World Health Organization

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**Prequalification Team**
**WHO PUBLIC INSPECTION REPORT**
**(WHOPIR)**
**Active Pharmaceutical Ingredient Manufacturer**

| **Part 1** | **General information** |
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| **Manufacturers details** | |
| Company information | |
| Name of manufacturer | **Lupin Limited** |
| Corporate address of manufacturer | 4th Floor, Kalpataru Inspire, Off W.E. Highway,<br>Santacruz (East) Mumbai -400 055, Maharashtra, India |
| **Inspected site** | |
| Address of inspected manufacturing site if different from that given above | Lupin Ltd<br>Plot 9,123, 123/1, 124, 125<br>GIDC Ankleshwar,<br>393 002,<br>Gujarat<br>India |
| Unit / block / workshop number | 124 |
| Manufacturing license number | G/501 |
| **Inspection details** | |
| Dates of inspection | 30 August 2017 – 01 September 2017 |
| Type of inspection | Routine GMP inspection |
| **Introduction** | |
| Brief summary of the manufacturing activities | Manufacture of APIs and API intermediates |
| General information about the company and site | Lupin was founded in 1968 and the factory at Plot 124 was established in approximately 1982. The site is located at GIDC site at Ankleshwar in Gujarat, north of Mumbai. The Company has 18 manufacturing sites (11 in India, 3 in Japan, 1 in Brazil, 1 in Mexico, 1 in Russia, 1 in US). Factories adjacent to the Lupin Tarapur site were chemical plants but there was no manufacture of agrochemicals or steroids.<br>Latest revenues were reported to be $ 2.56 Bn. It is claimed that Lupin are 2nd largest Indian pharmaceutical company by sales. Plot 124 at the Ankleshwar suite was concerned with the manufacture of non-cephalosporin APIs and intermediates. Plots 09, 123, 123/1 and 125 were for the manufacture of cephalosporin APIs and |

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| | intermediates. |
| History | The company was last inspected by the WHO in February 2012. |
| **Brief report of inspection activities undertaken** | |
| **Scope and limitations** | |
| Areas inspected | The inspection covered the following sections of the WHO GMP for Active Pharmaceutical Ingredients:<br>- Plot 124<br>- Warehouse 1<br>- Liquids storage<br>- Bulk tank farm<br>- Finished product storage<br>- AHU2<br>- Ethambutol Hydrochloride (ETB) production area<br>- Hydrogen chloride production area<br>- Water system<br>- QC Laboratory<br>- PQRs<br>- Internal Audits<br>- Training<br>- Preventive Maintenance<br>- Calibration<br>- Handling of Deviations<br>- Purchasing and Supplier Control<br>- Batch Release<br>- Equipment Qualification<br>- Cleaning Validation<br>- Process Validation<br>- Change Control<br>- Rejection & Reuse of Materials |
| Restrictions | Areas of no relevance to the manufacture of Ethambutol Hydrochloride |
| Out of scope | All areas not directly related to the manufacture of Ethambutol Hydrochloride. |
| WHO product numbers covered by the inspection | Ethambutol Hydrochloride (APIMF197) |

Abbreviations

| | |
|---|---|
| AHU | air handling unit |
| ALCOA | attributable, legible, contemporaneous, original and accurate |
| API | active pharmaceutical ingredient |
| APQR | annual product quality review |
| BDL | below detection limit |
| BMR | batch manufacturing record |
| BPR | batch packaging record |
| CAPA | corrective actions and preventive actions |
| CC | change control |
| CFU | colony-forming unit |
| CoA | certificate of analysis |
| CpK | process capability index |
| DQ | design qualification |
| EM | environmental monitoring |
| FAT | factory acceptance test |
| FBD | fluid bed dryer |
| FMEA | failure modes and effects analysis |
| FPP | finished pharmaceutical product |
| FTA | fault tree analysis |
| FTIR | Fourier transform infrared spectrometer |
| GC | gas chromatograph |
| GMP | good manufacturing practice |
| HACCP | hazard analysis and critical control points |
| HPLC | high-performance liquid chromatograph |
| HVAC | heating, ventilation and air conditioning |
| IR | infrared spectrophotometer |
| IQ | installation qualification |
| KF | Karl Fisher |
| LAF | laminar air flow |
| LIMS | laboratory information management system |
| LoD | limit of detection |
| LOD | loss on drying |
| MB | microbiology |
| MBL | microbiology laboratory |
| MF | master formulae |
| MR | management review |
| NMR | nuclear magnetic resonance spectroscopy |
| NRA | national regulatory agency |
| OQ | operational qualification |
| PHA | process hazard analysis |
| PM | preventive maintenance |
| PpK | process performance index |
| PQ | performance qualification |

