

## WHO PUBLIC INSPECTION REPORT

(WHOPIR)

### Finished Product Manufacturer

#### Part 1: General information about the inspection

Name of manufacturer	Lupin Ltd
Physical address	EPIP, Kartholi, SIDCO Industrial Complex, Bari Brahmana, Jammu (J&K) – 181133
Postal address	As above
Telephone number	91 1923 220046 / 220672 / 220676
Fax number	91 1923 220177
Summary of activities of manufacturer	Manufacturing, quality control and batch release of FPP oral solid dosage forms (tablets and capsules, dry powder suspension) and inhalers.
Focus of inspection - products in WHO PQ program covered in the scope at the time of inspection with the WHO reference number	<b>Prequalified products:</b> 1. TB 068 Isoniazid/ rifampicin 75mg/150mg tablets 2. TB 070 Rifampicin, Isoniazid, Pyrazinamide and Ethambutol HCl tablets 3. TB 177 Ethambutol 400mg tablets
Scope and type of inspection	Routine inspection, covering all aspects of GMP
Date of inspection:	16 - 19 August 2011
Project (if any):	Prequalification of Medicines Programme

## **Part 2: Summary**

### ***Background information***

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

Lupin's manufacturing facilities were located at:

- Ankleshwar in Gujarat,
- Aurangabad and Tarapur in Maharashtra,
- Mandideep in Madhya Pradesh,
- Verna in Goa,
- Bari Brahmana in Jammu,
- Pithampur, Indore in Madhya Pradesh,
- Dabasha in Baroda in Gujarat and
- As Kyowa Pharmaceuticals at Sanda in Japan.

The Corporate Head Quarters including Corporate Quality Assurance is located at 159, CST Road, Kalina, Santacruz (East) – Mumbai – 400 098, India.

The total number of Jammu employees engaged on the site for Production, Engineering, Production Planning and Control (PPC), QC/QA, Stores and Distribution was about 142 employees.

Lupin Jammu site was founded in March 2006, plant commissioning started in April 2007. Indian FDA approval was given in April 2007. First commercial batch was manufactured in April 2007.

### ***History of WHO or regulatory agencies inspections***

The site had never been inspected by the WHO team. The site was approved only by Indian FDA.

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

The inspection focused on the production and quality control of **TB 068** Isoniazid/ rifampicin 75mg/150mg tablets, **TB 070** Rifampicin, Isoniazid, Pyrazinamide and Ethambutol HCl tablets and **TB 177** Ethambutol 400mg tablets products. The inspection covered all sections of the WHO GMP, including premises, equipment, documentation, materials, validation, sanitation and hygiene, production, quality control and utilities.

Representatives of the Lupin corporate office were present during the inspection.

Lupin had applied for variations for already prequalified products:

- Change of manufacturing site of the FPPs with scale up of batch size
- Change of the site of quality control testing of the FPPs

Previously the above mentioned products for WHO were manufactured at Lupin site in Aurangabad, A-28/1, M.I.D.C. Industrial Area Chikalhana Aurangabad 431 210, India. At the Jammu site those products were manufactured for Indian market.

### ***Inspected Areas***

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- Quality assurance
- Good manufacturing practices for pharmaceutical products
- Sanitation and hygiene
- Qualification and validation
- Complaints
- Product recalls
- Contract production and analysis
- Self-inspection, quality audits and supplier's audits and approval
- Personnel
- Training
- Personal hygiene
- Premises
- Equipment
- Materials
- Documentation
- Good practices in production
- Good practices in quality control

## **2.1 QUALITY ASSURANCE**

A system for quality assurance was established and covered all the basic elements of GMP. Organization chart was reviewed and found to be acceptable.

### **Product Quality Review (PQR)**

SOP "Annual Product Review" was reviewed and found to be acceptable.

For the WHO variations all 3 products were manufactured in 2008 and placed on stability studies.

**PQR 2 FDC and 4FDC 2010- 2011** were presented and reviewed by the inspectors.

### **Deviation management**

Deviations were classified as:

- Major
- Minor
- Planned
- Unplanned

Risk assessment procedure was applied for the classification of deviations. Deviations were recorded in BMR's. Risk analysis was performed by considering the following parameters:

- Severity risk
- Detectability of risk
- Likelihood of occurrence of risk

Risk was evaluated based on the score of severity, detectability and likelihood of occurrence. The risk priority number was derived from these three factors. According to the SOP the deviation report should be investigated and closed within 30 calendar days of the occurrence. CAPA's should be proposed and recorded.

