

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	Chikalthana (Aurangabad) Unit,
Production Block	Rifa and Non-Rifa facilities, Blocks No.1, 2 and adjacent areas
Physical address	A-28/1, MIDC, Industrial Area, Chikalthana, Aurangabad 431 210, India
Contact address	gautampareek@lupinpharma.com
Date of inspection	17 to 20 June 2014
Type of inspection	Follow-up inspection
Dosage forms(s) included in the inspection	Solid Oral Dosage Forms
WHO product categories covered by the inspection	TB
Summary of the activities performed by the manufacturer	Production, packaging, quality control, stability testing

Part 2: Summary

General information about the company and site

The plant in Aurangabad started its operations in 1979. According to the opening meeting presentation, Lupin Ltd. is among the top 5 generic companies in the US. Lupin's other manufacturing facilities are located at Ankleshwar (Gujarat State), Mandideep and Pithampur (Madhya Pradesh State), Tarapur (Maharashtra State), Aurangabad, Nagpur (Maharashtra State), Verna (Goa state) and Jammu. They have a subdivision in Japan, called Kyowa Pharmaceuticals and a subdivision in South Africa as well.

There was a small R&D laboratory on site which was attached to Block 3. It had about 50 employees and was started in 2010. This area had not been covered by the previous WHO inspections. It was visited only briefly as part of this inspection.

There were 3 manufacturing blocks: Block 1 (dedicated rifampicin block), Block 2 (regular production block) and Block 3 (described as "small scale", but also described as "high potent" site in other documents). Submission batches for TB204 (cycloserine capsules), pending prequalification, were manufactured in Block 3.

Several improvements were made since 2012. For instance, the vast majority of equipment process controls were now run through programmable logic controllers (PLC), which enabled all of the critical process parameters to be monitored through print-outs. Temperature and RH measurements were now performed on line and monitored through a centralized electronic system located in production.

There was a total number of 245 full time staff at the site. Short-term contract staff was also employed.

History of WHO and/or regulatory agency inspections

This was the sixth inspection of this site by WHO Prequalification team. The previous inspections were carried out in June 2007 (routine), August 2008 (special), October 2009 (routine), December 2010 (special) and in March 2012 (routine).

The facility has been inspected by many regulatory authorities, including the Australian TGA and US FDA. The last US FDA inspection was performed in July 2012 and did not result in any 483's.

Focus of the inspection

The inspection focused on the production and control of anti-TB products. 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

- Quality Assurance
- Sanitization and hygiene
- Qualification and validation

- Complaints
- Recalls
- Self-inspection
- Personnel
- Training
- Personal hygiene
- Premises
- Equipment
- Materials
- Documentation
- Production
- Quality control

2.1 PHARMACEUTICAL QUALITY SYSTEM

Quality risk management

The SOP on Quality Risk Management, from Corporate Quality Assurance (Corporate QA), was reviewed. All of the WHO products were covered by a quality risk management. The report that was drafted for rifampin, isoniazid, pyrazinamide and ethambutol tablets, dated 17/02/2014, was reviewed.

The quality risk management report based on the last audit of the supplier, Amsal, was reviewed.

Quality risk assessments were performed systematically along with major deviations, change controls, and market complaints. This area was considered to be acceptable overall.

Product quality reviews (PQR)

The standard operating procedure (SOP) on Annual Product Quality Review (APQR) was reviewed. Further to the last WHO inspection in 2012, the company revised the PQR SOP to change the review period to the calendar year starting from regulatory approval, to include review of CAPAs and add supplementary annexes.

All of the CAPAs from the last WHO inspection were verified to have been implemented in the current version of the SOP.

The SOP shown was the corporate SOP and hence the list of corrections/revisions did not reflect the changes made to the original site SOP which was previously followed, at the time of the last WHO inspection. The corporate SOP was nevertheless acceptable overall.

The PQR for TB068 (Rifampicin/ Isoniazid 150 mg/75 mg Tablets) for 2013 was reviewed. It stated that all of the 210 batches listed were manufactured at Block 1. It was very comprehensive in the number of parameters that were trended.

Product batches for other markets which were covered by different pharmacopoeias and different specifications were covered by different PQRs.

Out-of-trends (OOTs) and out-of-specifications (OOS) were listed in the PQRs. Examples were selected and reviewed.

