

**Prequalification of Medicines Programme**  
**WHO PUBLIC INSPECTION REPORT**  
**Active Pharmaceutical Ingredient Manufacturer**

**Part 1: General information**

Name of Manufacturer	Lupin Limited
Unit number	Tarapur
Production Block	T1
Physical address	T-142, MIDC, Tarapur, India
Date of inspection	21 to 24-09-2009
Type of inspection	Routine
Dosage forms(s) included in the inspection	Rifampicin API
Summary of the activities performed by the manufacturer	Production and control

## **Part 2: Summary**

### ***General information about the company and site***

The site was located about 2 hours drive outside of Mumbai. There were two main manufacturing areas (T1 and T2). Rifampicin was manufactured in T1.

### ***History of WHO and/or regulatory agency inspections***

The site had been inspected previously by US FDA and a WHO prequalification team.

### ***Focus of the inspection***

The inspection focused on the production and control of Rifampicin (manufactured on site, all steps). It did not focus on the production of Rifampicin made from intermediates sourced from outside sources / suppliers.

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

### ***Inspected Areas***

After arrival, the inspectors introduced themselves and informed the company representatives about the prequalification programme. The company introduced personnel present and then made a presentation about the activities of Lupin. The company explained that they employed over 7000 employees. Products in the portfolio included -statins, -prils, cephalosporins and anti tuberculosis products and substances. The research and development unit was located in Pune, and head quarters in Mumbai. Other facilities were located in Aurangabad and Tarapur. The company had business presence in the USA, Europe and South Africa. The company informed the inspectors that it was ranked number 1 in the world in terms of the supply of ethambutol, rifampicin and pyrazinamide. It was the largest Rifampicin manufacturer in the world.

The site inspected at Tarapur had different areas for production including T1 and T2. T3 was under development. Commercial production of Rifampicin was started in 1993.

There were 561 persons on site of which 87 were in the Quality department and 269 in production, 98 in engineering.

The quality system of the company consisted of Quality Management, quality policies, systems and SOPs, validation and qualification, deviation and change control. QA was overseeing QC. Supplier Qualification was done, complaints were handled, master batch records were maintained and product quality review was done (checked for Rifampicin).

The rifampicin used in products manufactured for GDF was manufactured in T1 (CSP1, CSP2B). This included fermentation, and down stream processing steps.

The quality control laboratory was equipped with various instruments including HPLCs, GCs and an XRD.

Utilities included electricity supply, steam, water system, compressed air and nitrogen production. A waste management system for liquid and solid waste management was in place.

Several documents were requested for initial review. These included:

- Process flow chart
- Site layout
- PQR 2007 and 2008
- List of products manufactured in MPP4
- Process Validation protocol and report
- SAP printout of batches from own source of Rifamycin S
- Code numbers for all Rifampicin products (SAP)
- Code numbers for all Rifamycin S (SAP)
- Changes to batch processing - 082040107 and 126 (minor or major)
- Documentation for the return of batches of Rifampicin
- Investigation report for the complaint of 3 batches supplied to Svizzera
- Change control QA/CCP/054 (2007) for use of own Rifamycin S
- Code flow sheet
- List of production batches for Rifamycin S (300253) - 2008
- Harmonization of product codes (Rifampicin to 9 codes) - change control
- Synthetic/synthesis schemes

The inspectors reviewed the layout of the facility. It was explained that the administration building housed the warehouse (solid raw materials and finished product), QC laboratory and admin section.

Production was done in the following areas:

- Fermentation
- DSP 1 block: post harvesting
- CSP1: Rifa B to Rifamycin S and Rifampicin reaction
- CSP2B (Rifampicin block): concentration and crystallization
- Solvent recovery
- Fresh solvent storage area

Utilities (not inspected)

The water treatment system was DM/RO. Compressed air and nitrogen production took place in the utility block.

The inspectors were informed that the Chinese sourced Rifamycin S was no longer used for GDF / prequalified products.

## Product Quality Review (PQR)

The inspectors reviewed the PQR report for Rifampicin batches produced in 2008 (January to December). It was prepared by QA, reviewed by Production and QC - and then approved by QA. It covered basically:

- A review of critical raw materials, in-process control and critical API test results
- A review of all batches that failed to meet established specification(s)
- A review of all critical deviations or non conformances and related investigations
- A review of any changes carried out to the processes or analytical methods;
- A review of results of the stability monitoring program
- A review of all quality-related returns, complaints and recalls
- A review of adequacy of corrective actions

Several batches of Rifampicin manufactured in 2008 from Lupin's own Rifamycin S, and from outsourced Rifamycin S (NaRS). One batch was rejected in 2008 as it failed in one of the solvent content. The OOS report 00508022 was reviewed. The material was reprocessed. Two batches of API were returned from Lupin Aurangabad "due to business reasons". Process validation was done, and critical process parameters were identified. (For PQR, assay and yield were considered as indicators for process capability - these were different to those identified in process validation where 9 parameters were identified).

