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

#### Part 1
**General information**

<table>
<thead>
<tr>
<th>Manufacturers details</th>
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<tbody>
<tr>
<td>Company information</td>
<td></td>
</tr>
<tr>
<td>Name of manufacturer</td>
<td>Lupin Limited, Tarapur</td>
</tr>
<tr>
<td>Corporate address of manufacturer</td>
<td>4th Floor, Kalpataru Inspire, Off W.E Highway, Santacruz (East) Mumbai -400 055, India</td>
</tr>
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<table>
<thead>
<tr>
<th>Inspected site</th>
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<tbody>
<tr>
<td>Address of inspected manufacturing site if different from that given above</td>
<td>T-142, MIDC, Tarapur via Boisar, Taluka &amp; Dist. Palghar, Maharashtra, - 401506, India</td>
</tr>
<tr>
<td>Unit / block / workshop number</td>
<td>T1, T2 and T3</td>
</tr>
<tr>
<td>Manufacturing license number</td>
<td>KD/96 and KD/466</td>
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<table>
<thead>
<tr>
<th>Inspection details</th>
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<tbody>
<tr>
<td>Dates of inspection</td>
<td>21 - 24 August 2017</td>
</tr>
<tr>
<td>Type of inspection</td>
<td>Routine GMP inspection</td>
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#### Introduction
Brief summary of the manufacturing activities
Manufacture of APIs using classical organic chemistry and fermentation steps in the processes.

General information about the company and site
The site is located at MIDC site at Tarapur, north of Mumbai, in Maharashtra. 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. Latest revenues were reported to be $ 2.56 Bn.

It is claimed that Lupin are 2nd largest Indian pharmaceutical company by sales and largest producer of Rifampicin. As of 01/08/17, there were 1194 personnel on the Tarapur site.
### History

Previous WHO Inspection: June 2014

USAD August 2015, COFEPRIS July 2014, CDSCO July 2017, PMDA June 2015

**Changes made to APIMF since the last inspection:**

- Rifampicin (key starting material additional vendor GTBL)
- Pyrazinamide (400kg additional batch size introduced to another production block, earlier 800kg batch size approved)
- Ethambutol (no commercial batch since prequalification for WHO markets, main manufacturing site is Lupin Ankleshwar)
- TDF (under assessment), batches produced have not been commercialized to Lupin and to outside parties (the batches had been supplied to Lupin formulation sites for exhibit batches)

**Changes in key personnel since the last WHO Inspection**

Dr Rajiv Desai (EVP CQA) and Dr JP Khurana (VP CQA) joined since the last WHO inspection.

### 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:

- Manufacturing, QC and Warehouse areas T1, T2 and T3
- Microbiological Laboratory
- Process Development Laboratory
- Computer systems used in the QMS, Production and QC departments
- Purified Water system
- AHU
- Solvent Tank Farm
- PQRs
- Internal Audits
- Preventive Maintenance
- Calibration
- Handling of Deviations
- Purchasing and Supplier Control
- Batch Release
- Equipment Qualification
- Cleaning Validation
- Change Control
- Rejection & Reuse of Materials

**Restrictions**

APIs made with reference to WHO approved dossiers etc.

**Out of scope**

APIs and associated infrastructure, not directly related to the APIs being inspected.
WHO product numbers covered by the inspection

- APIMF040: Pyrazinamide
- APIMF028: Rifampicin
- APIMF317: Tenofovir Disoproxil Fumarate (under assessment)
- APIMF093: Ethambutol HCl

Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AHU</td>
<td>air handling unit</td>
</tr>
<tr>
<td>ALCOA</td>
<td>attributable, legible, contemporaneous, original and accurate</td>
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<td>API</td>
<td>active pharmaceutical ingredient</td>
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<tr>
<td>APQR</td>
<td>annual product quality review</td>
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<td>BDL</td>
<td>below detection limit</td>
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<td>BMR</td>
<td>batch manufacturing record</td>
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<tr>
<td>BPR</td>
<td>batch packaging record</td>
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<tr>
<td>CAPA</td>
<td>corrective actions and preventive actions</td>
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<tr>
<td>CC</td>
<td>change control</td>
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<tr>
<td>CFU</td>
<td>colony-forming unit</td>
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<tr>
<td>CoA</td>
<td>certificate of analysis</td>
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<td>CpK</td>
<td>process capability index</td>
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<td>DQ</td>
<td>design qualification</td>
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<td>EM</td>
<td>environmental monitoring</td>
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<td>FAT</td>
<td>factory acceptance test</td>
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<td>FBD</td>
<td>fluid bed dryer</td>
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<td>FMEA</td>
<td>failure modes and effects analysis</td>
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<td>FPP</td>
<td>finished pharmaceutical product</td>
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<td>FTA</td>
<td>fault tree analysis</td>
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<td>FTIR</td>
<td>Fourier transform infrared spectrometer</td>
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<tr>
<td>GC</td>
<td>gas chromatograph</td>
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<td>GMP</td>
<td>good manufacturing practice</td>
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<tr>
<td>HACCP</td>
<td>hazard analysis and critical control points</td>
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<td>HPLC</td>
<td>high-performance liquid chromatograph</td>
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<td>HVAC</td>
<td>heating, ventilation and air conditioning</td>
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<td>IR</td>
<td>infrared spectrophotometer</td>
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<td>IQ</td>
<td>installation qualification</td>
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<td>KF</td>
<td>Karl Fisher</td>
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<tr>
<td>LAF</td>
<td>laminar air flow</td>
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<td>LIMS</td>
<td>laboratory information management system</td>
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<tr>
<td>LoD</td>
<td>limit of detection</td>
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<tr>
<td>LOD</td>
<td>loss on drying</td>
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<td>MB</td>
<td>microbiology</td>
</tr>
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<td>MBL</td>
<td>microbiology laboratory</td>
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<tr>
<td>MF</td>
<td>master formulae</td>
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<td>MR</td>
<td>management review</td>
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<td>NMR</td>
<td>nuclear magnetic resonance spectroscopy</td>
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<td>NRA</td>
<td>national regulatory agency</td>
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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 issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