Deviation logs for 2010 and 2011 were reviewed:

### **Quality risk management**

The Quality risk assessment procedure was applicable to product quality risk management through the lifecycle of drug substances and drug products including development, manufacturing, distribution, surveillance, change management and the inspection and submission/review process. The following risk assessment tools were applied:

- Ishikawa diagram
- FMEA

### **Change control**

Change control was covered by the corporate level SOP from 2009.

## **2.2 GOOD MANUFACTURING PRACTICES (GMPs)**

Good manufacturing practices were implemented. The necessary resources were generally provided. Manufacturing steps were recorded in batch manufacturing and packaging records. Instructions and procedures were generally written in clear and unambiguous language. Qualifications and validations were performed, adequate premises and equipment were available for production, in-process controls and storage, and operators were trained.

## **2.3 SANITATION AND HYGIENE**

In general, premises and equipment were maintained at an acceptable level of cleanliness. The company had an SOP as the basis for its approach to personal hygiene and sanitation in its production facility.

## **2.4 QUALIFICATION AND VALIDATION**

### **Validation master plan (VMP)**

The company's approach to qualification, and validation was consistent with the WHO technical report series recommendations.

VMP was reviewed. The document was revised every year. VMP covered:

- Equipment Qualification
- Process validation
- Cleaning validation
- Personnel validation
- Analytical method validation
- Computer validation

Periodic requalification was carried out at the following intervals:

- HVAC systems and LAFs 1 year
- Water systems 5 year
- Compressed air 5 year
- Main production equipment and machines 5 year

- Autoclave 1 year
- Dry heat sterilizer 1 year

Ethambutol, 2 FDC and 4FDC process validations Protocols/reports were presented to the inspectors. Validations protocols/reports were spot checked, no remarks.

Cleaning validation was performed on the worst case product.

## **2.5 COMPLAINTS**

Responsible person for handling market complaints was the Quality head, deputized by senior executive QA. Complaints were classified as:

- Category I - Critical defect
- Category II - Major defect
- Category III - Minor defect

According to the procedure, where necessary, appropriate follow-up action, possibly including product recall, should be taken after investigation and evaluation of the complaint. If required Competent Authorities should be informed. Consideration should be given to whether other batches should be checked in order to determine whether they are also affected. Attention was given to establishing whether a complaint was caused because of a suspect product counterfeiting.

Complaint log book 2010 was reviewed, no remarks.

## **2.6 PRODUCT RECALLS**

Responsible person for recall was the Quality head, deputized by senior executive QA. The decision on recall of the defective product should be made within 24 hours of receipt of the information. Recall could be voluntary and statutory. Dummy recall was carried out once in two years for Indian market. Last dummy recall was executed in 2011. Recalls were classified as:

- Class I
- Class II
- Class III

There were three levels of recalls:

- Consumer or user level
- Retail level
- Wholesaler level

## **2.7 CONTRACT PRODUCTION AND ANALYSIS**

Production activities were not contracted out.

Some analysis was carried out on contract basis.

Other outsourced activities and services included:

- Testing of HEPA Filters and validation support of HVAC System
- Pressure gauge and thermal calibrations
- Cleaning of production and warehouse premises

- Pest control
- Washing and maintenance of production gowning

Contracts with service providers were valid; no remarks.

## **2.8 SELF INSPECTION AND QUALITY AUDIT**

Self inspection was carried out twice in a year for all departments and all the working shifts. Audit team members were qualified persons from Production, QC, QA, Warehouse, Engineering and Human Resources Departments. Check-lists were used to conduct the self inspection. Findings were recorded in the self inspection compliance report. CAPA's were proposed by the audited department. Implementation of CAPA's was checked by QA Head. QA head also was responsible for follow up of CAPA's. Self inspection results were reported to the management. Management review was carried out once in a year.

## **2.9 PERSONNEL**

In general, the personnel met and interviewed during the inspection were knowledgeable. Job descriptions of key persons were available and the following were reviewed by the inspectors:

- Production Manager
- Quality assurance (Deputy General Manager)
- Quality control (Senior Executive) responsible of raw materials, packaging materials and finished goods
- Quality Assurance (Senior Executive)

## **2.10 TRAINING**

The training needs were identified and training was organized as per the corporate level SOP, which was not checked in detail. Training was traceable. Analyst validation SOP was established by the site, records for two analysts were checked; no remarks.

## **2.11 PERSONAL HYGIENE**

Direct contact was avoided between operators' hands and starting materials, primary packaging materials and intermediate or bulk product. All changing rooms were provided with photographs which described the gowning procedures. Level of personnel hygiene was observed to be appropriate. Smoking, eating, drinking, chewing, and keeping and personal medicines were not allowed in working areas. Upon recruitment and at regular intervals (yearly) all personnel were required to undergo medical examination.

