World Health Organization

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**Prequalification Team Inspection services**
**WHO PUBLIC INSPECTION REPORT**
**(WHOPIR)**
**Desk Assessment of Finished Pharmaceutical Product (FPP) Manufacturer**

| **Part 1** | **General information** | |
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| **Company information** | | |
| Name of Manufacturer | Lupin Ltd | |
| Corporate address of manufacturer | Kalpatru Inspire,<br>3rd Floor, Off Western Express Highway Santacruz (East)<br>Mumbai 400 055, Maharashtra, India | |
| **Inspected site** | | |
| Name & address of manufacturing site | Lupin Ltd,<br>Unit 1, Plot No 2, Special Economic Zone,<br>Phase II SEZ, Pithampur, District Dhar,<br>Madhya Pradesh, 454 775, India | |
| Production Block/Unit | Unit 1 | |
| **Desk assessment details** | | |
| Date of review | 05 August 2020 | |
| Products covered by this desk assessment | RH091 (Ethinylestradiol/Levonorgestrel + Ferrous Fumarate Tablet, Film-coated 0.03mg/0.15mg + 75mg), (*Under Assessment*) | |
| **Part 2** | **Summary of SRA/NRA inspection evidence considered (from most recent to last)** | |
| *USFDA, USA* | Dates of inspection: | 3-11 February 2020 |
| | Type of inspection: | Routine re-inspection |
| | Block/Unit: | Unit-1 |
| | Type of products/Dosage forms covered: | Drug substance and oral solid dosage forms |
| *UK-MHRA, UK* | Dates of inspection: | 20-24 January 2020 |
| | Type of inspection: | Routine re-inspection |
| | Block/Unit: | Unit 1, 2 and 3 (new application) |
| | Type of products/Dosage forms covered: | Non-sterile dosage forms (APIs, sterile ophthalmic products, DPI dermatological products not inspected but manufactured at same site) |
| *USFDA, USA* | Dates of inspection: | 24-28 July 2017 |
| | Type of inspection: | Pre-approval inspection |
| | Block/Unit: | Unit 1 |
| | Type of products/Dosage forms | Non-sterile API by chemical |

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|---|---|---|
| | covered: | synthesis of Levothyroxine Sodium and Levothyroxine Sodium tablets |
| **Part 3** | **Summary of the last WHO inspection** | |
| Date and conclusion of most recent WHO inspection | WHO PQ Inspection Team have not previously inspected Lupin' Pithampur site Unit-1 for any FPP production | |
| **Abbreviations** | **Meaning** | |
| AHU | Air handling unit | |
| API | Active pharmaceutical ingredient | |
| BMR | Batch manufacturing record | |
| BPR | Batch production record | |
| CAPA | Corrective and preventive action | |
| CC | Change control | |
| GMP | Good manufacturing practices | |
| NC | Non conformity | |
| 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 Office of the Controller Food and Drugs Administration Madhya Pradesh, India has granted a Drugs Manufacturing Licence No 25/8/2010 and 28/6/2010 which were valid up to 30/06/2020. It was confirmed by the State Authority via a letter dated 27/06/2020 that these licences will be valid for 5 years i.e. up to 30/06/2025 (online vide application No: DHR2025R797 & DHR2028R799 dated 4th May 2020, refer Attachment-IV).

**b) Site master file (SMF):**

The manufacturer has provided a copy of the site master file (SMF/IN-1(F)/10 effective date 08/01/2020) of their formulation facility located on Unit-1, Plot No M-2 & M-2A, SEZ, Phase-II, Pithampur (refer Attachment-V). The formulation facility is surrounded by APIs manufacturing facilities (API-1, 2 & 3). The Unit-1 manufacture oral solid dosage forms (contraceptive including high potent drug products). The Unit-2 has separate OSD facility and ophthalmic facility which is out of the scope of this desk assessment. In general, the SMF provided a high-level overview of the manufacturing activities carried out at Unit-1 and found adequate.

