

WHO PUBLIC INSPECTION REPORT API Manufacturer
**WHO PUBLIC INSPECTION REPORT
(WHOPIR)
API Manufacturer**
Part 1: General information

Name of Manufacturer	Lupin Ltd
Unit number	Plant I
Production Block	Ethambutol (ETB) Plant
Physical address	Lupin Ltd (Ankleshwar), Plot 124, GIDC Estate, Ankleshwar – 393 002 Gujarat, India.
Contact person and email address.	Mr Rajeev Patil Telephone: .+91 22 66 40 2370 o Office : +91 22 6640 2370 o Mobile : +91 9820106282 Email : rajeevpatil@lupinpharma.com
Date of inspection	2, 3 and 4 February 2012
Type of inspection	Routine inspection
Active Pharmaceutical Ingredient(s) included in the inspection	Ethambutol Hydrochloride (APIMF197 = EP COS)
Summary of the activities performed by the manufacturer	Production, quality control, packaging, distribution of APIs and intermediates

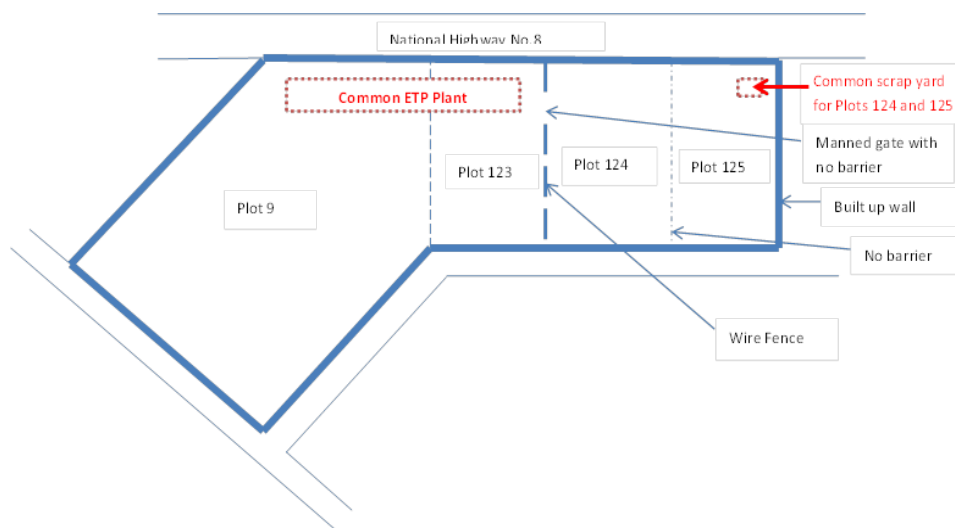
Part 2: Summary

General information about the company and site

Lupin Limited was established in April 1968, according to the Site Master File QA/SMF/001 effective 09/01/2012 and the presentation given at the opening meeting. The company corporate office is located at 159 CST Road, Kalina, Santacruz (E) Mumbai, 400098 India. It has manufacturing facilities located in Ankleshwar (APIs), Mandideep (APIs and FPPs), Tarapur (APIs), Aurangabad (FPPs), Goa (FPPs), Indore (APIs and FPPs) and Jammu (FPPs).

The site of Lupin Ltd at Ankleshwar, commissioned in 1982, is located 95km from Vadodara. It is located on **plots 9, 123, 124 and 125, GIDC Estate, Ankleshwar – 393 002 Gujarat, India**, measuring approximately 161,875m² (40 Acres). In view of the design and activities taking place, the four plots constitute one site. For example, one β -lactam API starting material was moved from a warehouse on plot 123 via plot 124 to plot 125 to make an intermediate used to make 2 cephalosporin APIs. The four plots also shared scrap yards and ETP plant. In fact, the licences (*Form 25: G/501 and Form 28: G/377 valid up to 31/12/2012*) issued by the Food & Drugs Control Administration of Gujarat State only mention plot 124 for the manufacture of both cephalosporins (*Form 28: G/377*) and other APIs including Ethambutol hydrochloride (*Form 25: G/501*).

Sketch of the Layout of Plots 9, 123, 124 and 125 of Lupin Ltd, Ankleshwar



API and intermediates manufactured on plot No.9, plot 124, Plot No. 125 were noted.

