WHO PUBLIC INSPECTION REPORT Finished Product Manufacturer

WHO PUBLIC INSPECTION REPORT

(WHOPIR)

Finished Product Manufacturer

Part 1: General information

Name of Manufacturer	**Lupin Limited**
Unit number	N/A
Production Block	N/A
Physical address	EPIP, Kartholi, SIDCO, Industrial Complex, Bari Brahma, Jammu (J&K) 181 133
Contact address	Mr. Rajeev Patil Senior Vice President – Regulatory Affairs rajeevpatil@lupinpharma.com Mr. Vinay Chaturvedi General Manager – Site Head vinaychaturvedi@lupinpharma.com
Date of inspection	17, 18, 19 and 20 February 2014
Type of inspection	Routine inspection
Dosage forms(s) included in the inspection	Solid dosage forms (tablets)
WHO product categories covered by the inspection	TB068 TB070 TB177
Summary of the activities performed by the manufacturer	Manufacturing, quality control and batch release of FPP oral solid dosage forms (tablets and capsules, dry powder suspension) and inhalers.

Part 2: Summary

General information about the company and site

Lupin Limited (hereafter referred to as Lupin) site located in Jammu, India was inspected by a WHO prequalification inspection team on above mentioned days. The Corporate Head Quarters including Corporate Quality Assurance is located at 159, CST Road, Kalina, Santacruz (East) – Mumbai – 400 098, India.

History of WHO and/or regulatory agency inspections

This was the second WHO inspection of Lupin Limited, Jammu. It was noted from the opening meeting presentation that the site had been inspected by Ukraine authority in 2013.

Focus of the inspection

The inspection focused on general principles of GMP and the production and control of oral solid dosage forms which included products prequalified by WHO PQT (**TB068, TB070 and TB177)**. The inspection covered most of 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: 17 February 2014

- Introductions
- Opening meeting
- Organization charts
- Job description: Site Head
- Job description: General Manager Quality Assurance
- PQR Rifaximin 200mg tablets
- Feedback on observations

Day 2: 18th February 2014

- Management of packaging material
- Production area (site inspection)
- Feedback on observations

Day 3: 19th February 2014

- Training
- Out of specifications
- Management review
- Inspection of quality control laboratory
- Feedback on observations

Day 4: 20th February 2014

- Training continued
- Cleaning validation
- Inspection of quality control laboratory continued
- Dust extraction system

2.1 QUALITY ASSURANCE

A quality assurance system was in general terms implemented and maintained. Quality Assurance (QA) and Quality Control (QC) departments were independent from production. The QA Head reported to the General Manager. Production and control operations were specified in writing. The necessary controls on starting materials, in-process checks and finished products were in place.

2.2 GOOD MANUFACTURING PRACTICES (GMPs) FOR PHARMACEUTICAL PRODUCTS

The necessary documentation, equipment and facilities were available to perform the manufacturing activities for TB products. Necessary resources were generally provided, including adequate premises and space, suitable equipment and services, appropriate materials, containers and labels, approved procedures and instructions, suitable storage, adequate personnel, laboratories and equipment for in-process controls. During the inspection it was noted that the areas were generally clean and tidy.

The observations raised from this section have been satisfactorily addressed, and will be verified during future inspections.

2.3 SANITATION AND HYGIENE

Specific SOPs were established to cover the hygiene program. Personnel entering the manufacturing area were required to put on the appropriate garments (such as suits, gloves, cap and face-mask) according to the gowning procedure. The facilities and equipment were found to be in a good state of cleanliness with cleaning records maintained.

2.4 QUALIFICATION AND VALIDATION

Not inspected

2.5 COMPLAINTS

The SOP for Complaints was reviewed. Complaints were categorized as critical, major or minor.

The observations raised from this section have been satisfactorily addressed, and will be verified during future inspections.

2.6 PRODUCT RECALLS

Not inspected

2.7 CONTRACT PRODUCTION AND ANALYSIS

Not inspected

2.8 SELF INSPECTION AND QUALITY AUDIT

Not inspected

2.9 PERSONNEL

The site employed 178 personnel to conduct production and quality control procedures. In addition, the site used a significant number of contracted personnel for various operations including but not limited to housekeeping, material handling and dispensing operations.

2.10 TRAINING

The company policy and procedures for training were reviewed. Training was managed through a computer system and covered e.g. induction training, functional, on the job, GMP and SOP training. The system was said to be validated.