On spot-checks, records on medical examination were available, including outsourced housekeeping personnel.

## **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. In Process Laboratory was located in the production block. Quality control

laboratories were separated from production areas. Sufficient space was given to avoid mix-ups and cross-contamination.

Access to the warehouses, production premises and Quality control laboratories was controlled.

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. In general the surfaces were smooth and free from cracks.

Production was carried out in 2 areas A and B. Production area A was already constructed for production involving Rifampicin API. Since 2009 it had been in use for other tablets, as there was no demand for Rifampicin products.

There were 3 dispensing booths, 2 were used for inactive materials and one for APIs dispensing. Dispensing was carried out under RLAF. One of the booths was connected to area A and can be dedicated for Rifampicin production.

Temperature, relative humidity and pressure differentials were regularly monitored.

#### Quality control areas

Quality control areas were separated from production areas. Sufficient space was provided for samples, reference standards, solvents and reagents.

### **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. Calibration due-date labels were attached to the equipment. Contract with an external calibration company was valid. FBD temperature sensors and QC reference PT100+datalogger were spot-checked for certificates; no remarks. Calibration of measuring devices in QC was not scheduled as was the practice in production (Excel).

Calibrated standard weights used for in-house checking of balances were available.

Daily checking of analytical balances was carried out using calibrated standard weights. Standard weights calibration certificates were presented to the inspectors. Balance Mettler Toledo JK/QC/IN/109 daily and monthly calibration was checked and found to be well done.

Preventative maintenance was scheduled; separately represented for HVAC, production equipment, utilities. On spot-checks indicated that the schedule was followed.

Production equipment was cleaned on a scheduled basis as per written SOPs. Cleaning status was shown by a cleaning label. Clean equipment hold time was specified. It was explained that equipment hold time studies were carried out, this was not checked during inspection.

## **UTILITIES**

### HVAC system

AHU No 1 serving the Granulation and paste preparation room was inspected. Engineering drawings indicated filters specifications in  $\mu$ . For example - 10 and 5  $\mu$  filters. HEPA filters were named TH. In general the technical floor was acceptably clean. Separate room was provided for filter cleaning and another separate room for spare filter storage.

### Compressed air

The system was inspected on general level. Drawings and maintenance records were available. Final filter was 0,2 micron. Air quality monitoring was not checked due to limited time.

### Water

Softening and ion-exchange were the last steps to produce DM water which was used as purified water in the production. Design, operation and maintenance were documented. The system was run on ambient temperature. Alert and action limits for microbial purity were relatively high and did not consider the normal level of microbiology results, thus not being indicative of any unusual incidents. Heat sanitization cycle of the PW tank and loop was temperature monitored.

## **2.14 MATERIALS**

Materials in the warehouse were managed by the SAP system. Incoming goods and finished products were quarantined until tested and released by QC.

A batch of Ethambutol API was checked in the actual stock and in the SAP; no remarks.

In general materials and products were stored under appropriate conditions established by the manufacturer. T monitoring print-outs were available and were checked daily.

Materials were stored in high bay mobile racks.

Materials and products were stored in a proper manner.

Left-over's of printed cartons were not returned to the warehouse, other materials - starting materials, primary packaging materials - were returned to the warehouse. Returns were entered in the SAP system and were respectively labelled in the warehouse.

## **2.15 DOCUMENTATION**

In general, the documentation system was established and maintained. Documents were approved, signed and dated by appropriate responsible persons, regularly reviewed and kept up to date. A system for version control was in place. Specifications and testing procedures were available. Documents related to batch release were stored for one year after the expiry date of the batch or 6 years whichever is longer.

The following SOPs were reviewed:

- SOP "Annual Product review"
- SOP "Duplicate weighing policy and bracketing standards for system suitability LCP"
- SOP "Dissolution test apparatus"
- SOP "Comparative dissolution" was not available; however comparative dissolution studies for all three products have been carried out recently. During inspection the received data were reviewed. Comparative dissolution studies were carried following "WHO Guideline on submission of documentation for a multicourse (generic) finished pharmaceutical product (FPP): Quality part", Appendix 1- Recommendation for conduction and assessing comparative dissolution profiles.
- SOP SAP"Allocation of batch number".
- SOP "Personal Hygiene"
- SOP "Management of stability studies "
- SOP "Deviation handling"
- SOP "Self inspection"
- SOP "Recall of drug products"
- SOP "Handling of market complaints for drug products"
- SOP "Quality Risk Management", effective date 15.06.2011.
- SOP "Cleaning and sanitizing of manufacturing A, B and packing area" (spot checked)
- SOP "Security operations" (spot checked)
- SOP "Sampling" (spot checked)
- SOP "Sampling of raw material"
- SOP "Visual inspection"
- SOP "Trend analysis of Quality parameters & out of trend investigation"
- SOP "Handling of Out of Specification test results"
- SOP "Reference standards, working standards and analytical standards management"

## **2.16 GOOD PRACTICES IN PRODUCTION**

The Jammu site had manufactured products for Indian market only.