Plot 124 included a plant dedicated to manufacture of Ethambutol hydrochloride (*hereafter called **ETB Plant***) and a multi-product plant. The facility inspected was the **ETB Plant**.

History of WHO and/or regulatory agency inspections

This was the second inspection by WHO prequalification programme and it was triggered by observations noted during inspection of a sister site at Tarapur. The first inspection of the Ankleshwar site took place 28, 29 and 30 November 2005. According to the company presentation, the site was also inspected and approved by EDQM (*July 2008*) and KFDA (*Nov. 2011*) with focus on one API.

Focus of the inspection

The inspection focused on the production and control of Ethambutol Hydrochloride (ETB HCL) API in the ETB Plant. The inspection covered most of the sections of the WHO Good Manufacturing Practices for Active Pharmaceutical Ingredients, including premises, equipment, documentation, materials, validation, sanitation and hygiene, production, quality control and utilities.

Inspected Areas

Day 1: 02 February 2012

The following area and aspects were covered during the first day of inspection:

- Opening meeting
 - Introductions
 - Update on the WHO Medicines Prequalification Programme
 - Brief introduction on the inspection process used by MHRA
- Brief presentation of the company and of the activities carried out on the site:
 - *Company overview, site description, production and QC capacities, quality management and assurance systems, summary of manufacturing processes, major equipment and product range, inspection history.*
- Personnel Policies: *Organization charts, Job descriptions.*
- Product Quality Reviews
- Quality Risk Management in relation to production of Ethambutol hydrochloride and cephalosporin containment.
- Quality management system and related activities:
 - *Documentation management*
 - *Batch numbering system*
 - *Complaints,*
 - *Recalls and returns*
- Visit of the storage facilities (including outdoor storages):
 - *For starting materials / intermediate products: reception, sampling, storage and records*

- *For solvents: Receiving (transport tankers), sampling and storage (drum yard and tank farms)*
- *For finished products (APIs): packaging, labelling, storage and records*
- Self-inspection
- Qualification of suppliers
- Management of changes and deviations
- Maintenance & calibration policy and records

Day 2: 03 February 2012

After providing the company with a summary of the observations from day 1, the inspection plan for day 2 was shared with the company. Inspectors proceeded to the review of the following aspects and documents:

1. Brief presentation of the manufacturing process with the associated facilities including
 - *Solvent and material recovery processes (e.g., mother liquors, tailings)*
 - *Water treatment plant, utilities (air handling units, compressed air...)*
2. Visit of the manufacturing facilities following the process flow:
 - *Production workshops : production equipment, documentation and instructions, sanitation, cleaning, maintenance, batch records, calibration, contamination control, in process controls*
 - *Solvent recovery premises and any premises for recovering/reprocessing material*
3. Batch record review
4. Validation approach
 - *Cleaning validation including microbial contamination studies if relevant*
 - *Equipment qualification and calibration*
 - *Process validation*
5. Personnel (qualification and training)

Day 3: 04 February 2012

After providing the company with a summary of the observations from day 2, the inspection plan for the day 3 was shared with the company.

1. Visit of QC laboratories
 - *Analytical control raw materials and finished products: procedures and records, sampling, impurity profile, validation of analytical method...*
 - *Stability program*
 - *Reference/reserve samples*
 - *Water sampling and testing records*

- *Handling of out-of-specification results*
 - *Microbiology testing*
2. A visit to the environment surrounding ETB plant
 - Warehouse 2 on Plot 123 where Cephalosporin starting materials were stored. This was adjacent to the ETB Plant.
 - The 7-APDCA plant on plot 125, following the movement of materials from warehouse 2 on plot 123 to plot 125. Aspects of containment and waste handling were reviewed.
 - A common solid waste area on the corner of plot 125.
 3. Debriefing meeting: closed meeting of inspectors
 4. Summary of observations for the day and Closing meeting with company representatives.
A summary of the deficiencies was presented to the company. There were 2 comments, 20 other observations and 2 major observations. These have been adequately addressed through CAPAs.