The observations raised from this section have been satisfactorily addressed and will be verified during future inspections.

2.11 PERSONAL HYGIENE

There were facilities and procedures for changing and entering into production areas which required staff members to wash their hands and change into clean factory garments. The facilities and procedures were generally adequate.

2.12 PREMISES

The premises were located, designed, constructed and maintained to suit storage, manufacturing, quality control and related operations. The layout and design of premises generally facilitated the logical flow of materials and personnel to minimize

the risk of errors and permitted effective cleaning and maintenance. The areas where dust was generated were fitted with dust containment and extraction systems.

There were separate warehouses for raw materials, packaging materials and finished goods. They were generally well designed, controlled and monitored to provide appropriate temperature and relative humidity conditions. There was a covered receiving bay and an area where incoming consignments were verified and cleaned.

The laboratory was located in the same building as the production activities but separated from production areas and consisted of microbiology laboratory, physico-chemical laboratory (chemical lab, instrument labs), stability and retention sample room.

2.13 EQUIPMENT

There were adequate numbers of equipment for the production and testing products manufactured at the site. The equipment reviewed were suitably designed, qualified and calibrated. Balances were calibrated and records of daily verification using standard weights were available. There were procedures and records for equipment use, cleaning and maintenance.

Heating, ventilation and air-conditioning (HVAC) system:
The layout of the site was inspected against a list of 52 AHUs. AHUs for compression cubicles were AHU02, and AHU11, and Granulation AHU01 and AHU10. AHU 10 served Granulation 1 and 2, and the air was re-circulated. There was no regular check to ensure that the make-up was 10 to 15% of fresh air. The frequency of the tests (area validation) was set as once in a year or once in two years for some tests, but there was no rationale for the tests selected or the intervals. There was no protocol that could be followed with a corresponding report for the area validation. Upstream concentration was checked only at the beginning of the installed filter leakage test. There was no record to show what the concentration of the PAO was at the time of testing. Particle counts: The SOP was not followed (as per ISO 14644) for square root of n-number of locations. The total area was calculated ($22m^2$) with 5 points (which included the RLAF and room). Separate calculations were not made for the different areas with different classes in one room such as ISO 8 and ISO 5 (e.g. dispensing 1). The UCL was not calculated for some areas including ISO 5 classified areas, where the number of locations was below 10 as required by ISO and the company SOP. There was no containment leakage test performed.

The observations raised from this section have been satisfactorily addressed, and will be verified during future inspections.

2.14 MATERIALS

Materials were managed through SAP.

2.15 DOCUMENTATION

A documentation system was in place to guide production and control of products. These included: Site Master File (SMF); Validation Master Plan (VMP); standard operating procedures (SOPs); Batch Manufacturing and Packaging Instructions and records (MIs, BMRs, BPRs); specifications of starting materials, packaging materials, packaging components and finished products; standard testing procedures, analytical records and certificates of analysis; qualification and validation protocols, schedules and reports; training schedules and records. There were corresponding records in form of reports, forms, checklists, logbooks, registers maintained as evidence of compliance with the procedures and specifications.

QA department was responsible for the coordination and control of preparation, review, approval, distribution and review of documents. The system was generally comprehensive and well managed.

2.16 GOOD PRACTICES IN PRODUCTION

Production operations were guided by approved written procedures in form of manufacturing instructions (MIs) and batch manufacturing records (BMRs). Records reviewed and practices witnessed indicated that records were made promptly in the BMRs and any deviations were also recorded and handled in accordance with an approved procedure.

Line clearance was conducted before and after production and packaging operations.

In-process controls were performed and documented at appropriate stages and intervals. There were provisions for checks on yields and reconciliation of quantities. Materials and equipment were adequately labelled with identity, stage of processing and status as appropriate.

The primary and secondary packaging was controlled with a number of automatic sensors based on photography, weight and bar codes.

The observations raised from this section have been satisfactorily addressed, and will be verified during future inspections.

2.17 GOOD PRACTICES IN QUALITY CONTROL

The laboratory was located in the same building as the production activities but separate from production areas and their functions were independent of other units including production. They were manned by qualified analysts and had adequate facilities in form of space, equipment, reagents and chemicals to test all starting material, packaging materials, intermediates and finished products before release for use or distribution.
The observations raised from this section have been satisfactorily addressed, and will be verified during future inspections.

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, Jammu, 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.