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|---|---|
| PQR | product quality review |
| PQS | pharmaceutical quality system |
| QA | quality assurance |
| QC | quality control |
| QCL | quality control laboratory |
| QRM | quality risk management |
| RA | risk assessment |
| RCA | root cause analysis |
| SOP | standard operating procedure |
| TAMC | total aerobic microbial count |
| TFC | total fungi count |
| TLC | thin layer chromatography |
| URS | user requirements specifications |
| UV | ultraviolet-visible spectrophotometer |

**Part 2**
***Brief summary of the findings and comments***

**1. Quality management**

In general the system for managing quality encompassed the organizational structure, procedures and processes. There were QA and QC departments that were independent of production. In general deviations from established procedures were documented and explained. Procedure was in place for notifying management of regulatory inspections, serious GMP deficiencies, product defects and related actions.

The traceability of records and documentation system were satisfactory.

The QA were responsible for the implementation of the QMS. Key clauses in WHO GMP Guidelines clause 2.22 were covered.

Self-inspections (Internal Audits) were conducted according to the procedure. This was a site-specific procedure rather than corporate. All departments were covered and the procedure was managed by QA. Auditors were trained in ICH Q7 and had undergone an auditing training skills certification course. Auditors should be competent and have the necessary qualifications and experience. Auditors were usually managers. Following an audit, CAPAs were implemented within one month. After this time a separate CAPA/Change Control would be applied for within the QMS system. However, such an extension would have to have a good justification. Reports were confidential and therefore not available for review.

Annual product quality review of drug substances and saleable intermediates was discussed. It was noted that annual product quality review planner for 2017 was available. Listed were Ethambutol Hydrochloride and D2-Amino-1-Butanol and recovered D2-Amino-1-Butanol. Minitab was used for generation of graphs of critical process parameters.

Deviation trend was done on quarterly basis. That for Oct-Dec 2016 was reviewed. Analysis of assignable causes were categorized into instrument error, others, human error, input material error, system error, process error and non-assignable.

Quality risk management procedure was discussed. The procedure classified risk into prospective and retrospective approach and FMEA tool was used for the risk assessment. The risk identification was done using fish-bone diagram. The severity, detectability and likelihood of risk were calculated wherein risk was classified into low (1-8), medium (9-64) and high risk (65-125).

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

**2. Personnel**

There were adequate numbers of personnel, of suitable qualification and experience, to conduct the tasks required to manufacture APIs to the required standards.

Training was conducted according to corporate procedure. Training programmes were tailored to each employee and were conducted on-line.

Protective clothing was a minimum of coat/overalls and helmet. Additional clothing was provided for entry into controlled areas and additional personnel protective equipment (PPE) was available as required.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

**3. Buildings and facilities**

Buildings were constructed of reinforced concrete. External finishes were adequate. Internal finishes were appropriate to the work being conducted. Installation and maintenance were satisfactory. The building, manufacturing departments and the facilities inspected were maintained to be acceptable in general.

Equipment Maintenance was conducted according to the procedure. Details in the SOP were satisfactory. The schedule for 2017 was checked and was acceptable.

Calibration of gauges was conducted according to the procedure. The SOP included an example of a calibration label. The schedule for 2017 was check and was satisfactory

Information security policy provided direction user access policy for internal users, naming convention of users, password management, and change every 42 days. Validation of computerized software system was discussed. The procedure was designed based on the ISPE GAMP 5 principle wherein different categories were defined for different systems and software'. Requalification of computerized software system was part of this procedure which defined the periodic review check points during requalification with frequency of once every 3 or 5 years.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

**4. Process equipment**

The design and installation of the process equipment was satisfactory for the process steps being conducted. Overall, standards of housekeeping and maintenance were adequate. Where possible, production operations were undertaken within closed systems and the degree of product exposure was minimal. The ETB manufacture was conducted on dedicated equipment.

There was an entry procedure to the "clean" area with addition clothing requirements. However, it appeared that the clothing requirements were excessive and it is suggested that the company reviews the requirements.

