

WHO PUBLIC INSPECTION REPORT

(WHOPIR)

Finished Product Manufacturer

Part 1: General information about the inspection

Name of manufacturer	Lupin Limited Rifa and Non-Rifa block No.2
Physical address	A-28/1 MIDC Industrial Area Chikalhana Aurangabad 431210 Maharashtra INDIA
Postal address	See above
Telephone number	+91-240-2485871, +91-240-2485872, +91-240-2485873, +91-240-2485874, +91-240-6612444
Fax number	+91-240-2484121, +91-240-2484223
Summary of activities of manufacturer (e.g. manufacturing, packing). Indicate dosage forms and type of products (e.g. tablets; cephalosporin containing products)	Manufacturer and packer of oral solid dosage forms (tablets and capsules) products in several therapeutic areas: anti-TB, neuro-tropics, NSAIDs, cardiovasculars, antimalarials, anti-virals, expectorants and herbals. No penicillin's or cephalosporin's are produced.
Scope and type of inspection	Specific GMP inspection, related to the data verification
Date of inspection:	29 September - 2 October 2009
Project (if any):	Prequalification of Medicines Programme

Part 2: Summary

Background information

Lupin Limited (hereafter referred to as Lupin) located in Aurangabad, Maharashtra, India was inspected by a WHO prequalification inspection team on above mentioned days.

Lupin's manufacturing facilities were located at:

- Ankleshwar (Gujarat State)
- Mandideep (Madhya Pradesh State)
- Tarapur (Maharashtra State)
- Aurangabad (Maharashtra State)
- Verna (Goa state)
- Jammu and Pithampur (Madhya Pradesh state).

The total number of Aurangabad employees engaged on the site for Production, Engineering, Production Planning and Control (PPC), QC/QA, Stores and Distribution was about 203.

The facility at Aurangabad was engaged in the manufacturing formulations such as Anti-TB, Cardio-Vascular, Anti malarial, Antibacterial, Antihistamine and Anti-inflammatory drugs.

The Aurangabad facility had recently been renovated - new manufacturing blocks were created. Separate manufacturing blocks were provided for Anti-TB & other product categories for solid dosage forms and for oral liquid dosage forms. The facility also had a separate finished goods warehouse and full-fledged utilities section.

The Rifa facility was upgraded in 2002, Non Rifa facility in 2003, IMS/Bulk packing area in 2007, Block III in 2008 and new liquid facility was commissioned in 2009.

History of WHO or regulatory agencies inspections

The site was last inspected by the WHO team on 14, 15, 16 June, 2007 (routine inspections) and on 20 to 22 August 2008 (specific inspection). The site was approved by various authorities such as:

- OGYI Hungary
- MCC South Africa
- MOH Ukraine
- Uganda
- Nigeria

Focus of the inspection

This was a special inspection, where some systems were being inspected focusing mainly on material management, quality control and documentation. Manufacture and quality control operations were inspected on spot checks.

2.1. Quality Assurance (QA)

A quality assurance system was implemented and maintained.

The QA and QC units were independent from production.

Change control, deviations

A change control procedure and change register was available for inspection.

It was discussed that the change control log should have an additional entry field for categorization into minor or major; it was noted that case records did include this information.

A system for deviation management was described in writing.

Batch manufacturing records reviewed (before 2009) did not have a clear section for documenting deviations occurring during the production.

It was noted that more recent records had a separate page/section for deviations.

Product quality review (PQR)

PQR's were available for all batches manufactured for the prequalification programme / Global Drug Facility.

Results of a particular year and comparative reviews (e.g. 2008 vs 2007) had been evaluated only on the basis on min, max and arithmetical mean.

It was noted that the company was drafting a new version of the SOP for PQR's to be implemented for the 2009 PQR's.

It was noted that the company was planning to open deviation cases if yields less than the established limits were to be observed.

2.2. Good manufacturing Practices for Pharmaceutical products

Good manufacturing practices were implemented and maintained:

- qualifications and validations were performed
- adequate premises and equipment were available for production, in-process controls and storage
- instructions and procedures were written in clear and unambiguous language
- operators were trained
- manufacturing processes were clearly defined and reviewed. Manufacturing steps were recorded in BMR's and BPR's.

2.3 Sanitation and Hygiene

The topic was not specifically covered during the inspection. No notable concerns were identified during the "walk through".

2.4 Qualification and Validation

Process validation

Validation studies were conducted in accordance with predefined and approved protocols. Written reports summarizing the results recorded and the conclusions reached were prepared and stored. Manufacturing Processes and procedures were established on the basis of the results of the validation performed.

Analytical work sheets were not retained for the validation batches. (It was noted that company had changed the policy and since the beginning of 2009 analytical work sheets were retained also for validation batches).

Records of preparation and usage of working standards were available. Requested chromatograms in electronic form were retrieved from back-up copies.

2.5. Complaints

Complaints were handled in accordance with written SOP. Complaint register and investigation records were available for inspection.

2.6 Product Recalls

There had been no recalls in last 7 years.

2.7 Contract production and analysis

Not covered during inspection.

2.8 Self inspection and Quality Audits

Not covered during inspection.

Suppliers' audits and approval

A written procedure was in place. SOP was reviewed and found to be acceptable. An audit schedule for API was available.

2.9 Personnel

Personnel met during inspection were experienced, skilful and conscientious.

