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**Prequalification Team Inspection services**
**WHO PUBLIC INSPECTION REPORT**
**(WHOPIR)**
**Finished Product Manufacturer**

| **Part 1** | **General information** |
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| **Manufacturers details** | |
| Company information | |
| Name of manufacturer | **Lupin Limited, Jammu** |
| Corporate address of manufacturer | Lupin Limited<br>Kalpataru Inspire 3rd Floor, Off Western Express Highway, Santacruz (East),<br>Mumbai 400055, India |
| **Inspected site** | |
| Address of inspected manufacturing site if different from that given above | EPIP, SIDCO Industrial Complex,<br>Bari Brahmana, Jammu (J&K) - 181133<br>India |
| Unit / block / workshop number | |
| Manufacturing license number, (delete if not applicable) | JK/01/07-08/123 (Form-25)<br>JK/01/07-08/124 (Form-28)<br>Valid until 25/04/2022 |
| CRM Inspection | *INSP-2014-0389* |
| **Inspection details** | |
| Dates of inspection | 12-16 March 2018 |
| Type of inspection | Routine GMP inspection |
| **Introduction** | |
| Brief summary of the manufacturing activities | Lupin Jammu was founded in March 2016. The site produces tablets, capsules and meter-dosed inhaler (MDI), primarily for the domestic markets. From the discussion, it was noted that products have been moved from Jammu site to a new site at Sikkim. One area has been completely dedicated for Rifa-4FDC formulations whereas there is no production activity running |
| General information about the company and | Lupin Limited was founded in the year 1968. It has manufacturing activities located at various sites across India and globally i.e. Dabhasa & Ankleshwar in Gujarat, Aurangabad, Tarapur and Nagpur in Maharashtra, Mandideep and Indore in Madhya |

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| site | Pradesh, Verna in Goa, Jammu in J&K, Visakhapatnam in Andhra Pradesh, Rangpo in Sikkim, Kyowa in Japan, Grin in Mexico, Gavis Pharma in New Jersey USA, Pharma Dynamics in South Africa, Multicare pharmaceuticals in Philippines, Medquimia in Brazil, Generic health in Australia Symbiomix Therapeutics LLC in USA. |
| History | This was the third WHO-PQ inspection of Lupin Limited, Jammu. The site was inspected by WHO-PQT in November 2011 and February 2014 |
| **Brief report of inspection activities undertaken** | |
| **Scope and limitations** | |
| Areas inspected | **Document reviewed including but not limited**<br>• Organization Chart<br>• Job descriptions for key personnel<br>• Product Quality Review<br>• Quality Risk Management<br>• Management Review<br>• Responsibilities of the quality units and production<br>• Complaints and Recalls<br>• Deviation control and change control<br>• OOS and investigation<br>• CAPA procedure<br>• Batch release<br>• Validation and qualification<br>• Data integrity<br>• Product release<br>• Sampling and testing of materials<br>• Batch processing records<br>• Materials management system<br>• Purified water system<br>**Site visited:**<br>• OSD Production operations with particular focus on block B, Granulation suite 1, Compression and Coating area<br>• Stability study QC laboratory and control system<br>• Starting material and finished Goods warehouse |
| Restrictions | Only products submitted for purposes of WHO Prequalification were covered |
| Out of scope | Products not submitted to WHO for Prequalification |
| WHO product numbers covered by the inspection | TB068: Isoniazid/Rifampicin Tablet, Film-coated 75mg/150mg<br>TB070: Ethambutol hydrochloride/Isoniazid/Pyrazinamide/Rifampicin Tablet, Film-coated 275mg/75mg/400mg/150mg<br>TB177: Ethambutol hydrochloride Tablet, Film-coated 400mg<br>TB350: Linezolid Tablet, Film-coated 600mg (under assessment) |

| Part 2 | Brief summary of the findings and comments (where applicable) |
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***Brief summary of the findings and comments***

**1. Pharmaceutical quality system**

A system for quality assurance was established, with procedures covering key quality elements in place. The procedures were reviewed and discussed during the inspection. Operations were specified in written documentation and GMP requirements were essentially being met. Managerial responsibilities were appropriately specified in written job-descriptions. Product and processes were monitored and the results taken into account during batch release; regular monitoring and reviews of the quality of pharmaceutical products were being conducted according to documented schedules and procedures.

Paperless systems were in place for handling of deviations, change controls, Complaint & CAPA (Caliber-QAMS) and for training (L2MS).

Annual product quality review (APQR) was performed according to a documented procedure. The procedure on annual product quality review of drug products was reviewed. Minimum 10 batches were required for statistical analysis. If less than 10 batches produced in certain year, batches from previous year were taken for review. If Cpk was found below 1, the procedure stated that assessment of the process was required to identify and eliminate cause for variability. Minitab software was used for statistical analysis of various parameters reviewed as part of the APQR.