2. Personnel
Personnel met during the inspection were suitably qualified through qualifications, experience and training in general. There were adequate numbers of personnel. Protective clothing was worn, with additional PPE 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 of painted masonry were adequate. Internal finishes were appropriate to the work being undertaken. Warehousing was suitably equipped with proprietary racking and internal finishes acceptable. For powder processing areas, finishes were of the easy-clean design and there were entry procedures including gowning requirements. Buildings of direct relevance to the APIs being inspected are given in the table:

<table>
<thead>
<tr>
<th>Areas</th>
<th>Rifampicin</th>
<th>Tenofovir DF</th>
<th>Ethambutol HCl</th>
<th>Pyrazinamide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Production</td>
<td>T1 DSP-I</td>
<td>T2 MPP5</td>
<td>T1 MPP4 (single stage process)</td>
<td>T1 DSP-II (stream-II) (dedicated)</td>
</tr>
<tr>
<td>Warehouse</td>
<td>Located in T1</td>
<td>Located in T2</td>
<td>Located in T1</td>
<td>Located in T1</td>
</tr>
<tr>
<td>Quality control</td>
<td>Located in T1 RM analysis (including bulk solvent and microbiology)</td>
<td>QC based in T2 used for intermediate testing and in-process tests. QC based in T3 used for finished product testing</td>
<td>QC based in T1</td>
<td>QC based in T1</td>
</tr>
</tbody>
</table>

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

Production equipment was of appropriate design and size for its intended use, cleaning and maintenance. Materials of product contact were glass or 316 stainless steel. Where possible, manufacturing operations were conducted in closed systems. Reactor systems were equipped with the required utilities. Logbooks were observed for noting equipment usage. Gauges etc observed were seen to be calibrated and in date.

Equipment was required to be cleaned according to documented procedures. Equipment usage logbooks were available. Records were maintained and equipment status was indicated by sign on each of equipment.

Calibration and preventive maintenance program was in place and was found satisfactory.

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
Documents related to the manufacture of API were prepared, reviewed, approved and distributed according to written procedures. Document control was the responsibility of QA. Specifications were established for raw materials, intermediates and APIs. The issuance, revision, superseding and withdrawal of documents were controlled with maintenance of revision histories. The Company had a policy to archive all logbooks and other documents.

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
Incoming material receipt procedure was described in an SOP on raw material, packaging material receiving and handling procedure. The supplier approval status was checked with the current version of a qualified supplier list. Sampling of raw materials was done by QC in a sampling room in the warehouse. Sampling instructions and procedure were available. For products produced on site procedure warehousing and distribution procedure of finished product applies.

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
The MPP-5 plant was inspected. The inspector followed the manufacturing process of Tenofovir as defined in the submitted manufacturing flow diagram. The first floor of MPP-5 was used for the manufacturing of intermediates. Starting materials were dispensed and stored in raw material dispensed material room of MPP-5. Before issuing these materials for charging, these dispensed materials were verified by the production operators. For TDF, solid materials were charged through manhole whereas solvents were charged through dedicated lines.

For Rifamycin, the initial stages, large scale fermentation and the finishing area were inspected. The fermentation was started in the Microbiology Laboratory in Building T1. Operation of the laboratory was by the Process Development Department. Individual BMRs were not issued but production details were recorded in logbooks, issued by QA and periodically reviewed by QA. The controlling SOP for the preparation of the working Cell Bank from the Master Cell Bank was reviewed. The master strain was kept in a locked room in a chamber at 2-8°C. An out-of-range alarm was installed. Working Cell Bank/Frozen Mycelia (FM) was kept at -70 ±10°C for up to 90 days. Product isolation, powder processing and packing of Rifamycin was conducted in dedicated equipment in block CSP-2B. The final milling, sifting, blending and packing steps were inspected. There was an entry procedure with an SOP and photographs on display. The requirements included gowning.

