

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

Name of Manufacturer	Lupin Ltd
Unit number	Rifa and Non-Rifa facilities
Production Block	Block No.1 and 2
Physical address	A-28/1, MIDC, Industrial Area, Chikalthana, Aurangabad 431 210, India
Contact address	Mr. Gautam Parekh, Site Head gautampareek@lupinpharma.com Mr. Rajeev Patil rajeevpatil@lupinpharma.com
Date of inspection	20 to 23 February 2012
Type of inspection	Routine GMP inspection
Dosage forms(s) included in the inspection	Oral Solid Dosage Forms
WHO product categories covered by the inspection	1. TB070: Ethambutol / Isoniazid / Pyrazinamide / Rifampicin tablets 275/75/400/150mg 2. TB177: Ethambutol hydrochloride tablets 400mg 3. TB068: Isoniazid/Rifampicin tablets 75/150mg
Summary of the activities performed by the manufacturer	Production, quality control and release of tablets and capsules

Part 2: Summary

General information about the company and site

The manufacturing site of Lupin Limited (hereafter referred to as Lupin) located at Chikalthana Aurangabad; Maharashtra, India was inspected by a WHO prequalification inspection team from 20th to 23rd February 2012.

Lupin's manufacturing facilities were located at the following places:

- Ankleshwar in Gujarat,
- Aurangabad and Tarapur in Maharashtra,
- Mandideep and Indore in Madhya Pradesh,
- Verna in Goa,
- Bari Brahmana in Jammu,
- Novadigm in Baroda in Gujarat and
- Kyowa in Japan.

Lupin Aurangabad plant started operation in 1979 and is the first plant of Lupin. The plant manufactures formulation dosage forms of tablets, capsules and oral liquids. The facility at Aurangabad was engaged in the manufacturing formulations such as Anti-TB, Cardio-Vascular, Anti-malarial, Antibacterial, Antihistamine and Anti-inflammatory drugs.

History of WHO and/or regulatory agency inspections

This was the fifth inspection of this site by WHO Prequalification team. The previous inspections were carried out in June 2007 (routine), August 2008 (special) and October 2009 (routine) and December 2010 (special).

Focus of the inspection

The inspection focused on the production and control of TB products (TB070, TB068 and TB177). The inspection covered all the sections of the WHO GMP text, including premises, equipment, documentation, materials, validation, sanitation and hygiene, production, quality control and utilities.

Inspected Areas

Day 1: 20th February 2012

- Opening meeting
- Product quality review
- Evaluation of vendors
- Deviations
- Job descriptions
- Batch release procedure
- Training of personnel
- Documentation review

- Self-inspection

Day 2: 21st February 2012

- Inspection of technical areas including AHUs,
- Water system and Compressed air system
- Inspection of receiving bay, raw material store including quarantine, approved, rejected area,
- Sampling area for raw and packaging materials,
- Material dispensing area,
- Block 1 (Rifampicin block)

Day 3: 22nd February 2012

- Primary packaging area
- Intermediate store (IMS)
- Intermediate store for blister/aluminium foil
- Finished goods store
- Packaging material store
- Wet chemistry laboratory
- Instrumentation area (HPLC, GC, IR)
- Stability study area
- Retention sample area
- Microbiology area

Day 4: 23rd February 2012

- Cleaning validation for block 1 and 2
- Hold time evaluation for cleaned equipment
- SOP on user maintenance in SAP
- Job description of Senior Manager QA
- Complaints for 2011
- Product and dummy recalls for 2011
- Change controls (Jan-Dec 2011)
- Handling of out of specification
- Deviations and
- Closing meeting

2.1 QUALITY ASSURANCE

In general, a system for managing quality was established. The quality department was independent of the production department. There was an organization chart and job descriptions specifying the titles and reporting relationships of the various staff. In general, this area found acceptable.

There were documented and approved procedures to guide routine operations and activities. Starting materials, intermediate products, finished goods were controlled and approved by QC/QA before release for use or distribution.

Policies and procedures were in place for qualification and validation of equipment and systems, change control and deviation management and product quality review. These were generally adequately implemented.

Product quality reviews were performed for WHO prequalification products. More attention is required on the review of starting materials including suppliers/vendors.

2.2 GOOD MANUFACTURING PRACTICES (GMPs) FOR PHARMACEUTICAL PRODUCTS

Products appeared to be consistently produced and controlled to the quality standards appropriate to their intended use and as required.

2.3 SANITATION AND HYGIENE

In general, premises and equipment were maintained at an acceptable level of cleanliness at the time of inspection.

2.4 QUALIFICATION AND VALIDATION

The company had identified the qualification and validation work to be performed in their validation master plan and associated documents. Requalification and revalidation were performed as per the plan and showed that the premises, supporting utilities, equipment and processes continued to operate in accordance with requirements. In general, this appears satisfactory.