The procedure for the handling of deviations was discussed. Deviations were handled using Caliber QAMS wherein individuals were given access to login the system using their credentials. Based on the QA assessment, deviation was classified as major or minor, with risk assessment performed for major deviations.

The SOP on change control (CC) programme was reviewed. The CCs were managed through Caliber QAMS. In case of failure of QAMS system, hard copies templates were available and used to track the process. The SOP required that QA classified changes as major and minor; QA was also responsible to approve or reject the change. The SOP applied to permanent and temporary changes according to the needs of initiator.

The Corporate SOP on management review of quality metrics. The procedure stipulated that management review be performed at a site level as well as at the corporate level. The MR was performed once every month.

Quality risk management corporate procedure was also discussed. The risk identification was assessed through the fish bone diagram and risk evaluation through FMEA and RPN based on severity, detectability and likelihood. The SOP stated that QRM applied for evaluation of other system based on the impact assessment (deviation, market complaint, change control, stability failure…).

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

## 2. Good manufacturing practices for pharmaceutical products

Good manufacturing practices were implemented and followed. Required staff and system resources were provided. Manufacturing processes were clearly defined and documented. Qualification and validation were performed. Operators were trained to carry out procedures correctly, and comprehensive records were made during manufacture.

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

## 3. Sanitation and hygiene

In general, premises and equipment were maintained at a satisfactory level of cleanliness. The company had a standard operating procedure as the basis for its approach to personal hygiene and sanitation in its production facility, with appropriate hand washing facilities.

Areas were cleaned frequently in accordance with approved written procedures. Environmental Monitoring of viable particles was regularly undertaken.

## 4. Qualification and validation

The company approach to validation was documented and explained in the Validation Mater Plan (VMP). The key elements of a qualification and validation programme were defined. Site validation master plan was discussed. The VMP was divided into several sections such as facility qualification, process validation, cleaning validation, analytical method validation, analyst qualification.

Qualification / validation planning and organization were briefly discussed. The procedure defined planning and organizing of validation activities, for facility/equipment and systems to ensure the product quality, safety and efficacy throughout its life cycle.

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

## 5. Complaints

The SOP on the handling market complaint for drug products was reviewed. The complaints were managed by Caliber-QAMS system. The notification was received either verbal or in writing which had to be uploaded in the e-system within one working day. The complaints were categorized as critical (investigation had to be concluded within 15 working days) major and minor (investigation had to be concluded within 30 working days). Annual trend analysis was required per procedure.

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

## 6. Product recalls

Recall of drug products were handled by the SOP which provided for classification of recalls in in class I and II (public announcements such as TV/newspaper were used to inform immediate recall was necessary); and class III. 24 hours was the time limit to intimate that a recall was necessary. The Head of QA was responsible to initiate a recall; the Head of regulatory authority (RA) was responsible to inform to the drug regulatory authority. The SOP stated that the corporate QA had to be informed. The SOP applied both to recall on voluntary basis and requested by all the regulatory authorities. A mock recall was required annually for one batch in case no recall was performed during the year.

## 7. Contract production, analysis and other activities

Lupin Jammu site management confirmed that no contract manufacturing is performed for any of the WHO prequalified and under assessment products. Testing had been contracted to commercial laboratories.

The corporate SOP for the selection and approval of laboratory for testing was reviewed. The SOP required the QC laboratory to be approved by the local FDA, to be a NABL (National Control Laboratory) or to be ISO or equivalent certified and follow GMP requirements in case of sampling testing.

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

## 8. Self-inspection, quality audits and suppliers' audits and approval

The SOP for self-inspection was reviewed. The SOP required QA preparing the annual plan at the beginning of the year. The beginning of the year was not specified. The internal auditors were selected on the basis of cultural background, experience (at least 5 years) and specific expertise. The list of lead auditors and auditors was available.

The SOP required an inspection of each department at least twice a year by auditors using a checklist. At the end of the inspection a report had to be issued and circulated to auditee within 30 days classifying observations as critical (direct impact on the quality) major (indirect impact) and minor (no impact). In case the reports required more than 30 days, an extension request was needed. The auditee had to submit the corrective action and the due date that QA was in charge to verify. This process was paper based.

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

## 9. Personnel

The manufacturer had an adequate number of personnel with the necessary qualifications and practical experience. Responsibilities of staff, and their specific duties were recorded in written job descriptions. Personnel interviewed during the inspection were aware of the principles of GMP in general. An organization charts and job descriptions were available. The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

## 10. Training

The SOP on training of personnel was discussed. Training process was managed through paperless system L2MS (SABA). The SOP required QA preparing the annual training programme at the beginning of the year. Three kinds of training were provided: web-based training, ILT (instructor lead training) in class-room and blended training (both via web and in classroom). In case of blended and web-based training, in LMS was available a questionnaire for training evaluation. The learners shall be considered qualified if they obtain a minimum of 100% marks in the SOP training assessment and a minimum of 80% marks in GMP/Functional training assessment, a maximum of three attempts was possible to repeat the evaluation test.

