- Grignard's reaction
- Liquid Ammonia reactions
- Optical Resolution
- Reformatsky reaction

History of WHO or regulatory agencies inspections

This was the first WHO inspection at this site.

Focus of the inspection

The inspection focused on the production and control procedures of Ethambutol API. The inspection covered several sections of WHO good manufacturing practices for active pharmaceutical ingredients, including premises, equipment, documentation, materials, validation, production and quality control.

Inspected Areas

- Quality Management
- Qualification and validation
- Complaints and Recalls
- Self-inspection
- Personnel Training
- Premises
- Equipment
- Materials
- Documentation
- Production
- Rejection and reuse of materials
- Quality control

2.1 QUALITY MANAGEMENT

In general, a system for managing quality was established. The quality department was independent of the production department.

Product quality review

PQR SOP (Annual product review) and Annual review for batches manufactured in 2011 were reviewed. Annual review was done before March every year. The regular quality review included aspects as per GMP. For Ethambutol HCl, the company identified two out-of-trend results – one for methanol content. An investigation was done to the root cause of the out-of-trend methanol content and CAPA was recommended. During the review period no batches were reworked and reprocessed. Three change controls were applied – related to the specification for method of analysis of Ethambutol HCl. There were no complaints, no recalls and no OOS results for Ethambutol HCl (in all 6 stages of manufacturing). In general, the PQR was acceptable.

Non-compliances observed during the inspection that were listed in the full report were addressed by the manufacturer to a satisfactory level.

Corrective action and preventive action

SOP for CAPA was applicable to:

- Deviations
- OOS
- Internal audits/external/customer audits
- APR (PQR)
- Product failures
- Customer complaints
- OOT
- Out of Calibration

Non-compliances observed during the inspection that were listed in the full report were addressed by the manufacturer to a satisfactory level.

Responsibilities of the quality and production units

Job descriptions for QA, QC and for Production personnel were available, addressing general responsibilities. The following job descriptions were spot checked:

- Head Quality
- Manager QC
- Assistant General Manager QA
- Sr. Manager Production

Non-compliances observed during the inspection that were listed in the full report were addressed by the manufacturer to a satisfactory level.

Internal audits (self-inspection)

SOP for Self-inspection was reviewed. Internal audits were performed in accordance with approved schedule and questionnaire every three months for all departments. During inspection it was discussed that internal audit reports should be improved and more attention should be paid listing observations and reviewing and approving CAPAs. Internal audit procedure should be improved.

Non-compliances observed during the inspection that were listed in the full report were addressed by the manufacturer to a satisfactory level.

Supplier approval

Glutamic acid manufacturer audit was carried out according to questionnaire, audit report, observations as well as preliminary questionnaire for vendor qualification and responses were presented to the inspectors. In general supplier approval was found to be adequate.

D,L-2-Aminobutanol manufactured was based in European Union and the site was approved based on the vendor self-evaluation questionnaire.

Product release

There was an SOP for the release of the finished API, and checklists were included as Annexes. Some batches were checked for compliance with the release procedure.

Non-compliances observed during the inspection that were listed in the full report were addressed by the manufacturer to a satisfactory level.

2.2 PERSONNEL**Personnel qualifications**

There were an adequate number of personnel qualified to perform and supervise the manufacture of intermediates and APIs.

Training

Training SOP was reviewed. According with the SOP the following types of training were specified:

- Induction training for new employees
- On the job training
- cGMP training for all employees
- External training

Training was evaluated by multiple choice questions and in some cases by descriptive questions.

Training records were kept in the common company training file. Some training assessments were reviewed. Reviewed training records showed that there was place for improvement e.g. training topics, training presentation and evaluation.

Non-compliances observed during the inspection that were listed in the full report were addressed by the manufacturer to a satisfactory level.

Procedure for validation of analyst

Predetermined sample was selected and coded and given for analysis.

Non-compliances observed during the inspection that were listed in the full report were addressed by the manufacturer to a satisfactory level.

Personnel hygiene

Direct contact with intermediates or APIs was avoided.

Consultants

Not inspected.

2.3 BUILDINGS AND FACILITIES**Design and construction**

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. Some warehouse areas require attention and maintenance.