2.1 QUALITY MANAGEMENT

a) Product Quality Review

This was performed under an approved SOP. The PQR for ETB HCL for the year 2011 was reviewed. It covered the period January to December 2011 with the following highlights:

- It described the manufacturing process adequately including recovery, control and use of materials and solvents.
- It covered several materials codes of ETB HCL (blend)

There were different material codes for the fresh and recovered API Starting Material (APISM). Fresh APISM was manufactured on Plot 124 and some from another site, Plot 2201/2202. Until January 2012, the APISMs from these sites were controlled under the same code. APISM from plot 2201/2202 is not used in the manufacture of APIMF197/EPCOS grade API .

The APIMF197/EPCOS did not include ETB HCL recovered from meso. Individual batches were controlled under one code for the APIMF197/EPCOS material while another code was used for BP/USP/IP/EP material. However, the material code was not indicated of the label on the drum. The commercial batch was a blend of at least 2 production batches.

- Some batches had been reprocessed. There were different Master Batch Control Records (BCRs) for reprocessing batches due to different reasons. A separate SOP provided for handling of balance ETB HCL quantity by blending.

The BCR for 3 of the reprocessed batches were reviewed.

- Some blend and individual batches had been rejected.
- There were a number of changes related to specifications documentation equipment, process, facility and packaging. One change was to provide for a separate code for the APISM from Plot 2201/2201. The process changes included tightening process parameters of critical steps which were submitted to and approved by EDQM through annual updates.
- There were a number of deviations: planned and unplanned. Several examples of deviations were reviewed.
- A number of Out-of-Specification (OOS) had been observed: several invalid and others valid.
- Several complaints had been received and addressed.
- No recall had been made but there were some returned batches.
- Process validation and qualification had been conducted.
- Trends were evaluated using tables, trend charts and process capability index (CpK) calculations. There was no provision for noting and follow up of borderline cases (e.g. $1 < \text{CpK} < 1.33$). Cases of $\text{CpK} < 1$ were noted but their evaluation was shallow.

b) Batch numbering system

This was controlled under an approved SOP. It had the format **XX YYY ZZZZ** where **XX** = Last 2 digits of the current year; **YYY** = material code (*e.g. 249 for individual batches while 250 for blended batches of ETB HCL*) and **ZZZZ** = sequential serial number. Reprocessed batches had the same batch numbering system – traceability was only in the BCR.

c) Batch release

Batch Release was covered by a written procedure on “Release of Finished Products [API and Saleable Intermediate]”. The procedure required QC OOSs and deviations to be investigated prior to release but not necessarily closed. A change control was raised to amend the procedure during the course of the inspection.

d) Deviation management

The company Deviations procedure covered both planned and unplanned deviations. The procedure was reviewed and found to be a generally satisfactory process however a relatively low number of unplanned deviations had been recorded. Examples of Unplanned deviations were reviewed and found to have been managed satisfactorily.

A planned deviation for use of 2nd crop mother liquors from the Tarapur site was reviewed but was deficient in that it did not require cleaning of equipment after this material was processed and before CEP material. This was (at the time of the inspection) a one off exercise and the following two batches were manufactured for the Indian (IP) market as the next batches in plant would have been mixed with residues of material from a non-licensed site. Adequate CAPAs have been put in place to address this observation.

Other examples of planned deviations were also reviewed and found to have been managed generally satisfactorily.

e) Quality Risk management

The companies Quality Risk Management process was reviewed and was essentially a reflection of ICH Q9/ EU GMP Part III and gave limited practical guidance on use in Lupin. The only formal risk management study offered to the inspector was an assessment of risk in the Ethambutol process however this did not include all risk areas e.g. supplied materials and there were no any requirements for or opportunities for risk reduction identified suggesting the process may have been relatively superficial. This was despite the fact that cephalosporin and PenGK were detected outside the cephalosporin block and area.

Additionally there had been no formal challenging risk assessment conducted of measures to assess risk of cross contamination with Penicillin/Cephalosporin manufacture on the same site and the inspectors readily found numerous risks in this area that required reduction. The study did not address the risk of spillage, the exhaust of AHU from Cephalosporin plants not studied, the failure modes of the measures in place not discussed. Appropriate measures were put in place including more rigorous containment, segregation, risk assessment and monitoring and the results so far presented indicated that the situation has been brought under control.

f) Self-inspection

Procedure “Self Inspection (Internal Audit)” was in place. Self-inspection was performed by a pool of 26 named auditors who were given internal and external audit training. All departments were audited on a biannual basis with each audit being performed by three auditors. The audit report was required to be issued within five working days and the corrective action plan by 15 working days. There was no requirement for serious findings to be reported or corrected within shorter timeframes.