The company had different codes for Rifamycin S and Rifampicin depending on their specifications and customer requirements. These were reviewed and checked by the inspectors on SAP. (See the section below for observations made by the inspectors).

Day 2 was devoted to the inspection of the facilities following the process flow:

Warehouse located on ground floor of the "Administration building; Fermentation block and DSP1:

It contained mainly solid raw materials and some liquid raw materials, key intermediates produced internally (rifa S, rifa O) or supplied from outside (Na rifa S (hereafter referred to as rifa S)) and finished products (pyrazinamide, rifampicin, etc.). The entire area was found clean and well maintained. Sufficient space was available for the orderly storage of raw materials. Nevertheless, the situation was less favourable for finished products since one out of the four specific storage area was full and pyrazinamide fibre drums were stored in the raw materials (RM) section. In terms of temperature monitoring, several observations were made. Sampling and dispensing rooms were also inspected as well as usage and cleaning log books. A positive list of RM that should be sampled and dispensed under LAF boot was available. Documentation present for two recent deliveries (liquid ammonia and anti-foam) was checked including the verification against the approved vendor list. An SAP query for these two materials as well as for returned rifampicin was made.

Fermentation block and DSP1:

From culture provided by the microbiological lab, a total broth containing Rifa B is obtained after three fermentation steps (pre-pre fermentation, pre-fermentations and fermentation). A specific focus was given on media preparation tanks (level 0) for commercial fermentors,

control room and batch records present from which data concerning the sterilization of the equipment and the monitoring of the different fermentation phases were reviewed.

DSP1 devoted to the isolation of slurry of pre-purified Rifa B was visited. Some equipment status displays were checked against corresponding usage and cleaning log books.

On the third day, the inspectors divided into two teams. Two inspectors continued the inspection of the facilities and the other inspector reviewed documentation.

Solvent storage areas (bulk and non bulk) were inspected. Documentation corresponding to different deliveries was checked. Even though a few minor observations were made, the whole management of this sector was found satisfactory.

#### Building CSP1:

This building - used to produce rifa O from rifa B & Rifa S from Rifa O - was extensively inspected. Several different batches at different stages of the synthesis were running which gave the opportunity to check on the spot corresponding BMRs. IPC laboratory and washing area were also covered.

#### Building CSP 2B:

Rooms where operations starting from the final crystallisation to the final packaging of rifampicine took place were visited. Only physical operations (e.g. sieving) were running at the time of the inspection. All aspects reviewed from gowning of the personnel, pressure cascade, cleaning procedures and records available were found satisfactory.

#### Solvent recovery unit:

A rapid tour with a brief presentation of the CH<sub>2</sub>Cl<sub>2</sub>-Aceton recovery process and an example of a corresponding batch record was done.

Various other documents were reviewed. These are described below.

#### Rejected batches:

Several (Six) batches of Sodium Rifamycin S were rejected due to a high impurity profile. The out of specification (OOS) investigation was reviewed (report number OOS09015) as well as the intimation note for vendor status (disqualification of vendor). Corrective action was submitted by the vendor, reviewed and the supplier was reactivated. The approved supplier's list (ASL) was updated to reflect the removal of the supplier.

Several batches of Dextrose solution (code 100133) were rejected. The Dextrose was obtained from 5 different suppliers. Of the 9 batches rejected in 2009, 5 were from one supplier (failing the absorbance test). No action was taken against the supplier. The total number of consignments received from this supplier in 2009 was 58. The COA from the supplier listed under "specification" for identification "complies with the test" and for "chlorides", "within limit test". Three batches from another supplier were rejected in 2009 (January to September) out of a total number of 64 batches / consignments from the latter supplier.

The periodic vendor evaluation was done for identified starting and key materials according to the company SOP. The periodic vendor evaluation/quality review for piperazine 2008 was inspected. The vendor evaluation for 1-amino-4-methyl-piperazine fwas also inspected.

The vendor qualification (SOP QA-037-02) was reviewed and the list of starting and key raw materials was checked. The vendor quality evaluation consisted of either a questionnaire to be completed, or a mandatory on site audit (in the case of starting / key raw material). At least three batches of material were tested and met the requirements.