Non-compliances observed during the inspection that were listed in the full report were addressed by the manufacturer to a satisfactory level.

Utilities

Not inspected on site. AHU re-qualification protocol/report was reviewed.

Non-compliances observed during the inspection that were listed in the full report were addressed by the manufacturer to a satisfactory level.

Water

Not inspected on site. Trend data for PW sampling locations SP 41, 30, 31 and 32 were reviewed for September and October 2012.

Non-compliances observed during the inspection that were listed in the full report were addressed by the manufacturer to a satisfactory level.

Containment

Highly sensitizing materials were not manufactured on site.

Lighting

Lighting was adequate.

Sewage and refuse

Not inspected.

Sanitation and maintenance

Specific attention was not paid to sanitization and maintenance during the course of this inspection, due to time constraints.

2.4 PROCESS EQUIPMENT**Design and construction**

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**Preventive maintenance (PM)**

PM was performed in accordance with approved schedule and check lists. Individual check lists were used for every piece of equipment. Several PM check lists were reviewed. In general the quality management system was found to be adequate.

Calibration

SOP and calibration schedule reviewed was applicable for production equipment and utilities. Equipment calibration was performed by a third party. Several calibration certificates were checked. In general calibration was found to be adequate.

Computerized systems

It was said that GMP-related computerized system (SAP) used for materials management in the warehouse was validated; however validation protocol/report was not checked during the inspection.

2.5 DOCUMENTATION AND RECORDS

Documentation system and specifications

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. In general documentation system was found to be adequate.

Equipment cleaning and use record

Cleaning records were spot-checked. No specific observations were made.

Records of raw materials, intermediates, API labeling and packaging materials

Some records were spot-checked. No specific observations were made.

Master production instructions

Master production instructions had been established and appropriately approved.

Batch production records

The specific batch record was checked against the batch record for one of the batches included in the validation. Batches and process operations were traceable.

Laboratory control records

Some laboratory records were spot checked.

Non-compliances observed during the inspection that were listed in the full report were addressed by the manufacturer to a satisfactory level.

Batch production record review

Written procedures were established for the review and approval of batch production and laboratory control records.

Non-compliances observed during the inspection that were listed in the full report were addressed by the manufacturer to a satisfactory level.

2.6 MATERIALS MANAGEMENT

General controls

In the warehouse, materials were managed using the SAP system. It was explained that the system had been validated. Validation documents had not been reviewed.

Receipt and quarantine

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. Primary packaging materials sampling plan was reviewed.

Non-compliances observed during the inspection that were listed in the full report were addressed by the manufacturer to a satisfactory level.

2.7 PRODUCTION AND IN-PROCESS CONTROLS

Production operations

Inspectors inspected Ethambutol API production block.

During inspection the following documents were spot-checked:

- Temperature mapping study finished goods area
- Calibration certificates
- FBD qualification
- Plant Modification Authorization
- Area qualification
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Ethambutol Hydrochloride was synthesized by a multistep process. No specific observations were made. In general production operations were found to be adequate.

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. The expiry or retest date of the blended batch was based on the manufacturing date of the oldest tailings or batch in the blend

2.8 PACKAGING AND IDENTIFICATION LABELLING OF APIs AND INTERMEDIATES

Not inspected.

Packaging materials

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

Label issuance and control

Finished product labels were generated by computer system by QA staff. Issuance and reconciliation of labels were QA responsibility.

2.9 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. Released and rejected materials were stored separately. Quarantine areas were identified.

Non-compliances observed during the inspection that were listed in the full report were addressed by the manufacturer to a satisfactory level.

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.

Non-compliances observed during the inspection that were listed in the full report were addressed by the manufacturer to a satisfactory level.

2.10 LABORATORY CONTROLS**OOS investigation**

There was an SOP for OOS result investigation. SOP should be updated according to the current guidelines.

Chemical and instrumental laboratories were inspected.

Non-compliances observed during the inspection that were listed in the full report were addressed by the manufacturer to a satisfactory level.

Microbiological laboratory

Not inspected on site. Some documents such as media preparation and sterilization, positive and negative controls as well as testing of finished API were reviewed. No specific observations were made.

