

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

Name of Manufacturer	Lupin Limited (Tarapur)
Unit number	T1
Production Block	Fermentation, synthesis and powder processing areas of T1 for Rifampicin
Physical address	Thane, T-142, MIDC, Tarapur, 401506 Thane, Maharashtra, India
Contact person and email address.	Mr Rajeev Patil Telephone: .+91 22 66 40 2370 o Office : +91 22 66402370 o Mobile : +91 9820106282 Email : rajeevpatil@lupin.com
Date of inspection	10 to 13 June 2014
Type of inspection	Routine inspection
Active Pharmaceutical Ingredient(s) included in the inspection	1. APIMF093: Ethambutol HCL USP 2. APIMF040: Pyrazinamide USP 3. APIMF028: Rifampicin IH
Summary of the activities performed by the manufacturer	Fermentation, chemical synthesis, purification, packaging, quality control and batch release of Active Pharmaceutical Ingredients

Part 2: Summary

General information about the company and site

The site inspected was the T1 facility of Lupin Limited, located at T-142 MIDC area, Tarapur, 401 506 Thane, Maharashtra, India, hereafter called Lupin Tarapur (T1). The company corporate office was located at 159 CST Road, Kalina, Santacruz (E) Mumbai, 400 098 India.

According to the Site Master File Document No SMF/TR/01/00 effective 02/06/2014 and the presentation given at the opening meeting, Lupin Limited was established in April 1968. Lupin Tarapur, established in 1992, is located 120km from Mumbai on a 157,000m² plot with a built up area of 141,000m². The site had 3 facilities: T1 (*Fermentation and synthetic APIs*), T2 (*Generic APIs*) and T3 (*Generic APIs*).

According to the company presentation, the site employed a total of 938 people (Manufacturing 465, QA/QC/RA 196, Process development 54, Engineering 145, Support services 67 and R&D (Micro) 11).

Rifampicin is produced in T1 area. The manufacturing process starts with fermentation wherein Rifamycin B is produced through fermentation process (stream 1), subsequent chemical synthesis & processing steps are performed in DSP-1 (stream 1), Rifamycin S and O in CSP-1 (stream 1) and Rifampicin in CSP-2B (stream 1). It was noted that Pyrazinamide is produced in DSP-2 (stream 2).

It was noted that Ethionamide (filed to WHO and currently under assessment) is micronized at this facility (T1 MPP4J and T2 MPP9) but API is bought from outside . . Due to time constraint, this area could not be inspected.

Although APIMF of Ethambutol HCl has already been accepted by WHO, it was informed during the inspection that the site is not manufacturing Ethambutol HCl for supply of WHO prequalified drug product. The site manufactures Ethambutol HCl for the US market since 2008 & for Japan in 2014. It was confirmed that Lupin Tarapur is an additional site in case required in future & variation related to it is already approved. At present, Ethambutol is being supplied from Ankleshwar site where the site has an approved CEP as well.

History of WHO and/or regulatory agency inspections

According to the SMF and company presentation, the site was licensed by the local authority. Following regulatory agencies have inspected the site:

MHRA Approval	–	June 2010
KFDA Approval	–	January 2010
USFDA Approval	–	July 1997/ July 2005/ June 2009/ June 2012

WHO-GMP Approval – December 2003/ December 2004/ December 2005

October 2008/ April 2010/ June 2011

ANVISA Approval- December 2012

PMDA Approval- 2013

Focus of the inspection

The inspection focused on the production and control of APIs as mentioned under Part 1. The inspection covered all the sections of WHO GMP guidelines for active pharmaceutical ingredients, including premises, equipment, documentation, materials, validation, sanitation and hygiene, production, quality control and utilities.

Inspected Areas

Day 1, 10th June 2014

- Introductions
- Opening meeting
- Product quality review (PQR) procedure and review of PQR of Rifampicin
- Organization chart
- Job descriptions of key personnel
- Training
- Supplier approval
- Review of CAPA from previous inspection

Day 2, 11th June 2014

- Feedback on day 1 observations
- Supplier approval (contd.)
- PQR of Pyrazinamide production in 2012
- Review of PQR of Rifamycin S (key starting material for Rifampicin produced on site)
- Inspection of production area (fermentation, seed microbiology laboratory, synthesis of Rifamycin S, O and Rifampicin)

Day 3, 12th June 2014

- Feedback on day 2 observations
- Market complaints and product recall
- Out of specification (OOS)
- Deviations
- Reprocessing
- Reworking
- Review of process validation of Rifampicin

Day 4, 13th June 2014

- Feedback on day 3 observations

Inspection of quality control laboratory covering:

- sample logging management
- verification of in-process sample analysis
- verification of HPLC and GC with Head Space system for use of integration parameter, audit trail, password management, backup,
- microbiology laboratory
- Inspection of warehousing
 - o Solids raw materials
 - o Corrosive raw materials
 - o Sampling area
 - o Dispensing area
 - o Solvent drum area
 - o Finished Goods store
 - o Tank Farms
 - o Day tank area
- Maintenance workshop
- AHU for Rifampicin controlled area
- Nitrogen plant
- Compressed air plant
- Purified Water Plant
- Purified Water system documents
 - o Qualification/validation
 - o Data from 2013
- Finished Goods Store Temperature mapping
- Meeting between inspectors
- Exit meeting with the site representatives

2.1 QUALITY MANAGEMENT

There were arrangements for evaluations and monitoring of the quality of the systems, procedures and products through self-inspection procedures and annual product reviews. There were procedures for equipment and systems qualification and validation of procedures and processes. The observations raised following the inspection were appropriately corrected.

2.2 PERSONNEL

Generally the standards with regard to the number of qualified staff, organization and job descriptions were on an appropriate level. The organization charts were completed down to the level of the different production blocks. The linking between all organizational charts was found adequate. The observations raised following the inspection were adequately corrected.

2.3 BUILDINGS AND FACILITIES

Building and facilities for production were, as far as covered during the inspection, suitable for production of APIs. In production areas there was sufficient space for handling of equipment and materials. For handling of APIs from the last purification step a clean room area with classification 100 000 (ISO 8) was available. Material- and personnel flow were defined and allowed a logical order of goods processing. In the clean room area environmental conditions were controlled and suitable for APIs. The observations raised following the inspection were adequately corrected.

2.4 PROCESS EQUIPMENT

The process equipment in the most sections of production areas was not dedicated and was used to manufacture various APIs. Like in the other production areas, process parameters were controlled manually. Status of equipment was indicated on labels, usage of equipment was recorded in log books. The observations raised following the inspection were adequately corrected.

2.5 DOCUMENTATION AND RECORDS

Procedures, reviewed during the inspection were in general prepared, suitably detailed, authorized and represented the current status. The observations raised following the inspection were adequately corrected.

2.6 MATERIALS MANAGEMENT

Materials management was checked in detail. The flow of raw materials for the production of various APIs was sufficiently described. The handling of some of the key starting materials, was found to be inadequate as some were not stored at an appropriate conditions. The observations raised following the inspection were adequately corrected.

2.7 PRODUCTION AND IN-PROCESS CONTROLS

The production area was covered during the inspection including areas for micronizing and packing of finished product. Raw materials were sampled and dispensed in day store area in the production department. The controlled environment in these areas was in general sufficient.

2.8 PACKAGING AND IDENTIFICATION LABELLING OF APIs AND INTERMEDIATES

The inspection covered procedures for packing and labelling of materials in detail. In general, packaging and labelling of APIs and intermediates was found acceptable.

2.9 STORAGE AND DISTRIBUTION

Raw materials and intermediates were stored in a warehouse under different ambient conditions. During the inspection, warehouses for solid raw materials and the finished API warehouse were covered. A cold room existed for materials that required to be stored between 2⁰ - 8⁰C. APIs were stored in an environmentally controlled warehouse.

2.10 LABORATORY CONTROLS

The quality control laboratories, including chemical, instrumental and microbial analyses as well as validation of analytical methods, were covered during the inspection and found adequate in general. The observations raised following the inspection were adequately corrected.

2.11 VALIDATION

Validation Master Plan Tarapur (VMP/TR/01-01 dated 12/2/2013) provided validation policy of company with objective, scope, periodic review. The VMP covers facility description and design including critical utilities including AHUs, purified water system, nitrogen and compressed air. The validation activity included DQ, IQ, OQ, PQ, requalification, preventive maintenance, cleaning validation, re-validation, vendor qualification, process validation, analytical method validation, computer system validation, analyst qualification and change control system. The observations raised following the inspection were adequately corrected.

2.12 CHANGE CONTROL

Elaborate procedures for change control were in place. Changes were generally adequately documented, well evaluated and implemented. The frequency and use of certain type of temporary changes and deviations should be monitored and checked.

2.13 REJECTION AND RE-USE OF MATERIALS

Processes of approval and rejection of raw materials were covered in detail during the inspection. Approval or rejection of manufactured APIs was recorded in the batch production records. The materials were reprocessed and reworked as per company procedure. Material and solvents were recovered in-house, tested and reused. The recovery procedures were validated and specifications used were generally adequate. Batches produced with recovered material and solvents were included in validation and stability studies.

2.14 COMPLAINTS AND RECALLS

The procedure for the handling of complaints was described in the SOP for procedure for handling of complaints. Complaints were listed in a register; investigations were recorded in detailed files. The investigations reviewed during the inspection were complete.

2.15 CONTRACT MANUFACTURERS (INCLUDING LABORATORIES)

This area was not inspected.

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, APIs manufactured at *Lupin Limited (Tarapur), 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.