#### Re-testing:

A re-test report was run from SAP on a monthly basis. The re-test report for Rifampicin 300267 (for 2009) was requested. The company informed the inspectors that the proposed shelf life for the products (APIMF) were for PZA and Ethambutol - 5 years - and for Rifampicin USP - 3 years.

#### Stability testing:

The stability testing protocol was inspected. In addition, the stability testing SOP and schedules for Rifampicin and PZA were requested and inspected.

According to SAP, several batches of Rifampicin (for WHO/GDF) were manufactured in 2008. The following documents were also reviewed:

- SOP for batch number allocation
- Batch register non GDF 2008
- Batch register GDF 2009

The SAP printout for all reprocessed batches of Rifampicin (tr02) was inspected.

Copies of the two pages of the stability schedule were requested.

#### Process validation protocol and report:

Process validation for Rifampicin was done in 2008. The protocol and report were requested for review. Some elements of the validation report were reviewed. This included the main steps subjected to validation, and the results and raw data recorded at the time (compared the tabulated results to the BMR data). Steps included the oxazino reaction, AMP reaction, crystallization and drying. Blending was done for 2 hours, samples were withdrawn at defined intervals (60, 90, 120 minutes) and analysis performed (including tapped density and related substances). The tabulated data were reviewed against the raw data and chromatograms acquired for the sample analysis. (Batch numbers 072049002 / 3 / 4).

On the fourth day, the inspectors focused on the inspection of the quality control laboratory. They separated into two teams for this purpose, after having been briefed about the layout and areas of the laboratory. The QC laboratory was divided into different sections. The sample inward registers were looked at.

#### Documents reviewed included:

- Analytical report for Rifampicin BN 092048081;

- Analytical data corresponding to fresh and recovered methylene chloride used for Rifamycin S, starting point for above Rifampicin;
- Qualification report of working standard WS/TR/R1/6 and storage of Rifampicin EP, USP and WS standard;
- Preparation and verification records (certificate of the pH standard solution) of one pH buffer prepared for IPC lab in production;
- Periodic qualification of FTIR I 001 with a focus on the last one dated of 20/06/09 performed before this equipment was declared out of order;
- All BMRs for Rifampicin BN 092048081 were reviewed in order to establish the traceability back to the WCB used (RS/09/02). In the microbiological lab, storage areas for WCB and MSB were checked as well as documentation available regarding the history of the microorganism. The genealogy tree was presented. WCB RS/09/02 was derived from MSB R/950.
  
- Other documents requested and reviewed then included:
  - API specification
  - API USP and EP monographs
  - Stability reports for selected batches at defined conditions and intervals (042049001 at 24 and 36 months long term (LT) conditions - the raw data was verified and compared against the tabulated submitted data for testing parameters, preparation and testing of reference standards; and 092048077 at 3 months for accelerated conditions)
  - Test results verification of description, ID, pH, LOD, related substances and assay
  - General test procedures e.g. GTP U036
  - WS/TR/R1/3 and 4 tested against USP RS Lot J
  - Instrument log book (IR Shimadzu - which was no longer in use)

The electronic data acquired for the sample analysis was verified on the computer for batch 092048077 (assay). The printed chromatograms were compared against the raw data. Some discrepancies were identified (see observations below). The calibration of the HPLC was looked at for parameters including the performance of the pump, gradient and injector.

The stability chambers E007 and 008 were inspected including temperature and relative humidity records, the temperature mapping study of the E007 and associated certificates of calibration. During the mapping study, temperature and RH were monitored in 8 identified locations every 15 minutes over a 24 hour period. The acquired data was reviewed (see observations below).

The control sample storage area was then inspected. Control samples were kept for one year after the expiry date of the material and batch records for 6 years. Control samples were looked at for selected batches from 2008 and 2009. The temperature record was reviewed and it was noted that minimum and maximum temperatures were recorded twice daily.

The qualification of the VTD (D) was inspected. A protocol and report were in place. The VTD was moved from one area to another in 2006. The change control procedure was followed and requalification was done. (See observations below)

## **I. QUALITY MANAGEMENT**

(Numbers in brackets refer to sections of the ICH guideline Q7)

**A. Principles (2.1).**

A quality management system was implemented. Quality Assurance was responsible for the implementation and coordination of the system. Quality management included validation, change control, vendor approval, deviation control, handling of complaints and recalls, internal audits, stability monitoring, training handling Out of specification results, annual product quality review etc.