**c) List of regulatory inspections performed in the last 3 years and their outcome:**

The manufacturer was inspected by the following regulatory authorities in the last 5 years (refer Attachment-I):

| S. No. | Regulatory Agency / Country | Period of Inspection | Outcome of inspection |
|---|---|---|---|
| 1. | UK- MHRA (UK) | 20-22 May 2015 | The inspection was concluded as satisfactory and certificate received |
| 2. | LAGESO Berlin (Germany) (Unit-1) | 5-10 June 2015 | The inspection was concluded as satisfactory and certificate received |
| 3. | USFDA (USA) (Unit-1) | 27 July- 05 August 2015 | The inspection was concluded as satisfactory and EIR received |
| 4. | CDSCO (India) | 28- 29 December 2015 | The inspection was concluded as satisfactory and certificate received |
| 5. | The Federal Budgetary Institution State Institute of Drugs and Good Practices, Russia | 20-23 January 2017 | The inspection was concluded as satisfactory and certificate received |
| 6. | USFDA (USA) | 24-28 July 2017 | The inspection was concluded as satisfactory and EIR received |
| 7. | CDSCO (India), WC Certification | 11-12 June 2018 | The inspection was concluded as satisfactory and certificate received |

| S. No. | Regulatory Agency / Country | Period of Inspection | Outcome of inspection |
|---|---|---|---|
| 8. | CDSCO (India) | 17-19 July 2018 | The inspection was concluded as satisfactory and certificate received |
| 9. | UK- MHRA (UK) | 20-24 January 2020 | The inspection was concluded as satisfactory and certificate received |
| 10. | USFDA (USA) | 03-11 February 2020 | The inspection was concluded as satisfactory and EIR received |

**d) List of all the products and dosage forms manufactured on-site:**

The manufacturer has provided a list of products manufactured at Unit-1. A total of 62 products (hormones and high potent drugs, refer Annexure-16 of Attachment-VI) are manufactured at Unit-1. These contraceptive and high potent drug products are produced in an oral contraceptive facility using shared equipment.

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

The PQR of Levonorgestrel and Ethinyl Estradiol Tablets 0.15mg/0.03mg (RH091, review period October 2018 to September 2019, SFG Product Code: 311140) was reviewed. The finished product is for the European market under different Finished Goods (FG) codes and packs size. A total of 2 Semi Finished Goods (SFG) batches were manufactured and 4 FG batches were released. The PQR included review and trending of critical process parameters, batch yields, in-process results and finished product results beside review of APIs, excipients and utilities. The PQR included the review of the quality management system including but not limited to change controls, deviations, rejections, complaints, adverse drug events, CAPA, recalls, qualification & validation and environmental monitoring. In general, the PQR appeared to be adequate.

The manufacturer has claimed that the manufacturing formula for the intended product (RH091) for WHO market (Product Code: 834232) is the same as for the Europe market (Product Code: 311140). The product for the Europe market was considered for stability study (as per WHO market) and subsequent filing. Now the product code (834232) for WHO filing has been separated and will be submitted to WHO for filing.

The PQR of Ferrous Fumarate 75mg (for RH091, review period June 2019 to May 2020, Product Code: 319633) was reviewed. The product is manufactured for the USA market. During the review period, a total of 77 batches (34 SFG manufactured and 43 FG batches released). It was noted that no batch was rejected, returned, recalled and repacked. The PQR included the review of critical process parameters, batch yields, in-process and finished product results beside review of the quality management system. In general, PQR appeared to be adequate.

The manufacturer has claimed that the intended Ferrous Fumarate 75mg tablets for WHO filing is having the same formula as that of Ferrous Fumarate 75mg tablets which are a direct compression product as per the revised strategy under the application RH091 under prequalification.

It was noted that the manufacturer has not manufactured any batch of the RH091 for WHO market and therefore submitted the APQR of the product from which the stability study and filing was done (Europe market).

