

Prequalification Team Inspection services WHO PUBLIC INSPECTION REPORT

Desk Assessment of Active Pharmaceutical Ingredient (API) Manufacturer

Part 1	General information
Company information	
Name of Manufacturer	Lupin Ltd
Corporate address of manufacturer	Kalpataru Inspire, 3rd Floor, Off Western Express Highway, Santacruz (East), Mumbai, Maharashtra, 400055, India
Inspected site	
Name & address of manufacturing site	Lupin Limited, Plot No. 130, Road No. 11, Parawada (M), J.N. Pharma City, Visakhapatnam (Vizag), Andhra Pradesh, 531019, India (Note: site is called “Lupin Vizag” by the company and “Lupin Parwada”[Sic] in CRM)
Synthetic Unit/Block/Workshop	Multi product plant 1 (MPP1), Multi product plant 2 (MPP2 and MPP2A), Hydrogenation Block, Solvent recovery unit
Manufacturing license number	No. 02/VP/AP/2016/B/G, 22-01-2016, GMP certificate from Government of Andhra Pradesh Drugs Control Administration, valid to 21/01/2021.
Desk assessment details	
Date of review	12 June 2020
APIs covered by this desk assessment	Dolutegravir sodium Process A (APIMF384) Pyrazinamide USP (amendment (AAME-2019-0094) for APIMF040 to include an additional site for the production of the API (pyrazinamide). Linezolid USP (Form II) (APIMF408)
List of documents submitted	-List of regulatory inspections performed in the last 4 years -Documentation related to USFDA inspections -CDSCO EU Written confirmation for Raltegravir potassium conforming to EU GMP, dated 28 Jan 2019, valid 3 years from the date of issue. -Test License for Chemical and Instrumental analysis for 12-04-2018 to 11-04-2021 -GMP certificate from the Government of Andhra Pradesh Drugs Control Administration, dated 30-10/2017, valid for 2 years (hence expired) -GMP certificate from the Government of Andhra Pradesh Drugs control Administration, valid up to 21/01/2021 -Site Master File drawings -List of APIs manufactured -APQR of Dolutegravir Sodium 2018 -Executed BPRs, including the analytical part for the most recently released batch of dolutegravir sodium (process A)

	-Declaration regarding recalls at the site -Confirmation of a full self-inspection or external audit -Master batch production record for dolutegravir sodium, dated 10.08.2019. -Declaration re warning letters or equivalent regulatory action, dated 3/9/2019 -Description of recent or foreseen out-of-stock situations, dated 3/9/2019 -Declaration on upcoming inspections dated 5/10/2019 -Declaration regarding part of the dolutegravir manufacturing process coverage by inspections by SRAs. -Documentation related to Korean MFDS inspection (submitted 24 Jan 2020) -Inspection documents related to January 2020 USFDA inspection (submitted 24 Jan 2020) -Response to queries and related GMP documents.	
Any documents missing?	Korean FDA inspection report and certificate were missing. The company was emailed on 23 Jan 2020 to request the missing documentation as well as the renewal of the local GMP certificate for the entire facility. The company responded that there were no GMP certificate issued per se as per usual procedure of Korean MFDS when inspecting foreign sites. This is acceptable.	
Part 2	Summary of SRA/NRA inspection evidence considered (from most recent to last) and comments	
Korean FDA	Dates of inspection:	18/02/2019-20/02/2019
	Type of inspection:	Not specified
	Block/Unit/Workshop:	Not specified
	APIs covered:	(Dapagliflozin Premix)
US FDA	Dates of inspection:	11-13/08/2017 (3 man days)
	Type of inspection:	Pre-announced pre-approval inspection
	Block/Unit/Workshop:	Not specified
	APIs covered:	APIs by chemical synthesis
US FDA	Dates of inspection:	13-17/01/2020
	Type of inspection:	GMP pre-approval inspection (pre-announced)
	Block/Unit/Workshop:	MPP2, QC for MPP1 and MPP2 products and ancillary areas used for APIs by chemical synthesis
	APIs covered:	APIs by chemical synthesis
Part 3	Summary of the last WHO inspection	
Date and conclusion of most recent WHO inspection	Not applicable. This site has not been inspected by WHO	
Brief summary of manufacturing activities	Manufacture of APIs (see Part 4c of this report for a full list).	