2.10 Training

Training program was reviewed using SOP. Where the induction training planner was given by the Human Resource department and other individual departments established their annual department training plans.

2.11 Personal Hygiene

The level of hygiene observed and the measures taken to maintain this were considered sufficient.

Changing rooms were provided with photos describing the gowning procedures.

2.12 Premises

Premises were designed to minimize the risk of errors, potential contamination and cross-contamination, to facilitate proper cleaning and maintenance and ensure the logical flow of materials and personnel.

Premises were protected from entry by insects, birds and animals.

Premises were clean and well maintained.

Storage areas

Sufficient space was provided for storage of different materials. Appropriate storage conditions were provided. Temperature mapping was carried out.

Production areas

Production area was laid out to allow the production to take place in a logical order. The surfaces were smooth and free from cracks.

Temperature, relative humidity and pressure differentials were regularly monitored.

Quality control areas

Quality control areas were separated from production areas.

2.13 Equipment

Process equipment was installed and maintained in a way that minimizes risk of error, contamination and cross contamination.

Production and quality control equipment was identified as to its content or purpose and cleanliness status and appropriately indicated by labels.

2.14 Materials

Materials in the warehouse were handled by the SAP system.

Incoming goods and finished products were quarantined until tested and released by QC.

Materials and products were generally stored in a proper manner.

Each container of starting material used for production of GDF products were sampled for identity test purpose. ID tests were performed on each of container of API and excipient.

2.15 Documentation

In general, the documentation system was well established and maintained.

Documents were designed, prepared, reviewed and distributed with care. Documents were approved, signed and dated by the appropriate responsible persons. Documents had unambiguous contents and were laid out in an orderly fashion and were easy to check. Documents were regularly reviewed and kept up to date.

Analytical work sheets were filled on paper format; data for CoAs were entered manually into the computer. The company was in the process of moving to in-time electronic entries.

BMR's were not constructed in a way to enable clear yield evaluation of each production stage; yields were calculated with reference to the start of batch production (it is remarked here that bulk may be packaged in several separate packaging runs).

It was noted that the company had drawn new BMR/BPR formats in MS Word to enable the evaluation in question, and also to include additional data for equipment settings (e.g. compression speed).

2.16 Good practices in production

Line clearances were performed and recorded before processing operations were started.

Batch numbering system was discussed – “mother” batch and “child” batches (mother batch can be packaged into different package types for different markets) bear the same number, according to the company there had not been cases where a mother batch was packaged on the same day for the same market in more than one run.

2.17 Good practice in Quality Control

For general information please see previous reports.

Out of Specification (OOS) results were evaluated and investigated in accordance with a written procedure.

The following procedures and related documents were reviewed

- Annual product reviews (APR):
- Process validation reports and links to batch documents
- Process validation source data (samples, chromatograms)
- Stability program and raw data (samples, chromatograms)
- Batch Manufacturing Records
- Master document code numbers and versions
- Deviations
- Change control
- Complaints
- Out of Specifications
- Material codes for APIs
- Certificates of analysis for API and FPP
- Specifications for API and FPP
- Analytical test methods for API and FPP
- SAP management
- Transfer of codes
- Use of correct API (code) in batches
- Approved vendors list
- List of performed vendors audits
- Vendors audit reports
- Vendors audit schedule for API
- Stability monthly plan: August 2009-09-30
- Finished product specification (product release specifications) Ethambutol/Isoniazid/Pyrazinamide/Rifampicin Tablets 275mg/75mg/400mg/150mg
- Finished product specification (product release specifications) Rifampicin/Isoniazid Tablet 60/30 mg
- "Product in process specifications Rifampicin, Pyrazinamide&Ethambutol Hydrochloride tablets USP
- "Product release specification Rifampicin part (150 mg)"
- Log for deviations 2008 and 2009
- Market complaints log year 2008
- Market complaints log year 2009
- Review report Market complaints year 2008
- Dummy recall validation report
- Log for OOS test results - 2008
- Log for OOS test results - 2009
- SOP's
 - "Material/product transfer in SAP and documentation"

- "Selection, approval, qualification and periodic evaluation of vendors (manufacturers)". Vendors audits should be performed once per 3 years.
- "Management of stability studies"
- "Hardness tester", calibration section
- "FBD operation and cleaning", cleaning section
- "Change control"
- "Deviations"
- "Backup"
- "Handling of market complaints for drug products"
- "Recall"
- "Quality risk management" (draft)
- "Handling and investigation of OOS results"

Validation and stability protocols/reports were reviewed together with batch manufacturing records (BMR) and analytical raw data. This included verification of API used, codes, approved suppliers against the approved suppliers list (ASL). Analytical raw data was inspected, including chromatograms and calculations.

Tabulated data was verified against analytical raw data and chromatograms were inspected.

SAP system

The SAP system was inspected for the various codes for selected APIs. Checks were made to verify which code API was used in which batches of products. Print outs of rejections in 2008 and 2009 for selected material groups were requested.

Quality control results for raw and packaging materials were entered in SAP, results for intermediates and finished products were not entered in SAP.

API code transfers were indicated in the SAP system. SAP provided traceability of movements executed for a particular batch.

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 Rifa and Non-Rifa block No 2, A-28/1 MIDC Industrial Area, Chikalthana Aurangabad 431210 Maharashtra, 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 3 years, provided that the outcome of any inspection conducted during this period is positive.