The Self Inspection Schedule for each year was prepared at the end of the previous year and the plan for 2011 showed two audits for each department, one in the first half and one in the second half of the year. Whereas there was no evidence to suggest that any previous Self Inspections were re-scheduled, the company was encouraged to build controlled deferral into its procedure.

2.2 PERSONNEL

The full time workforce on plot 124 was presented as totalling 276 (22 *managers*, 84 *officers*, 11 *staff* and 159 *workmen*) of which 95 were involved in the manufacture of Ethambutol while 25 were in QA/QC. There was approximately 100 contract staffs involved in housekeeping and providing support services in the warehouse, material movement, engineering and utilities.

There were organisation charts and job descriptions to guide staff identify their functional and reporting responsibilities and relationships.

Staff training was guided by an approved SOP. It provided for induction, GMP, on-the-job, functional and self-development training. New staff only performed duties after induction, GMP and SOP training. Training modules were organised according to staff work groups. Examples were selected from each of ETB powder processing area, QC finished product testing, QA batch release and maintenance/utilities work groups and their curriculum, training and evaluation records reviewed. The system was in transition from a manual to a computerised system, and although some gaps in coherence and availability of training records were noted, the officers responsible were aware of the issues and were working on them. Records indicated that some staff that joined as way back as 2006 were still categorised as “Trainee Helper”. Generally speaking, the staff met had the skills and competence to perform assigned responsibilities.

All personnel on site wore company uniform appropriate to their area of work. The staff in the warehouses, ETB HCL synthetic areas put on white short sleeved over coats, head cover plus shoes/shoe covers, while those in clean and powder processing areas put on white long sleeved overcoats, trousers, masks, head cover plus shoes/shoe covers. There were facilities for washing hands and well segregated toilet facilities.

2.3 BUILDINGS AND FACILITIES

a) Design, construction and containment

The facility for Ethambutol (ETB Plant) was a separate dedicate building within plot 124 on Plant 1 in the facility complex. It had separate sections for synthesis, purification and powder processing and was generally in a good state of repair. The Ethambutol facility was separated from other buildings on site however penicillin G was handled near the Ethambutol facility and the final stage and intermediates of Cefadroxil were sensitising molecules.

The company had not conducted a formal risk assessment although they had conducted annual monitoring (largely airborne). This had indicated some airborne contamination of Penicillin G across the road way from the Cefadroxil facility but not reaching as far as the Ethambutol facility. However the study was not sufficiently thorough and did not fully assess Cefadroxil or 7APDCA contamination levels or opportunities and as there were no terminal HEPA filters on the Ethambutol air intake, the risks did not appear to have been fully established. A walk round the

perimeter of the Cefadroxil facility on plot 125 identified multiple areas of loss of containment of sensitising molecules.

An MSDS for 7APDCA confirmed that the molecule is a sensitiser.

A visit to Warehouse 2 on Plot 123 where Cephalosporin starting materials were stored identified evidence of powder spillage at the offloading bay. Inside the warehouse, there was evidence of ineffective de-dusting of drums and powder spillage on the floor. Materials were transported from here in closed containers across plot 124 to plot 125 for synthesis of a Cephalosporin API. Adequate CAPAs in form of containment, segregation and monitoring measures were but in place address these observations.

b) Utilities

The purification and powder processing areas which were controlled but not classified areas were supplied with single pass, filtered and air conditioned air (HVAC system). The qualification of the HVAC system that supplied the powder processing area was reviewed.

The Sifter room, quarantine room, packaging/weighing room and air-lock 2 were supplied by Air handling unit AHU-2 while AHU-5 supplied the dryer room, Wet ETB HCL storage room and PM storage room. There was a series of air filtration system including Primary, Secondary, Terminal and Return Air filters. The HVAC system was qualification in 2005, 2007 and 2010 covering temperature (T^0), relative humidity (RH), pressure differentials (ΔP) and air changes (ACPH). The area was not classified, so no-viable particulate counts were not determined. The microbial environmental monitoring was only by settle plate method. There was no documented risk assessment to determine and justify the locations used. The quarantine room volume used to calculate the ACPH varied between different documents and times. On the day of inspection, the pressure differential of the quarantine room with respect to the airlock was seen to be at the lower limit (6 – 8mmWC).