General information about the company and manufacturing site	According to the documentation submitted, the manufacturing facility consist of 3 blocks for production of intermediates and powder processing areas for the APIs: -MPP1: Consists of 3 Streams, A, B, C with micronizer areas and spray dryer areas -MPP2: Consists of a single stream. -MPP3: Exclusively for Oncology Molecules. The facility is not operational - MPP2A -Facility was operational by May 25,2020 & this facility consists of single stream. There are also QC laboratories: -QC laboratory for MPP1 and MPP2 Production batches -QC laboratory for MPP3 Products (Not in function) -Central microbiological laboratory The facility started its operations in 2016 and was manufacturing only APIs. The site plans to expand to oncological products once a new block (MPP3) is built. Lupin has in total 11 manufacturing sites in India. The Visakhapatnam site employed approximately 181 personnel (in 2017) with 3 shifts covering 24 hours.
Abbreviations	Meaning
BMR	Batch manufacturing record
BPR	Batch production record
CAPA	Corrective and preventive action
CC	Change control
GMP	Good manufacturing practices
NRA	National regulatory agency
PQR	Product quality review
PQS	Pharmaceutical quality system
QA	Quality assurance
QC	Quality control
QCL	Quality control laboratory
QMS	Quality management system
QRM	Quality risk management
RA	Risk assessment
RCA	Root cause analysis
SOP	Standard operating procedure

Part 4	Summary of the assessment of supporting documentation
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a) Manufacturing authorization and GMP certificate granted by the local authority:

The company submitted the following documents:

- CDSCO EU Written confirmation for raltegravir potassium conforming to EU GMP, dated 28 Jan 2019, valid 3 years from the date of issue.
- Test License for Chemical and Instrumental analysis for 12-04-2018 to 11-04-2021
- GMP certificate from the Government of Andhra Pradesh Drugs Control Administration, dated 30-10/2017, valid for 2 years (hence expired)
- GMP certificate from the Government of Andhra Pradesh Drugs Control Administration, valid up to 21/01/2021.

This is considered acceptable.

b) Site master file (SMF):

The most recent Site Master File and drawings were submitted. The information contained in the site master file was incomplete in that it did not specify if it manufactured/sold chemicals other than finished APIs.

c) List of all the APIs or other products (intermediates, dosage forms) manufactured on-site:

The following APIs are manufactured: Fenofibrate, Duranavir Ethanolate (Process B), Raltegravir potassium USP, Raltegravir potassium crystalline, Dolutegravir sodium (Process A), Dolutegravir sodium (Process B), Tenofovir Alafenamide fumarate, Tenofovir Alafenamide fumarate (Process B), Efinaconazole, Empagliflozin, Sofosbuvir pre-mix, Dapagliflozin premix, Canagliflozin hemihydrate, Propranolol hydrochloride USP, Sacubitril calcium, Sacubitril valsartan trisodium complex, Ledipasvir, Linezolid USP (Form-II), Sitagliptin phosphate, Cysteamine bitartrate, Ziprasidone hydrochloride USP, Rabepazole sodium, Pyrazinamide USP, Azilsartan kamedoxomil, Celecoxib, Acotiamide hydrochloride, tenofovir disoproxil fumarate, Dapagliflozin propanediol, Zolpidem tartrate USP, Ivacaflor.

As Sartan APIs are manufactured on site (Azilsartan Kamedoxomil and Sacubitril valsartan trisodium complex) the company was requested to provide information on whether there is any shared equipment with the WHO API. See review of response below.

d) List of all regulatory inspections performed in the last 3 years and their outcomes:

- CDSCO: 12-13/10/2017 (Satisfactory)
- USFDA: 11-13/08/2017 and 13-17/01/2020 (FDA 483's issued and EIRs received for both inspections)
- CDSCO: 08-09/08/2018 (Satisfactory)
- Korean FDA: 18-20/02/2019 (Satisfactory)

e) Most recent product quality review(s) (PQR)(s) of the concerned WHO API(s):

i. For Dolutegravir sodium: The APQR for the period of January to December 2018, for dolutegravir sodium was submitted. It was reviewed and considered acceptable in the most part.

ii. For linezolid (form II): APQRs were submitted for 2017, 2018 and 2019. They were reviewed and considered acceptable in the most part.

f) Batch manufacturing and packaging record(s), including the analytical part, for the most recently released batch of relevant API(s):

i. For Dolutegravir: BPRs were provided for batch Z8900017 of the micronized API and for the previous stages (last batch of each stage).

ii. For Linezolid (Form II): BPRs and analytical records were provided for one batch of each stage (from API starting materials FMA and LNA-1 (certificates of analysis only), Intermediate Stage 1, Intermediate Stage 2, finished API (Stage-3) (Input batch size is 90.0 Kg of LNA3, completed in December 2017). The finished stage includes milling and micronization.

g) Master batch manufacturing and packaging record(s) of the API(s) of interest:

i. For Dolutegravir: Blank BMRs were provided for each stage of the process. The BMRs for dolutegravir sodium, do not indicate that they are for process A. This issue was raised to the company in a query and the company clarified. This is acceptable.