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

## 11. Personal hygiene

Changing and washing before entry to production areas followed a written procedure. Direct contact was avoided between the operator's hands and starting materials, primary packaging materials and intermediate or bulk product. No concerns of note were identified during the inspection. The approach to sanitation and hygiene was in general acceptable.

Personnel flow and protective garments were found inadequate in some activities. Personnel flow for sampling/dispensing activities was not logical as operators used the common corridor for going into the dispensing area and for going out after dispensing was completed. IPQA personnel were not required to wear additional protective gowning for entering into the core processing areas.

## 12. Premises

Generally, the premises were located, designed, constructed and maintained to suit the operations to be carried out. The layout and design of premises minimize the risk of errors and permit effective cleaning and maintenance in order to avoid cross-contamination. OSD and inhalation products were manufactured in the same building and physically segregated.

Manufacturing areas were generally of a good standard and suitable for the activities conducted therein. Exposed surfaces were smooth, impervious and unbroken to minimize the shedding or accumulation of particles or microorganisms and permitted the repeated application of cleaning.

Storage areas were of sufficient capacity. Receiving and dispatch bays were separated and protected materials and products from the weather. Segregation was provided for the storage of rejected, recalled, or returned materials or products.

QC laboratories were separated from production areas. Adequate space was provided for samples, reference standards, solvents, reagents and records.

Three areas for sampling and dispensing of raw materials were available for APIs, for excipients and dedicated to rifampin. Sampling and dispensing were done under RLAF having HEPA filtered air supply. Sampling of

primary packaging materials was done under LAF. Desired conditions were maintained for material storage. Monitoring of temperature and relative humidity in warehouse was done through Data Acquisition System. Warehouse Management System was through SAP. Weighing & Dispensing system was implemented in raw materials and packaging materials warehouse to eliminate any weighing errors during dispensing.

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

**13. Equipment**

Equipment installed for tablet manufacturing was generally of a good standard. The facility and equipment appeared to be running well with no significant stoppages. The detailed procedures for the operation of key equipment were generally well documented. Laboratory equipment and instruments were suited to the testing procedures undertaken.

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

**14. Materials**

Starting materials and packaging materials were purchased from approved suppliers. Printed packaging materials were stored in secure areas. Finished products were held in quarantine in production area until their final release, after which they were transferred to and stored under appropriate and monitored conditions in a separate store, in a different building across the road. Rejected materials and products were marked as such and stored in designated secure areas.

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

**15. Documentation**

In general, documentation was designed, prepared, reviewed and distributed according to a documented procedure. Documents were regularly reviewed and kept up to date.

Approved, signed and dated testing procedures and specifications were available for starting and packaging materials and for finished products of Linezolid tablets.

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

## 16. Good practices in production

The block B, multipurpose manufacturing area, was inspected. It was used for manufacturing Linezolid tablets (namely granulation II 200 liter, compression II 45 stations). The block B was designed with two main corridors which maintained overpressure in respect to the processing rooms. The manufacturing areas included 2 granulation areas, 2 blending areas, 2 compression areas, 2 coating rooms, 1 inspection room; 8 primary packaging cubicles (3 strip lines, 4 blister lines, 1 manual line) and area for secondary packaging. The core processing area was ISO 8 classified with T/RH continuously monitored by DAS system.

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

## 17. Good practices in quality control

The QC function was independent of other departments. Adequate resources were available to ensure that the QC arrangements are effectively and reliably carried out.

The laboratory was divided into two labs (lab 1 and lab 2). Laboratory 1 has wet chemistry, instrumentation and microbiology sections whereas laboratory 2 has wet chemistry, GC, stability chambers and working standard. The incoming samples (in-process, semi-finished, finished, raw materials and packing materials) were received by lab 1. The test data sheet (TDS) was generated using SAP system which is a network-based system. The laboratory manager was supported by different section heads (raw material, finished goods, stability, Good Laboratory Practices section and microbiology section).

The laboratory was equipped with instruments like HPLC, UV – Vis, FTIR, GC etc. The microbiology lab was classified as Class 1,00,000 (background) whereas microbial limit test was performed under Class 100 (LAF). Data security and integrity through networking and back up procedures were maintained. Calibration & AMC program for all analytical instruments. Separate PM Testing Lab.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall 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, *Lupin Limited, EPIP, SIDCO Industrial Complex, Bari Brahmana, Jammu (J&K) – 181133, India* was considered to be operating at an acceptable level of compliance with WHO good manufacturing Practices for pharmaceutical products.

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***

1. 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/

2. 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/

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 artemisinin 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