In view of the penicillin/cephalosporin containment issues noted on the site, the air filtration and frequency of requalification of the HVAC system for the ETB plant was considered inadequate. These were consequently adequately addressed.

c) Water

Demineralised (DM) water was only used in small quantities in the ETB HCl hydrochlorination reaction and the final product rinses were made with an organic solvent. Accordingly there was no requirement for water of a higher (e.g. purified) standard. DM water was generated using a small standalone Millipore unit which had been installed in 2007. Industrial water was provided for input by the local development corporation and was shown by fortnightly checks to be of consistent quality. The Millipore unit was serviced on a regular basis by the vendor and no servicing or maintenance of the unit was performed by the site. The unit was fitted with an on-line conductivity system which automatically dumped the water if the conductivity rose above a set limit. The UV lamp was replaced annually under a

service contract. Distribution of DM water was by pumping from the 30 litre storage tank to user points located at the hydrochlorination reactors. There was no recirculation loop – the company stated that they had found that draining 5 litres of water from the system prior to sampling or usage had given sufficient assurance of quality. Documentation to support this claim was available under the title “Water Drain Time Validation”. The distribution line was sanitised monthly with a proprietary sanitisation agent.

The system was monitored by chemical and microbiological testing on a daily and weekly basis respectively. Data for all sample points for periods during 2011 were reviewed and found to be consistently low throughout.

d) Pest control

Pest Control at the site was managed by an appointed contractor according to a documented procedure. A current contract was in place and required the contractor to be accompanied by Lupin staff at all times whilst on site. No pesticides were used in production, packaging and storage areas and no fumigation was undertaken. Placement of rodent control devices was controlled according to an approved location plan and records of maintenance visits were available along with an agreed list of pest control agents (e.g. rodenticides) that could be used at the site.

2.4 PROCESS EQUIPMENT

a) Design and construction

The major equipment used in the manufacture of ETB HCL included reactors (SS316 and MSG), centrifuge (SSRL), Rotocone Vacuum Dryers (SS316) and sifters (SS316). They were installed to facilitate logical process of manufacturing and were identified with an asset/process number and process lines were identified with content and direction of flow.

b) Equipment maintenance and cleaning

Procedures and schedules were in place to guide the cleaning and maintenance of the equipment. Log books and other records were maintained for their cleaning and maintenance. Pieces of equipment were always labelled with their status of use or cleanliness. Cleaning was mainly using portable water with final rinsing with DM water and/or IPA.

Centrifuge bags were washed in a common area on the 1st floor. The bags were not identified with centrifuge number or stage of processing.

Preventative Maintenance (PM) was covered by an approved procedure: “Equipment Maintenance Procedure”. The PM schedule for each year was drawn up during the fourth quarter of the previous year. The schedule indicated target and actual dates for the work and no overdue tasks were seen for January 2012. A tolerance of ± 15 days was allowed for PM required at six-monthly intervals. Individual procedures were available for PM tasks for each equipment type e.g. “Preventive Maintenance of

MSG L Reactor". The most recent record of PM for hydrochlorination reactor was reviewed without comment and evidence of lubricating oil compliance to food grade standards was seen.

In general, process equipment was in a good state of repair and appropriately cleaned.

c) Calibration:

Reactors were controlled by local temperature control systems utilising fixed sequence temperature ramps – although the units had been calibrated, there had been no overall qualification of the control systems.

The calibration of equipment and devices was performed by a contractor, according to established schedules using their SOPs, some of which had been evaluated and approved by Lupin. The audit of the vendor conducted 20/04/2011 and the contract agreement dated 15/06/2011 did not cover temperature sensors and related SOPs. This has since been addressed.

Selected examples were reviewed:

- Temperature Sensor for a Rotocone Vacuum Dryer. The calibration range was from the minimum range to 140°C.
 - Temperature Sensor for a reactor. The calibrated range covered was ~50 – 200°C.
- It was noted that the related PLC systems had not been fully qualified.