ii. For Linezolid (Form II): Blank BMRs were provided for each stage of the process. No issues were found.

h) Recalls in the past three years related to APIs with quality defects:

The company declared that no recalls have taken place for any product manufactured at the site.

i) Confirmation by the senior quality assurance representative that a full self-inspection or external audit dedicated to the API(s) has been performed and all matters dealt with:

The company stated that no specific audit had been conducted for the WHO APIs. The company considered that the full self-inspection for the quality system and external audits were sufficient.

j) copy of any warning letter, or equivalent regulatory action, issued by any authority for their market, to which the site provides or has applied to provide the API(s):

The company declared that no warning letter or equivalent had been issued. This is acceptable.

k) Out-of-stock situations:

The company declared that no out of stock situation had occurred or was foreseen.

l) Additional documents submitted: Various responses to queries were submitted during the course of this desk assessment.

Part 5	Conclusion – Desk assessment outcome
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Based on the GMP evidence received and reviewed, it is considered that a desk assessment is acceptable in lieu of a WHO onsite inspection. The site **Lupin Limited**, located at **Plot No. 130, Road No. 11, Parawada (M), J.N. Pharma City, Visakhapatnam (Vizag), Andhra Pradesh, 531019, India** is considered to be operating at an acceptable level of compliance with WHO GMP guidelines for APIs.

This WHOPIR will remain valid for 3 years, provided that the outcome of any inspection conducted during this period is positive.

Part 6	List of guidelines referenced in this inspection report
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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. **Short name: WHO GMP for APIs or TRS No. 957, Annex 2**
<http://apps.who.int/medicinedocs/documents/s20119en/s20119en.pdf>
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. **Short name: WHO GMP Guidelines or WHO TRS No. 986, Annex 2**
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_986/en/
3. WHO guidance on good practices for desk assessment of compliance with good manufacturing practices, good laboratory practices and good clinical practices for medical products regulatory decisions. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-second Report. Geneva, World Health Organization, 2018 (WHO Technical Report Series, No. 1010), Annex 9. **Short name: WHO TRS 1010, Annex 9**
https://www.who.int/medicines/areas/quality_safety/quality_assurance/TRS1010annex9.pdf?ua=1
4. 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.
Short name: WHO TRS No. 970, Annex 2
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_970/en/
5. 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.
Short name: WHO TRS No. 929, Annex 4
http://whqlibdoc.who.int/trs/WHO_TRS_929_eng.pdf?ua=1

6. Guidelines on heating, ventilation and air-conditioning systems for non-sterile pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-second Report Geneva, World Health Organization, 2018 (WHO Technical Report Series, No. 1010), Annex 8. **Short name: WHO TRS No. 1010, Annex 8**
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_1010/en/
7. 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.
Short name: WHO TRS No. 937, Annex 4
http://whqlibdoc.who.int/trs/WHO_TRS_937_eng.pdf?ua=1
8. 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).
Short name: WHO TRS No. 961, 957, Annex 1
<http://www.who.int/medicines/publications/44threport/en/>
9. 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.
Short name: WHO TRS No. 957, Annex 2
<http://www.who.int/medicines/publications/44threport/en/>
10. 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.
Short name: WHO TRS No. 961, Annex 6
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1
11. 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.
Short name: WHO TRS No. 961, Annex 7
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1
12. 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. **Short name: WHO TRS No. 961, Annex 9**
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

13. 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. **Short name: WHO TRS No. 943, Annex 3**
http://whqlibdoc.who.int/trs/WHO_TRS_943_eng.pdf?ua=1
14. 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.
Short name: WHO TRS No. 961, Annex 2
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1
15. 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.
Short name: WHO TRS No. 981, Annex 2
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_981/en/
16. 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.
Short name: WHO TRS No. 981, Annex 3
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_981/en/
17. 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.
Short name: WHO TRS No. 961, Annex 14
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1
18. 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. **Short name: WHO TRS No. 992, Annex 3**
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf
19. 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. **Short name: WHO TRS No. 992, Annex 4**
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

20. 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. **Short name: WHO TRS No. 992, Annex 5**
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf
21. 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. **Short name: WHO TRS No. 996, Annex 5**
http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex05.pdf
22. 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.
Short name: WHO TRS No. 996, Annex 10
http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex10.pdf
23. 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
Short name: WHO TRS No. 992, Annex 6
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf
24. Stability testing of active pharmaceutical ingredients and finished pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-second Report Geneva, World Health Organization, 2018 (WHO Technical Report Series, No. 1010), Annex 10.
Short name: WHO TRS No. 1010, Annex 10
http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex10.pdf