Out-of-trends (OOT)

The SOP on OOTs from Corporate QA, was reviewed. It provided detailed instructions on how OOT results should be identified. Full investigations were done for OOTs which involved the same parameters as for OOS. Specific criteria were defined for the different test parameters that could be OOT. This area was acceptable overall.

Out-of-specifications (OOS)

The SOP on OOSs, Corporate QA, was reviewed. The SOP applied to microbiological tests but not to sterility (note: no sterility tests performed at the Lupin Aurangabad site). The SOP was considered appropriate overall and included the necessary details on how OOS investigations should be conducted, etc. Trending of OOS results was to be done every 6 months. The trend analysis included a classification of OOS results based on the potential root causes (analyst error, instrument error, method/specification error, equipment error, process error, human error in manufacturing, input material etc.) Thorough forms and checklists were attached in annexure to the SOP. Hypothesis error testing was done.

The registers for 2013 and 2014 were reviewed for all finished products manufactured at the plant. For 2014, selected reports were reviewed.

There was a separate procedure for stability testing that covered what should be done for OOSs.

Change controls

The SOP on Change Control, was reviewed. It covered all changes that affect or have the potential to affect the quality of a product. It allowed for the classification of changes as permanent or temporary and as minor, or major. A separate SOP was available for changes relating to software and this was covered under SOP ITP-025 “Change control for computer software system”.

The following registers for 2013 and 2014 were reviewed.

- Register for Block No. 3.
- Register for warehouse and engineering.

Examples of relevant change controls were reviewed. Revised SOPs were also seen as covered by Change controls. This area was considered satisfactory overall.

Deviations

An example of a deviation for Duomax, was reviewed.

2.2 GOOD MANUFACTURING PRACTICES FOR PHARMACEUTICAL PRODUCTS

Similarly to the last WHO inspection, 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. All of the areas seen during the inspection were generally clean, tidy and well-maintained.

2.3 SANITATION AND HYGIENE

Premises and equipment were generally maintained at an acceptable level of cleanliness at the time of inspection.

2.4 QUALIFICATION AND VALIDATION

Recently performed qualification

The 2014 qualification for the packaging corridor was presented. The construction design plans, verification of construction as per design and qualification were reviewed.

The final schematic air flow diagram for change room and process corridor was reviewed. The performance qualification protocol for the HVAC system for the packaging corridor was reviewed and included all of the necessary ISO 14644 elements.

Microbiological environmental monitoring was done using settle places. All of the results were within limits, but there was no documentation that this has been reviewed and found to be acceptable.

Poly-alpha-olefin (PAO) was documented to be used for the HEPA filter integrity test.

Process validation

The process validation report was reviewed for a product that was still undergoing assessment with WHO Prequalification.

Vendor qualification

The supplier of calcium carbonate was reviewed. It was registered through a “manufacturer registration form”, and the “manufacture quality system self-assessment questionnaire” dated February 2012. The range of documents included a list of products supplied, a BSE/TSE certification, stability data. A decision on whether an audit is necessary, according to the procedure on “Approval and periodic Evaluation of Vendor for materials used in drug product manufacturing”, is “availability of US or European DMF for the product, customer base, Forms major

part of the formulation (more than 50%), susceptibility to microbial contamination, information provided in self-assessment questionnaire”.

Calibration and qualification of stability chambers

Schematic diagrams were available showing where the contract service provider responsible for qualification of stability chambers, had placed the probes. These were placed next to the probes of the company. This was last done in February 2014. This was acceptable overall.

2.5 COMPLAINTS

The market complaints from 2014 were recorded in a register for all products. Examples were reviewed. Root-cause investigation and CAPA were acceptable.

2.6 PRODUCT RECALLS

This area was considered acceptable overall.

2.7 CONTRACT PRODUCTION AND ANALYSIS

The company did not sub-contract production of their finished products or analytical tests.

2.8 SELF INSPECTION AND QUALITY AUDIT

Please see the previous inspection report for details on this area.

2.9 PERSONNEL

Temporary employees were used as helpers in the packaging process. Temporary contractual staff was hired, trained, used until the end of their contracts through service providers. There were different service providers for housekeeping and packing operations.

An operator from production working in compression, was randomly selected for an interview. He stated that he possessed a M.Sc. in Chemistry, which was confirmed in his records. His job description was signed in 2013. The job description adequately described his functions and matched what was stated during the interview.