**B. Responsibilities of the Quality Unit(s) (2.2), C. Responsibility for Production Activities (2.3), D. Internal Audits (Self Inspection) (2.4).**

Some elements of the quality unit including the quality control section was inspected and considered to be acceptable.

**E. Product Quality Review (2.5).**

The annual product quality review report for 2008 (Rifampicin) was reviewed. Deviations, complaints, recalls, OOS results were reflected. Some batches/consignments were returned by customers due to "commercial reasons".

**II. PERSONNEL**

The training record for one of the employees was inspected. Although training was given, the records showed that insufficient emphasis was placed on initial GMP training for the new employee.

**A. Personnel Qualifications (3.1), B. Personnel Hygiene (3.2), C. Consultants (3.3).**

Not inspected

**III. BUILDINGS AND FACILITIES**

**A. Design and Construction (4.1), B. Utilities (4.2),**

The flow of material was inspected, as well as all relevant areas (receiving, sampling, dispensing, production and quality control). The warehouse was clean and organized - but space was lacking in some areas. Environmental conditions were not always acceptable (temperature and RH).

**C. Water (4.3), D. Containment (4.4), E. Lighting (4.5), F. Sewage and Refuse (4.6).**

Not inspected

**G. Sanitation and Maintenance (4.7).**

The warehouse and production areas were generally clean and well maintained. It was however noted that some adapters lacked maintenance (rust was observed) and cleaning required attention.

#### **IV. PROCESS EQUIPMENT**

##### **A. Design and Construction (5.1), B. Equipment Maintenance and Cleaning (5.2).**

Equipment was mostly designed with controls of the process to be done and monitored. Access to change alarm settings were not appropriately controlled.

##### **C. Calibration (5.3).**

Certificates and labels for calibration inspected were acceptable.

##### **D. Computerized Systems (5.4).**

Not inspected in detail. (See IV A above). Not all computers in the QC laboratory were CFR 211 compliant and an audit trail was not available for these (e.g. 4 HPLC systems). In the one case inspected, the records showed that the chromatograms were modified by an analyst not responsible for the analysis, about a month after the analysis. The reasons for this and the modification could neither be traced nor explained at the time of the inspection.

#### **V. DOCUMENTATION AND RECORDS**

##### **A. Documentation System and Specifications (6.1).**

The company had a documentation system in place consisting of organization charts, SOPs, protocols, records, reports, computer printouts etc. SOPs, specifications and BMRs for the product existed.

Several SOPs were inspected pertaining to the activities associated with the product processing and cleaning of equipment.

The SOP for batch number allocation was inspected. The company allocated different batch numbers for production batches and reprocessed batches.

Generally, SOPs were available and detailed to an acceptable level. A common SOP for sampling and dispensing applicable for production blocks T1 and T2 was not specific enough in the sense that it prescribed that both operations could be carried out in the same area which was not the case for T1 block.

Other documents inspected included vendor and contract manufacturer qualification and quality monitoring evaluation records.

### **B. Equipment Cleaning and Use Record (6.2).**

Equipment cleaning and use records were generally in place. Some discrepancies were however noted in the logs.

### **C. Records of Raw Materials, Intermediates, API Labeling and Packaging Materials (6.3).**

Records including an approved suppliers list (listing general raw materials and key materials respectively) were available. The company however considered some key materials as "general" materials in the PQR. Labelling in general was considered acceptable.

### **D. Master Production Instructions (Master Production and Control Records) (6.4).**

Master Production Instructions (Master Production and Control Records) existed for different stages of the production of Rifampicin and were considered generally acceptable.

### **E. Batch Production Records (Batch Production and Control Records) (6.5).**

The batch production record for batches was inspected and generally considered acceptable.

### **F. Laboratory Control Records (6.6).**

Requested laboratory control records for Rifampicin were available and presented for inspection. Source data were verified for testing including working reference standards, test procedures, use logs, instrument registers, spectra and chromatograms. The stability protocols, schedules and source data were verified for the testing of selected batches. Some calculations were verified - and found to be acceptable.

### **G. Batch Production Record Review (6.7).**

Not inspected.

## **VI. MATERIALS MANAGEMENT**

### **A. General Controls (7.1), B. Receipt and Quarantine (7.2), C. Sampling and Testing of Incoming Production Materials (7.3), D. Storage (7.4).**

Materials were received and checked prior to storage. The sampling plan was based on an n-plan for all materials. There was insufficient control over the storage conditions in the warehouse.

### **E. Re-evaluation (7.5).**

Not inspected in detail. An SOP did address re-testing of materials with a re-test date.

## **VII. PRODUCTION AND IN-PROCESS CONTROLS**

### **A. Production Operations (8.1).**

Production operations were inspected and observed and considered generally acceptable.