Hydrogen chloride gas was generated on-site by the treatment of concentrated hydrochloric acid with concentrated sulfuric acid. Two units were available for this step, HGU01 and HGU02.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

**5. Documentation and records**

Document control was the responsibility of QA. Most documents were managed electronically. Manual documents that were checked were seen to be completed correctly.

The batch production record of Ethambutol HCl (Blend stage) was reviewed and noted that BPR was printed from SAP and label issuance history was on SAP. The environmental monitoring was done by the plant using the data acquisition system by printing the data for every 24hr. If there is any deviation, it will be reviewed by QA as part of batch release. Batch numbering and materials traceability were checked for certain batches and were found satisfactory.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

**6. Materials management**

Supplier qualification was conducted according to "Vendor Qualification" procedure. Details included the requirements to audit suppliers of KSMs.

Warehouse 1 was used for storage of raw materials and finished goods. Inspection of warehouse-1 covered loading/unloading of raw materials and finished goods respectively. For raw materials, there was a dedusting procedure. The approved supplier list was available in SAP. Finished goods were stored in several locations on the ground floor (store 1, 2 & 3) and first floor. At the time of the inspection, on the ground floor, the temperature/RH were $32.8^0$C and 79.3%. There was only a fresh air supply and no extraction. Hot spots were identified for all stores of ground floor (Store 1, 2 and 3) and first floor. There was a sampling booth but there was no separate personnel airlock.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

## 7. Production and in-process controls

Since cephalosporins were handled on the sites adjacent to the ETB site, no 124, contamination control was checked. Protocol for cross contamination study of penicillin G potassium & cephalosporin products in Ethambutol HCl for 2016-2017 was discussed. The layout of Plot No 124 (Ethambutol), Plot No 125 (Cefadroxil and /APDCA intermediate) and Plot No 123 (Warehouse 2 for storage of Cephalosporin and Penicillin G) was reviewed. Total 136 sampling points (107 by air sample and 27 swab samples, 2 water samples) were used for cross contamination taking three finished batches of Ethambutol, three batches of D2-Amino-Butanol and DM water. The testing was done on yearly basis using a validated HPLC method which was able to detect four Cephalosporin products. The last study was started in October 2016 and completed in March 2017. The analytical method was validated with LOD of 0.01ppm and LOQ of 0.03ppm and this was set the acceptance criteria.

Tail end etc material was blended according to “Handling Tail End Material” procedure. Not more than 150 Kg of tail end material can be blended in a finish product batch.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

## 8. Packaging and identification labelling of APIs and intermediates

Final packing of ETB was conducted in the controlled area of the ETB building in Plot 124, after the sifting step. Standard packing was double polyethylene bags which were put into an HDPE container which was sealed with a lid, held in place with a clamping band. After packing, the material was moved to the quarantine area, pending results from QC. It was observed that the packed material was stored on aluminum pallets.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

## 9. Storage and distribution

The SOP for release of finished product (API & saleable intermediate) procedure was discussed which provided procedure for release of API and saleable intermediates. A list of responsible persons for usage decision in SAP system was available. The release was conducted by QA. On approval, the status of the material was changed in SAP.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

## 10. Laboratory controls

The first floor housed microbiology lab, chemical and instrumentation whereas second floor housed stability, hot air equipment, raw material and finished goods sampling management through SAP. IPC samples were manually managed.

The laboratory had three HPLC and three GCs with Chromeleon server based software. The date/time were locked, and there was a logbook electronically maintained for those equipment which were not connected to Chromeleon. The recycle bin was removed from PC. Column management was handled through SAP. There was no LIMS as activities covered through SAP. There were two IT administrators and two IT tech support personnel.

Backup and restore procedure described daily, monthly and yearly backup which were stored in magnetic tapes. Monthly tapes were backup for 3 years, yearly backup for 8 years. A backup log was maintained for daily backup (incremental backup), one full back-up on monthly basis and weekly basis for Chromeleon. Chromeleon system data restore verification was done one per year

Information security policy provided direction user access policy for internal users, naming convention of users, password management, and changed every 42 days.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

**11. Validation**

Process validation was conducted according to the procedure. Cleaning validation was conducted, when required, according to the corporate SOP "Cleaning Validation for Intermediates and Drug Substances". It was stated that since the ETB plant was dedicated, validation of cleaning was not required.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

**12. Change control**

Change controls were managed according to corporate procedure. Change controls were managed by QA and controlled within the QAMS system.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