The equipment usage logbook for centrifuge was reviewed. The equipment cleaning record (ECR) is issued for the product changeover and cleaning was performed in accordance to ECR instructions. In addition, periodic cleaning was done every 30 days. For cleaning of reactors, rinse samples sent for testing whereas swab sample was sent for centrifuge and dryers. The validity of cleaning was 48 hours. The procedure on cleaning of equipment was briefly reviewed and noted that no sample was sent to QC for testing for periodic cleaning whereas sample was sent to QC for testing after product to product cleaning. The gauges were calibrated once every 6 months whereas temperature sensors were calibrated once every year.
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
The packing batch record was reviewed. Details were satisfactory. It was noted that the SAP system printed a bar code on the packing batch records. Material was packed in polyethylene bags and heat sealed in an aluminum laminate bag. Oxygen busters were supplied by Hsiao Sung in heat sealed polyethylene bags, 15 sachets in a bag. A procedure was in place stating that unused sachets were discarded after a batch had been packed. Approved packing materials were stored in an adjacent side room. Standards were satisfactory.

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 batch release system for API and intermediates was discussed. The procedure described procedure for releasing of batches of commercial / exhibit APIs or intermediate which was done through SAP. There was no clarity as to whether “exhibit” batches could be commercialized. The QC department was responsible for releasing of non-saleable intermediates whereas QA is authorized to release.

An example of Rifamycin BP was in the finished goods quarantine area. It was observed that uniquely numbered seals were installed in the locking bands on the lids of the HDPE containers.

For final product release, QA would sample products in the final powder processing area and send the samples to QC for analysis.

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 QC Laboratories in T1 and T2were inspected. Standards of housekeeping were acceptable and the laboratories were being run in an orderly and tidy manner. The range of equipment was adequate for the tasks being conducted. Labels were observed to be correctly filled in and, where relevant, were in date.

Samples of finished APIs under analysis were stored in dedicated, labelled drawers. In-process samples were submitted by Production and details entered in a QA-approved logbook. Test sheets were issued in OMNIDOC. Results were returned to Production on the white copy of the sample submission form. The yellow copy was kept with the analytical results sheet.

Four stability cabinets were available.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.
11. Validation
The SOP for cleaning validation for drug substances was discussed. The procedure defined procedure for cleaning validation of drug substances and cleaning verification of intermediates so that the cleaning process is capable of consistently meeting the predefined quality attributes. The procedure included the design/development of cleaning process, cleaning process validation and maintenance of validated status.

Corporate procedure was concerned with Process Validation. This SOP was not reviewed. However, details of process validation were included in the PQRs and are discussed in this report in the section on PQR, above.

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 the procedure. It was noted that this SOP did not cover changes to computer software. This topic was covered under Change Control for Computer Software Systems. This SOP was not reviewed. QA were responsible for managing Change Controls. All documents were managed electronically. The effectiveness of the change was reviewed and documented electronically.

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
Two SOPs were relevant to the recovery of solvents, PE (Process Engineering) or PD (Process Development) departments would prepare a recovery procedure. For every batch of recovered solvent, PD would undertake a trial study. Recovered solvents would only be used in the same stage of the same process in which they were used originally used. No reprocessing was permitted. Documents were managed in SAP.

The reprocess and rework of drug substances / intermediates procedure was discussed. The procedure defined terms used in the procedure including batches which might be revalidated if reprocessing and reworking was done. It was noted that reprocessing was done on WHO products (Rifampicin and Pyrazinamide). It was confirmed that reworking was not performed on any of the WHO APIs.

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
The SOP on handling of market complaints for drug substances and intermediates was discussed. The complaints were handed through QAMS and were classified into critical, major and minor. The procedure cross refer to recall and QRM procedure. The timeline for the closure of complaint was defined. The trending of complaints was done on yearly basis.
The SOP for recall of API / saleable intermediates was discussed. The procedure provided a flow diagram of the recall procedure and site QA was responsible for overall recall disposition and follow-up. The procedure also described effectiveness of the recall procedure on an annual basis for domestic and export market.

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: Pyrazinamide (APIMF040), Rifampicin (APIMF028), Tenofovir Disoproxil Fumarate (APIMF317/under assessment) and Ethambutol HCl (APIMF093) manufactured at Lupin Limited, Tarapur, located at T-142, MIDC, Tarapur via Boisar, Taluka & Dist. Palghar, Maharashtra, - 401506, India were 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

http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_970/en/

http://whqlibdoc.who.int/trs/WHO_TRS_929_eng.pdf?ua=1

http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

http://whqlibdoc.who.int/trs/WHO_TRS_937_eng.pdf?ua=1


http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1


http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex03.pdf

http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex05.pdf


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