2.5 DOCUMENTATION AND RECORDS

Document Control was handled according to the following procedures:

- "Preparation, Review, Approval and Control of Standard Operating Procedures"
- "Preparation, Distribution and Control of Documents" and
- "Waste Management System" which dealt with document retention and controlled disposal.

Procedures were encoded according to XXX-YYY-ZZ where XXX referred to the type of procedure e.g. CQA = Corporate QA etc. and YYY was a sequential number. Procedures were reviewed every three years ±15 days. Batch records were retained for expiry plus one year.

The company had an unusual way of documenting date of activities and as a result dates recorded would not always reflect actual dates. This was due to the fact that on a night shift staffs were instructed not to record the change of date at midnight but to continue recording the previous date until 07.00 when shift change occurred.

2.6 MATERIALS MANAGEMENT

a) Starting Materials

The supplier approval and periodic re-evaluation process was reviewed and found to be a generally satisfactory procedure. The system included use of questionnaires to gather information as well as monitoring performance of suppliers and required QA to

consider requirement for audit of the manufacturers. However when reviewing the process in practice several significant issues were identified. A starting material was classified and managed as a solvent; however, in the context this was used by Lupin, it was a key starting material as it formed a significant part of the final molecule. As such there was no audit or questionnaire assessment of the manufacturer. The manufacturers on the approved list did not fully match those used by the company – particularly for this starting material. There was only evidence of one audit having been conducted on suppliers. However there was not sufficient information in the report to confirm which suppliers tanks/systems were reviewed as part of this audit. The delivery company for this solvent/starting material had not been assessed as to their suitability. Documents for the supply of this solvent/starting material did not clearly provide traceability to the manufacturer. There was also lack of clarity between plot 2201/2202, Plant II and one SAP code with respect to source of the APISM.

Status control of materials was primarily via labels affixed to containers; however, the company operated SAP and this also tracked material status. The company was proposing to move to SAP only status control for finished product using a bar code system and no QC pass labels. SAP does not allow despatch of under test product although the inspectors did not see validation of this control.

During the tour of the tank farm, it was noted that there was no QC approval label on one of the tanks and two discharge tubes were greatly worn out and stored in dirty conditions. The volume level of one organic solvent in the storage tank could not easily be established from the view glass at the time of inspection.

b) Compliance with TSE Guidelines

The company did not use materials of high risk with respect to TSE contamination.

2.7 PRODUCTION AND IN-PROCESS CONTROLS

Some bulk volume reagents were dispensed/ charged via a separate room on the ground floor. New and recovered APISM was stored on the ground floor in storage tanks.

Variable quantities of new and recovered API starting material were used in the process depending on the quantity of recovered available. The quantity of one reactant required for the condensation reaction was calculated on a batch to batch basis but the formula used to calculate the quantity was not defined in writing.

The vessels for the final reaction were located inside a separate room with overshoes required for access – the requirement for this control was not clear as the product was not routinely exposed to the room environment and the company appeared to be applying the rule because the output was final product rather than considering the risks from a fully enclosed reactor.

The system for removing samples was a relatively standard vacuum draw system but the pipework was not adequately cleaned/ flushed and there was a risk that samples were contaminated, particularly by water used to flush the line.

Following isolation on a series of centrifuges the wet cake product was packed into poly bags/kegs for transport to the next room where two large dryers were available for drying product. The unit in use at the time of the inspection was generating very loud noises which the company claimed was due to gases in the steam jacket – it was unclear how this impacted on the drying cycle. This was subsequently rectified.

The final product was vacuum transferred to bags/containers for sieving in the adjacent room – three sieves of varying size were available depending on batch size.

Critical parameter requirements were documented in the batch record.

A Meso recovery process was utilised by the company although this was not part of the CEP manufacturing scheme. Several common reactors and sifters were used to process material recovered through the Meso process but none of these were cleaned to remove residues of Meso source process prior to manufacture of the CEP process and as a result small quantities of a non-licensed process would be mixed into the licensed process. A similar situation also occurred with residues from the Tarapur site. Appropriate segregation and cleaning procedures were subsequently put in place

2.8 PACKAGING AND IDENTIFICATION LABELLING OF APIs AND INTERMEDIATES

Final product (API) was packed into double poly bags in HDPE containers (fibre board for Indian market) and sealed with tamper evident seals bearing the company name. The label on the drum did not indicate the material code of the API, thus reducing traceability and a vital linkage to the approved production process.