2 FDC and 4 FDC were manufactured for Indian market in 2007 and 2008. Ethambutol (Combuto) tablets had been continuously in production since 2007.

Handling of materials and products was done in accordance with written procedures and was recorded; checks on yields and reconciliation of quantities were carried out. During processing, materials, bulk containers, equipment, rooms and packaging lines were labeled. In-process controls were performed within the production area.

T and RH were controlled and monitored in all production rooms.

Punches and dies were stored properly in stainless steel (SS), locked cupboards. Punches and dies were numbered and rotation was ensured. Food grade lubricant was used. The following documents were available for the punches and dies:

- Approved drawings
- Inspection reports
- Usage reports

Punches and dies subsets were removed from manufacturing after compression of 10 000 000 tablets (round shaped) and 8 000 000 tablets (other than round shaped).

Finger bags for FBD were product dedicated and were also stored properly in SS, locked cupboards.

Metal sieves were found to be in good conditions and were stored properly in SS, locked cupboards.

Metal detectors were installed on all compression machines.

Mainly SS utensils were used in production. See section observations.

Silicone (Si) sleeves used in granulation and compression were used for all products on the production list.

In secondary packaging there were 9 lines:

- 4 blister packaging lines
- 3 strip packaging lines
- 1 dry powder inhaler packaging line
- 1 meter dose inhalers packaging line

Cartons to the secondary packaging department were transported in locked metal cages. Packaging lines were physically segregated.

Line clearance was performed and recorded before processing operations were started.

## **2.17 GOOD PRACTICES IN QUALITY CONTROL**

The QC function was independent from other departments. Samples of starting materials, packaging materials, intermediate products, bulk products and finished products were taken by approved methods. Sufficient samples of starting materials and products were retained to permit future examination of the product.

AQL was applied for sampling of packaging materials. Critical, major and minor defects were defined in SOP "Visual inspection".

### **Handling of Out of Specification test results**

As per the SOP, OOS investigation should be completed within 30 working days of occurrence. OOS results were trended every 6 months. There were three OOS logs:

- Raw materials/packaging materials
- Finished products

- Stability samples

OOS logs for 2010 for finished products and aw materials/packaging materials were reviewed, no remarks.

Microbiology laboratory had separate OOS SOP.

**Trend analysis of Quality parameters & out of trend investigation**

Minitab software I-MR was used to record all analytical results. UCL and LCL were defined. Results in the software were entered by the person who reviews tests data sheet, no remarks.

The following instrument calibration SOPs and reports were checked and found to be acceptable:

- Dissolution tester
- HPLC
- GC
- UV
- IR

IR grade KBr was stored in a dry box at 60 °C temperature.

HPLC grade water was used for buffer solution preparations. HPLC columns were properly stored and labelled. Columns usage was recorded.

Control samples were stored in mobile racks. Temperature in the room was monitored by SCADA system continuously. T monitoring print-outs were available: T was recorded every 30 minutes. FPP control samples were stored expiry date + 1 year. API control samples were stored 6 years.

Stability chambers were equipped with alarm system. T mapping was carried out for all stability chambers, T was monitored regularly. On going stability samples were stored in chamber with T 30 °C and RH 65%. One batch per year was placed on on going stability. In case of larger number of batches per year the site should consider inclusion of additional batch(es) into the programme.

All reference substances were stored in the fridge at T 2 - 8 °C. Pharmacopoeia standards were available as well as working standards (WS). WS were dispensed under RLAF. WS were dispensed in two different ways. Some WS were dispensed in single use amber glass vials, some in bigger bottles for multiple uses. WS in bigger bottles were used for 3 months. Reference standards register was available and showed to inspectors.

Refrigerator for storing reference standards was temperature monitored by the sensor of the fridge, the sensor was calibrated annually.

Log books were available for all laboratory instruments.

Class A volumetric glassware was used in the laboratory.

### **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, a decision on the compliance of Lupin LTD, located at EPIP, Kartholi, SIDCO Industrial Complex, Bari Brahmna, Jammu (J&K) – 181133, 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 years, provided that the outcome of any inspection conducted during this period is positive.