### **B. Time Limits (8.2).**

Time limits were established including holding times.

### **C. In-process Sampling and Controls (8.3).**

The batch record review showed that in process sampling and controls were done. Source data results were verified during the inspection of the QC lab and found to be compliant.

### **D. Blending Batches of Intermediates or APIs (8.4).**

Not inspected

### **E. Contamination Control (8.5).**

Production activities were done in a dedicated area for Rifampicin, followed by cleaning. The cleaning procedures were not specifically verified. Pressure cascades were in place.

## **VIII. PACKAGING AND IDENTIFICATION LABELING OF APIs AND INTERMEDIATES**

### **A. General (9.1), B. Packaging Materials , C. Label Issuance and Control (9.3) , D. Packaging and Labelling Operations (9.4)**

Not inspected and there was no operation at the time of the inspection.

## **IX. STORAGE AND DISTRIBUTION**

### **A. Warehousing Procedures (10.1), B. Distribution Procedures (10.2).**

Finished product of Rifampicin was stored in a temperature controlled warehouse. Materials were managed through SAP.

## **X. LABORATORY CONTROLS**

### **A. General Controls (11.1), B. Testing of Intermediates and APIs (11.2).**

The quality control laboratory was inspected focusing on the control of selected batches of intermediates and finished products, reference standards, testing procedures and data verification of selected batches. Source data, equipment use logs, temperature and RH records for the stability chambers were reviewed.

Working reference standards were tested against official standards.

**C. Validation of Analytical Procedures (11.3).**

This was not inspected.

**D. Certificates of Analysis (11.4).**

COAs were generally acceptable, excluding the observations made below for starting materials.

**E. Stability Monitoring of APIs (11.5).**

There were stability protocols/plans and procedures in place. The programme for testing for Rifampicin was reviewed and source data inspected for a selected time points. The company performed on-going stability testing at 25 degrees Celsius and 60% RH .

**F. Expiry and Retest Dating (11.6), G. Reserve/Retention Samples (11.7).**

Retention (control) samples were kept in a separate storage area, in a controlled environment.

**XI. VALIDATION**

**A. Validation Policy (12.1), B. Validation Documentation (12.2).**

Lupin had a validation policy, procedures, protocols and reports for validation and qualification of processes, procedures, equipment, utilities etc.

Only selected validation and qualification protocols and reports were inspected. These included the process validation protocol and report for Rifampicin, temperature mapping studies and the vacuum tray dryer.

**C. Qualification (12.3), D. Approaches to Process Validation (12.4), E. Process Validation Program (12.5), F. Periodic Review of Validated Systems (12.6).**

In general, qualification reports were available. Methods and procedures followed for calibration and testing were reviewed.

Some of the records and reports were reviewed during the inspection. Re-qualification was done by the company (e.g. VTD) - some results for the qualification and mapping studies were inspected. Several parameters were included in the qualification. The test procedures were not always clearly described or referred to, and some actual results such as measurements were not reflected.

**G. Cleaning Validation (12.7).**

The efficiency of the cleaning procedures required attention. (It was noted that the areas (T1) were dedicated to the production of Rifampicin).

#### **H. Validation of Analytical Methods (12.8).**

This was not verified during the inspection.

#### **XII. CHANGE CONTROL**

The procedure (SOP) for change control was not inspected. It was however noted that the change control procedure was followed (e.g. VTD transfer) - and was recorded in the company required format.

#### **XIII. REJECTION AND RE-USE OF MATERIALS**

##### **A. Rejection (14.1), B. Reprocessing (14.2), C. Reworking (14.3), D. Recovery of Materials and Solvents (14.4).**

The company had procedures in place to standardize activities such as reprocessing and reworking. Records were maintained through SAP, and BPRs.

##### **E. Returns (14.5).**

The company managed returns through SOPs and SAP.

#### **XIV. COMPLAINTS AND RECALLS**

The company had SOPs and formats for the handling and investigation of complaints.

#### **XV. CONTRACT MANUFACTURERS (INCLUDING LABORATORIES)**

Not inspected.

#### **XVI. AGENTS, BROKERS, TRADERS, DISTRIBUTORS, REPACKERS, AND RELABELLERS**

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, Lupin Limited, Tarapur, India, was considered to be operating at an acceptable level of compliance with ICH Q7 GMP guidelines for the production and control of Rifampicin manufactured from their own produced Rifamycin S.

#### **Part 4: References**

1. *Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients, Q 7. International Conference of Harmonization. (www.ich.org)*