2.9 STORAGE AND DISTRIBUTION

Finished active substance was packed in double poly bags/ HDPE drums for worldwide supply although Indian product was packed in fibre board kegs. The active substance was shipped around the world at ambient temperature but the company did not have any stability/stress data above 40⁰C to demonstrate the stability of the molecule and also did not have any knowledge of temperature fluctuations of product in transit. The company were advised that inspectors are aware of goods shipped from India by sea reaching peak temperatures of 59⁰C.

Records of batch distribution were maintained but QA instructions to store on the batch and material code to dispatch were not clearly legible on the examples evaluated during inspection. This could result in a client receiving API produced according to a process other than that approved.

2.10 LABORATORY CONTROLS

A large open-plan laboratory was available for standard wet chemistry and instrumental analyses; separate IPQC and microbiology labs were sited adjacent to the main lab and hot work and stability storage was located on the upper floor. Retention samples were stored in another building adjacent to the QA office. QC was manned by 16 staff of whom 4 worked in the IPQC lab on shifts.

Samples received into QC were booked into a register where an analytical reference number was assigned. Specifications were in place for the APISM and ETB HCl the latter being seen to be compliant with Ph. Eur. VII. Data for testing of the APISM and randomly selected batches of ETB HCl were traced back from certificates of analysis (which were issued via the SAP system) to raw data with no issues identified. Volumetric solution standardisation, instrument calibration (balances, HPLCs, GCs and IR) and periodic maintenance (HPLC) were reviewed and found to be well managed. Column logs were in place. HPLC data was captured by Chromeleon and integrated automatically; manual integration was not allowed but would be visible in the data audit trail for the sequence. Mobile phases were handled adequately. Minor deficiencies were found with the controls for thin layer chromatography.

Reference standards were stored in a refrigerator. The current EPCRS for ETB HCl was seen to be in place and quarterly documented checks were made to ensure continued currency of standards.

Three stability chambers were located on the second floor for long term, intermediate and accelerated storage conditions. Samples of ETB HCl in both HDPE and fibre drums were seen to be stored under long term conditions.

Stability testing of APIs was covered by an SOP “Stability Study” wherein at least one batch of API per year of manufacture was required to be entered into the stability programme. Other reasons for placing samples on stability were detailed in an appendix. Adequate controls were in place for sample withdrawal and testing after withdrawal. A batch of ETB HCl made in January 2006 was placed into long term storage under a stability protocol and all data up to 72 months was seen to be well within specification.

Suitable controls were in place to mitigate for chamber failures.

Retention samples of key raw materials and APIs were seen to be stored in roller compactors in a room adjacent to the QA office. Adequate controls for quantities being stored and retention periods were in place.

The procedure for “Handling of Out-of-Specification Results” was reviewed. Unique identifying numbers were applied after conclusion of the initial laboratory investigation. Investigations were to be completed within 30 days or an interim report issued. The procedure was thorough and described a logical process whereby simulation of potential causes followed by manufacturing investigation were undertaken in the event of no lab error cause having been found. Separate registers were in place for raw materials and finished APIs. Example investigation reports were

selected for review including two examples where despite no lab error cause having been found, permission was given by QA to initiate retesting with no simulation or manufacturing investigation having been performed. In both cases retesting was justified on the basis that the failure types had not been encountered before, however the inspectors did not accept that this was sufficient to omit (particularly) the manufacturing investigation. It should be noted that both investigations were covered by the previous version of the SOP which was not dissimilar from the current version with regard to actions to be taken following no lab error cause having been determined. The previous version of the SOP did allow original results to be invalidated on the basis of two acceptable retest results however this had been increased to three replicates in the current version. Further changes were subsequently made to address this matter.

The test method for residual solvents was revalidated under an approved protocol and a report was in place. Whereas the protocol did not specify that the Limits of Detection and/or Quantitation should meet the requirements of ICHQ3c, the method was shown to be capable of so doing. The report did not state the range of the method.

Media plates used in the microbiology laboratory were prepared in-house with appropriate growth promotion tests (GPT) using reference culture which were used up to 3 passages.

