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

Part 1	**General information**
Manufacturers details	
Company information	
Name of manufacturer	**Lupin Limited, Tarapur**
Corporate address of manufacturer	4th Floor, Kalpataru Inspire, Off W.E Highway, Santacruz (East) Mumbai -400 055, India
Inspected site	
Address of inspected manufacturing site if different from that given above	T-142, MIDC, Tarapur via Boisar, Taluka & Dist. Palghar, Maharashtra, - 401506, India
Unit / block / workshop number	T1, T2 and T3
Manufacturing license number	KD/96 and KD/466
Inspection details	
Dates of inspection	21 - 24 August 2017
Type of inspection	Routine GMP inspection
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 Jun 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

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
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 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:

Areas	Rifampicin	Tenofovir DF	Ethambutol HCl	Pyrazinamide
Production	T1 DSP-I CSP-I CSP-II B	T2 MPP5	T1 MPP4 (single stage process)	T1 DSP-II (stream-II) (dedicated)
Warehouse	Located in **T1**	Located in **T2**	Located in **T1**	Located in **T1**
Quality control	Located in T1 RM analysis (including bulk solvent and microbiology)	QC based in T2 used for intermediate testing and in-process tests. QC based in T3 used for finished product testing	QC based in T1	QC based in T1

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^{0}C. An out-of-range alarm was installed. Working Cell Bank/Frozen Mycelia (FM) was kept at -70 ±10^{0}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

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