2.5 COMPLAINTS

Dealing with complaints was specified in a written SOP. It is recommended to handle the complaints on their merits.

2.6 PRODUCT RECALLS

This area was not inspected as no recalls had been declared by the company.

2.7 CONTRACT PRODUCTION AND ANALYSIS

Not inspected.

2.8 SELF INSPECTION AND QUALITY AUDIT

The company had a basic self-inspection program which consisted of semi-annual reviews of all of its operations, and production activities. There was a standard operating procedure to cover the basic approach to self-inspection, and an annexed set of checklists designed to cover different manufacturing activities in different areas.

2.9 PERSONNEL

There were organization charts and job descriptions to guide personnel. Most of the personnel interviewed had adequate knowledge and skills to perform assigned duties. More attention must be paid on having recruiting and retaining adequate personnel to carry out various QA tasks on time.

2.10 TRAINING

In general, training to the personnel found satisfactory. It is strongly recommended to hire permanent staff at least for production, packaging and sampling activities. In addition, contract staff be treated or trained in a similar way as permanent staffs were. More attention is needed to maintain training records appropriately and be readily available for inspection.

2.11 PERSONAL HYGIENE

Personnel gowning was appropriate to the different area classifications being entered. Detailed instructions were available regarding hand washing which was performed before entering production areas and signs to this effect were posted. More attention is needed to improve and maintain the entry/exit procedures.

2.12 PREMISES

In general the buildings and facilities used for manufacture and quality control were located, designed, and constructed to facilitate proper cleaning, maintenance and production operations. Premises were designed to ensure the logical flow of materials and personnel.

Quality control laboratories were separated from production areas. Sufficient space was given to avoid mix-ups and cross-contamination. Sufficient space was provided for samples, reference standards, solvents and reagents.

Sampling of raw and packing materials was conducted in either of 2 sampling rooms provided with pass box, material air lock, personnel airlock, and a “Reverse laminar flow”.

2.13 EQUIPMENT

Balances and other measuring equipment with appropriate range and precision were available for production and control operations and were calibrated on a scheduled basis. However, at one place standard weights were not identified and their calibration was found inadequate as well. Calibrated standard weights used for in-house checking of balances were available. Calibration due-date labels were attached to the equipment.

HVAC

The HVAC system was designed and maintained reasonably.

Purified Water System

The Purified Water system was designed and maintained reasonably.

2.14 MATERIALS

Materials were mainly sourced from approved suppliers. All incoming materials and finished products were quarantined immediately after receipt until they were released for use or distribution. More attention is required on the assessment of suppliers serving suspension or warning from any stringent regulatory authorities.

Materials were properly quarantined and released by QC. Temperature was controlled. Printed packaging materials were stored in a locked area.

Materials were received via unloading platform; proper checks according the check list were carried out for incoming materials. Approved vendors list was available in the warehouse. All incoming materials were de-dusted before placing to the quarantine area.

100% sampling plan was applied for API sampling for identity tests. Printed packaging materials were sampled following AQL.

There were two sampling and two dispensing rooms for raw materials which had separate personnel and material entrances. Sampling and dispensing was carried out under the RLAF.

2.15 DOCUMENTATION

Most documents were adequately designed, prepared, reviewed and distributed. Documents were approved, signed and dated by the appropriate responsible persons.

2.16 GOOD PRACTICES IN PRODUCTION

Handling of materials and products was done in accordance with written procedures and was recorded.

The manufacturing activities were organized in a logical stepwise manner; processes were completed in accordance with authorized batch manufacturing records, similarly, the packaging effort was conducted in accordance with authorized Batch Packaging Records.

Punches were stored properly, were numbered and rotation was ensured. Food grade lubricant was used for punches and dies lubrication.

2.17 GOOD PRACTICES IN QUALITY CONTROL

Organization, documentation and release procedures were in place to ensure that the necessary and relevant tests were carried out.

In general, there were adequate facilities, personnel, approved procedures for sampling, inspecting and testing of starting materials, packaging materials, etc. Records were made demonstrating activities performed.

Wet Chemistry and Chromatography

All reagents were clearly labelled and expiry dated based on the date of opening or preparation. Volumetric glassware was in acceptable condition. Equipment, such as HPLCs, GC and IR were in good order. There were some issues noted on access control and use of manual integration.

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, Lupin Limited, Block No.1 and 2, A-28/1, MIDC, Industrial Area, Chikalthana, Aurangabad 431 210, India was considered to be operating at an acceptable level of compliance with WHO GMP guidelines.

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 three(3) years, provided that the outcome of any inspection conducted during this period is positive.