Packaging materials were sampled and tested before approval for use. There was fixed sample size for LDPE bags. ISO 2859 was not used.

2.11 VALIDATION

Process validation had most recently been repeated in 2011 following introduction of a number of changes deemed 'minor' by the company. One of these changes was to the drying temperature where issues were noted. The final product batches were tested to standard specification with conclusion that the validation was successful as the batches passed specification. However the results had not been compared to typical data pre change and there was no trail of review back to bio batches.

One organic solvent had been recovered from and re-used in the ETB HCl process on-site for many years however the process had never been validated although the recovery plant had been recently qualified.

2.12 CHANGE CONTROL

The change control procedure was reviewed and the process used was generally satisfactory. Selected changes were reviewed and found to be satisfactory.

2.13 REJECTION AND RE-USE OF MATERIALS

A recovered solvent was used in the process including final wash of the finished active substance. Despite this the recovery process had not been formally validated to

provide adequate confidence on the process particularly for use as a final wash even although the solvent was tested. The recovery process was subsequently validated.

The recovered solvent was tested to a formal specification which was different from the fresh solvent specification and the differences were satisfactorily explained. A total impurities limit was in place to check for carry-over etc. of residues. The water content of the recovered solvent was typically higher than that of the fresh solvent however the use of the recovered solvent had been included in “ETB Development Report”.

There was no control on the ratio of fresh/recovered solvent used or the number of recovery cycles to prevent build-up of degradation products.

Reprocessing of APIs was managed according to an established procedure “Reprocessing of Drug Substance”. A Reprocessing Form (Annex 1 of the procedure) was completed and approved prior to any reprocessing being undertaken and given a unique number according to the scheme RP-XXX-YY/ZZZ where RP denoted “Reprocessing” and XXX the initiating department e.g. ETB. Example reprocessing forms and batch records for reprocessed batches were reviewed. The batch sheet for reprocessing of ETB HCl required the pH to be adjusted to a defined range, however, there was no prompt on the batch sheet to record the pH obtained.

Reworking of APIs was covered by procedure “Rework of Drug Substance”. No reworks had been performed at the site to date.

2.14 COMPLAINTS AND RECALLS

a) Complaint handling

Written procedure “Handling of Market Complaints for Drug Substances (APIs) and Intermediates” was reviewed. Details of complaints were recorded in a “Log of Market Complaints” which was issued for each calendar year wherein complaints were given a unique number according to the system ANK-YY-ANNN. Three complaints had been received in 2010 and four in 2011. The procedure required complaints to be classified as major or minor, initial responses to and closure of complainants were required after specified periods. Complaints were reviewed for trends on an annual basis and the trending report for 2011 was seen. Three complaints referring to Ethambutol (ETB) were reviewed and all were found to have been adequately documented with corrective and preventative actions recorded where relevant.

b) Recall procedures

Recalls were managed according to procedure “Recall of API/Saleable Intermediate”. Recalls were numbered according to the system RCL/YY/XX. The procedure required a decision to be made to recall or otherwise within specified hours of reporting and to be closed out within specified days. A recall committee was formed to oversee progress and the list of members on the committee had not been updated for a recent retirement. The site had not been involved in any live recalls and the most

recent dummy recall had been performed according to protocol “Dummy Recall Validation” and reported in report of the same name. Whereas the recall reconciliation sheet applied different treatments to customers (converters) versus trading companies, a client was treated as a converter for the purposes of the exercise. Based on the name of the recipient (and subsequent information gleaned from the internet) the inspector requested confirmation that the client was a converter rather than a trading company. The site was unable to provide confirmatory evidence to this effect during the course of the inspection. It was however subsequently provided.

c) Handling returns

Returns were managed according to procedure “Handling of Returned Goods” which required such goods to be stored in the Bonded Storage Room (BSR).

2.15 CONTRACT MANUFACTURERS (INCLUDING LABORATORIES)

One technical agreement was reviewed and it reflected compliance with requirements of EUGMP II/ICH Q7.

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, **Ethambutol hydrochloride** manufactured at ***Ethambutol Plant of Lupin Ltd Plot 124 and 125, GIDC Estate, Ankleshwar – 393 002 Gujarat, India*** was 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.