**13. Rejection and re-use of materials**

Reprocessing and reworking was conducted according to the procedure. It was stated that no reworking was performed.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

**14. Complaints and recalls**

Complaints were handled according to corporate procedure, "Handling of Market Complaints for Drug Substances (APIs) and Intermediates". Details were managed in the QAMS system.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

**15. Contract manufacturers (including laboratories)**
Not inspected due to time constraint.

**PART 3**
***Conclusion***
Based on the areas inspected, the people met and the documents reviewed, and considering the findings of the inspection, including the deficiencies listed in the Inspection Report, as well as corrective actions taken and planned: Ethambutol Hydrochloride (APIMF197) manufactured at Lupin Limited, located at Plot 9,123, 123/1, 124, 125, GIDC Ankleshwar, 393 002, Gujarat India was considered to be manufactured in compliance with WHO GMP for Active Pharmaceutical Ingredients.

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.

**PART 4**
***List of GMP guidelines referenced in the inspection report***
1. WHO good manufacturing practices for active pharmaceutical ingredients. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957), Annex 2.
   http://www.who.int/medicines/publications/44threport/en/

2. WHO good manufacturing practices for pharmaceutical products: main principles. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-eighth Report Geneva, World Health Organization, 2014 (WHO Technical Report Series, No. 986), Annex 2.
   http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_986/en/

3. WHO Good Manufacturing Practices: water for pharmaceutical use. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fourth-sixth Report. Geneva, World Health Organization, 2012 (WHO Technical Report Series, No. 970), Annex 2
   http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_970/en/

4. WHO guidelines for sampling of pharmaceutical products and related materials. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-ninth Report. Geneva, World Health Organization, 2005 (WHO Technical Report Series, No. 929), Annex 4
http://whqlibdoc.who.int/trs/WHO_TRS_929_eng.pdf?ua=1

5. WHO guidelines on good manufacturing practices for heating, ventilation and air-conditioning systems for non-sterile pharmaceutical dosage forms. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 5
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

6. Supplementary guidelines on good manufacturing practices: validation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fortieth Report. Geneva, World Health Organization, 2006 (WHO Technical Report Series, No. 937), Annex 4
http://whqlibdoc.who.int/trs/WHO_TRS_937_eng.pdf?ua=1

7. WHO Good Practices for Pharmaceutical Quality Control Laboratories. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957, Annex 1
http://www.who.int/medicines/publications/44threport/en/

8. WHO Good Practices for Pharmaceutical Products Containing Hazardous Substances. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957), Annex 2
http://www.who.int/medicines/publications/44threport/en/

9. WHO good manufacturing practices for sterile pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 6
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

10. WHO guidelines on transfer of technology in pharmaceutical manufacturing WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 7
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

11. Model guidance for the storage and transport of time-and temperature-sensitive pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 9
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

12. General guidelines for the establishment maintenance and distribution of chemical reference substances. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-first Report Geneva, World Health Organization 2007 (WHO Technical Report Series, No.943) Annex 3 http://whqlibdoc.who.int/trs/WHO_TRS_943_eng.pdf?ua=1

13. WHO good practices for pharmaceutical microbiology laboratories. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 2 http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

14. WHO guidelines on quality risk management. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-seventh Report Geneva, World Health Organization, 2013 (WHO Technical Report Series, No. 981), Annex 2 http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_981/en/

15. WHO guidelines on variation to a prequalified product. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-seventh Report Geneva, World Health Organization, 2013 (WHO Technical Report Series, No. 981), Annex 3 http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_981/en/

16. WHO guidelines for drafting a site master file. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 14 http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

17. WHO Guidelines on good manufacturing practices: validation, Appendix 7: non-sterile process validation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 3 http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

18. WHO General guidance on hold-time studies WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 4 http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

19. WHO Technical supplements to Model Guidance for storage and transport of time – and temperature – sensitive pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 5 http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

20. WHO Recommendations for quality requirements when plant – derived artemisin is used as a starting material in the prosecution of antimalarial active pharmaceutical ingredients. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 6 http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

21. WHO good manufacturing practices for biological products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fiftieth Report Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 3 http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex03.pdf

22. Guidance on good data and record management practices. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fiftieth Report Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 5 http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex05.pdf

23. WHO general guidance on variations to multisource pharmaceutical products. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fiftieth Report* Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 10 http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex10.pdf

24. WHO good manufacturing practices for biological products. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fiftieth Report* Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 3 http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex03.pdf