Testing of intermediates and APIs

Laboratory tests for intermediates were performed in the QCL. Instrumentation and facilities were adequate to conduct the tests required. Impurity profiles were established.

Certificates of analysis

Certificates of analysis (CoA) were issued for each batch of API.

Stability monitoring of APIs

The SOP, master planner, protocol, results and related documents for Ethambutol HCl were checked. In general, the records were acceptable.

Non-compliances observed during the inspection that were listed in the full report were addressed by the manufacturer to a satisfactory level.

Reserve/retention samples

Reserve samples of APIs were stored in the same packaging system in which the bulk APIs were stored. Retention samples were stored for 6 years.

2.11 VALIDATION

Qualification

Qualification of AHU

AHU re-qualification report/protocol was reviewed.

Non-compliances observed during the inspection that were listed in the full report were addressed by the manufacturer to a satisfactory level.

Qualification of FBD

Qualification documentation was reviewed.

Non-compliances observed during the inspection that were listed in the full report were addressed by the manufacturer to a satisfactory level.

Process validation programme

The process was validated in November 2012 (and previously in 2008). Three batches were included in the process validation in 2012. (This was repeated as not all key steps / stages were covered in the 2008 validation).

Non-compliances observed during the inspection that were listed in the full report were addressed by the manufacturer to a satisfactory level.

Temperature mapping studies (warehouse)

Temperature mapping studies report was reviewed. Several data loggers were used in different locations (and temperature and relative humidity (RH) results were reviewed. Results were within limits. (There was no temperature storage condition required for Ethambutol). Although the RH was not controlled or monitored on a routine basis, the company was of the opinion that the stability data show that the material can be stored under the conditions as were obtained in the warehouse.

Cleaning validation

The cleaning validation approach was superficially discussed during the inspection. Cleaning validation following equipment bracketing was done for each product, three consecutive batches.

Swab and rinse samples were used in the cleaning validation as well as visually clean criterion. A list of products manufactured in the ETA block was presented to inspectors.

Swab and rinse samples were taken for analysis to verify cleaning effectiveness after product changeover, visually clean criterion also was applied.

Swab recovery studies were done for SS and glass surfaces. In general cleaning validation was found to be adequate.

Validation of analytical methods

Not inspected.

2.12 CHANGE CONTROL

There was an SOP for change control. In general SOP was widely applied. Changes were classified as:

- Minor
- Moderate
- Major
- Temporary

A format was used for managing changes.

Non-compliances observed during the inspection that were listed in the full report were addressed by the manufacturer to a satisfactory level.

Deviations

There was an SOP for deviation control. Deviations were defined as unplanned deviations from manufacturing process. A format was used for managing deviations.

Two deviations were reviewed during the inspection.

Non-compliances observed during the inspection that were listed in the full report were addressed by the manufacturer to a satisfactory level.

2.12 REJECTION AND RE-USE OF MATERIALS**Rejection**

Not inspected, SOP was available.

Reprocessing and reworking

SOP was reviewed.

Non-compliances observed during the inspection that were listed in the full report were addressed by the manufacturer to a satisfactory level.

Recovery of materials and solvents

There was an SOP for recovery of solvents; recovered solvents were used in the same product the same stage.

Non-compliances observed during the inspection that were listed in the full report were addressed by the manufacturer to a satisfactory level.

Returns

SOP was reviewed. Returned APIs were identified as such and quarantined. The decision on disposition of returned goods was the responsibility of QA.

2.13 COMPLAINTS AND RECALLS

Complaints

There was an SOP for complaint handling and investigation. Complaints were recorded and investigated. QA was responsible for handling of complaints.

Non-compliances observed during the inspection that were listed in the full report were addressed by the manufacturer to a satisfactory level.

Recalls

There was an SOP for handling recalls. There were no recalls registered till the date of the inspection. No specific observations were made.

2.14 CONTRACT MANUFACTURERS (INCLUDING LABORATORIES)

N/A

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 a decision on the compliance of manufacture of Ethambutol API manufactured at Cadila Pharmaceuticals Limited (Unit I, ETA block) 294 GIDC Industrial Estate, Ankleshwar 393 002, Gujarat, India was considered to be operating at an acceptable level of compliance with WHO GMP guidelines 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.