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

The batch manufacturing, packaging and analytical part of Levonorgestrel 0.15mg and Ethinyl Estradiol 0.03mg tablets were provided as follows:

1. Batch Manufacturing Record of Levonorgestrel 0.15mg and Ethinyl Estradiol 0.03mg tablets (Batch No L000607, Product Code 308383 for the USA market)
2. Test Data Sheet and Certificate of Analysis of Levonorgestrel 0.15mg and Ethinyl Estradiol 0.03mg tablets (Batch No L000607)
3. Batch Manufacturing Record of Inert Tablets for Levonorgestrel and Ethinyl Estradiol tablets (Batch No L000604, Product Code: 308614 for the USA market)
4. Test Data Sheet and Certificate of Analysis of Inert Tablets for Levonorgestrel and Ethinyl Estradiol tablets (Batch No: L000604)
5. Batch Packaging Record: Batch No L000734 (for the UNFPA)

In addition, a copy of the intended batch manufacturing record (Product Code: 834232) of Levonorgestrel 0.15mg and Ethinyl Estradiol 0.03mg tablets (RH091) was provided. Similarly, a copy of the intended batch manufacturing record (Product Code: 834714) of Ferrous Fumarate 75mg Tablets was also provided. As RH091 is currently under PQ assessment, there were no copies available for the executed batch manufacturing, packaging and analytical part of Levonorgestrel 0.15mg and Ethinyl Estradiol 0.03mg tablets.

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

The manufacturer has claimed that the Master Manufacturing Formula for Levonorgestrel 0.15mg and Ethinyl Estradiol 0.30mg tablets (Intended product code: 834232 for WHO) is the same as for the Europe (Product Code: 311140) market. Similarly, it was also claimed that the Mater Manufacturing Formula for Ferrous Fumarate 75mg tablets (Intended product code: 834714 for WHO) is the same as for the USA (Product Code: 319633) market.

The manufacturer informed that the intended Master Formula for WHO product (RH091) will be filed to WHO PQT. As such, there is no approved (by WHO PQ) Master Batch Manufacturing and Packaging Record available.

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

It was noted that Lupin' Unit-1 site has recalled 8 products between January 2017 and June 2020 for the batches distributed into the US market. Out of 8 recalls, two recalls have been completed whereas 6 are currently ongoing. Most of these recalls were classified as Class II due to OOS results noted during stability testing, market complaint and weakness in investigation review.

**i) Confirmation by the senior quality assurance representative that a full self-inspection or external audit dedicated to the product(s) has been performed and all matters dealt with:**
A confirmation has been provided by the Manager QA that a full self-inspection has been performed covering products under Prequalification. Refer Attachment X.

**j) Copy of any warning letter, or equivalent regulatory action, issued by any authority to which the site provides or has applied to provide the product:**
The manufacturer has confirmed that they have not received any cGMP violation or warning letter from any of the regulatory authorities (USFDA, MHRA, Russian authority, CDSCO) in the last three years and before. Refer Attachment-XII.

**k) Out-of-stock situations:**
The manufacturer has confirmed that they do not foresee out-of-stock situation, hence stated as not applicable.

**l) Additional documents submitted:**
The manufacturer has provided information related to the use of shared facility & equipment for the manufacturing of WHO Prequalified and under assessment products. It was also confirmed that WHO Prequalified and under assessment products had not been covered by any stringent regulatory authorities. For detail, refer Attachment-XIII.

In addition, the manufacture has confirmed that the Russian authority is scheduled for an on-site GMP inspection during August 2020.

| **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 Ltd (UNIT-1) Plot No. M-2 & M2-A, SEZ, Phase-II, MISC Zone, Apparel Park, Pithampur, Distt. Dhar – 454775, Madhya Pradesh, India*** is considered to be operating at an acceptable level of compliance with WHO GMP guidelines. However,

- due to the nature and extent of the deficiencies raised by *USFDA (inspected 3-11 February 2020)*,
- inability to verify corrective and preventive actions as committed to USFDA due to travel restrictions, and
- seeing that Unit-1 (for FPPs) has never been inspected by WHO PQ inspection team

the compliance status of the desk review shall be valid only for a limited period of 9 months from the date of this report with the intention of WHO PQT: Inspections to conduct an on-site inspection within approximately **6 to 9 months' time** or soonest.

This WHOPIR will remain valid until **4th April 2021**, 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 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 ***TRS 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. ***Short name: WHO GMP for APIs*** or ***WHO TRS No. 957, Annex 2***
   http://apps.who.int/medicinedocs/documents/s20119en/s20119en.pdf

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 HVAC Guidelines*** *or* ***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 GPPQCL guidelines* or *WHO TRS No. 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

n19. 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 GDRMP guidelines*** or ***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. 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