2.10 TRAINING

Training records were maintained in LIMS for all permanent staff and on paper for contractual staff. Records were requested for the operator for near-infrared spectroscopy (NIR). He was trained on the SOP for NIR specific to the instrument in use.

Training was performed and electronically recorded. The system in place recorded the SOPs for which they were trained, mode, mark, whether the trainee was successful or not. Examples were randomly selected and verified for reliability and thoroughness.

2.11 PERSONAL HYGIENE

Adequate hand-washing and foot washing facilities were seen for employees entering production Block No. 1. Personnel gowning was appropriate in the different areas entered. The instructions to be followed were sufficiently clear when it came to personal hygiene.

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.

Recent improvements had been made through the redesign and reconstruction of some areas to provide change rooms to enter the primary packaging areas further to an observation given during the last WHO inspection performed in February 2012.

Premises were considered to be acceptable overall.

2.13 EQUIPMENT

The equipment seen in production, quality control and warehousing was found in an adequate state of function and maintenance.

2.14 MATERIALS

Materials were sourced mainly from approved suppliers. A risk assessment was available to justify the use of APIs sourced from a non-GMP compliant supplier.

Materials were managed through SAP. Verifications were made during the inspection.

2.15 DOCUMENTATION

General

Most documents were adequately designed, prepared, reviewed and distributed. Documents were approved, signed and dated by the appropriate responsible persons. Many of the site specific SOPs had been recently replaced with corporate quality system SOPs – these included changes made as corrective actions from inspections performed at other Lupin sites. Only operational SOPs from Lupin Aurangabad were still being applied.

Documentation control was seen to be generally adequate. Logbooks were controlled, released and closed by QA. They were found to be adequately completed.

Documentation was well organized in general in its logic, structure and was well kept. The fact that all of the documents requested arrived promptly upon request, is a good indicator of this.

The Lupin Aurangabad site SOPs were replaced with Corporate QA SOPs. It is only the operational SOPs that are specific to the site. Corrective actions from other sites were used to implement changes to the Corporate QA SOPs.

Master batch production documentation

Master production documents were reviewed for WHO-prequalified products and products under assessment by the WHO.

There was only one master production document per code. These were generally considered to be acceptable.

2.16 GOOD PRACTICES IN PRODUCTION

General

Block 1 (Rifampicin block) was kept in acceptable condition.

Prevention of cross-contamination and bacterial contamination during production was ensured by the flows of materials, man, personnel. Temperature and humidity were controlled.

Entrance to the Block 1 production facility was done through a single change room where personal removed street clothes and wore fully covering gear.

Gloves, head/face/neck covers/overalls were worn by all staff and visitors as well.

The absence of any visible powder build-up on the walls of the compression booths suggested acceptable function of the dust control equipment.

Processing operations

Some of the bulk transfer bins had a large number of dents. The surfaces on the inside and outside were nevertheless found to be clean.

Packaging operations

The challenge test using camera system was recorded in the BMRs for packing. Weight checkers were verified to be installed and in use at each packaging station. Pre-start checks and challenge tests were done with broken tablets, overlapping tablets, inverted tablets, foreign particles and empty pocket. Batch number was done visually by the human checker but was initially certified at the beginning of each batch.

2.17 GOOD PRACTICES IN QUALITY CONTROL

Control of starting materials and intermediate, bulk and finished products

In-process products were tested by production staff in the in-process control laboratory. Tests such as individual tablet weight were automatically entered through an electronic recording system which would plot charts.

Test requirements

Tests were performed in line with their associated specifications.

Batch record review

BMRs were reviewed for WHO-prequalified products. No issues of concern were found.

Stability studies

The register for Stability OOTs was also reviewed for 2014. The laboratory had a system effective at recording OOTs. Examples were reviewed.

Data integrity

The procedure in place, entitled “Assigning user/system policies and management of electronic data in Chromeleon network”, was reviewed. It described the different

audit trails available in Chromeleon[®], namely the daily audit trails, sample audit trails, modification history and user management history report. The daily audit trail stores the entire GLP relevant data that is related to the status of a specific time base. The daily audit trail also includes the preconditions before the sample run. Secondly, the modification history, which completely documents important changes and operations performed in specific objects and files.

Printouts were automatically date and time stamped.

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 Aurangabad, Chikalthana, Blocks No.1, 2 and adjacent areas, 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 3 years, provided that the outcome of any inspection conducted during this period is positive.