World Health Organization

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

Part 1	**General information**
Company information	
Name of Manufacturer	Laboratorios Leon Farma
Corporate address of manufacturer	Telephone Number: 34-987-878-000 (24h) Fax Number: 34-987-878-048 Email Address: fxqa@fxpharm.com
Inspected site	
Name & address of manufacturing site	Laboratorios Leon Farma C/La Vallina s/n, Polígono Industrial Navatejera, Villaquilambre, León,24008, Spain D-U-N-S No. 467782459 GPS details: N42°38′27.6″, W5°35′26.5″
Production Block/Unit	• Tableting: Line 1 • Tableting: Line 2 • Tableting: Line 3 • Tableting: Small Batch Size line • Packaging Line (for tablets): EVO 1 and EVO 2
Desk assessment details	
Date of review	27 December 2019
Products covered by this desk assessment	• RH071: Ethinylestradiol/Levonorgestrel + Placebo Tablet, Film-coated + Tablet, Film-coated 0.03mg/0.15mg + 0mg (Under Assessment) • RH070: Ethinylestradiol/Levonorgestrel Tablet, Film-coated 0.03mg/0.15mg (Under Assessment) • RH069: Levonorgestrel Tablet 1.5mg (Under Assessment) • RH068: Levonorgestrel Tablet 0.75mg (Under Assessment) • RH067: Desogestrel/Ethinylestradiol Tablet, Film-coated 0.15mg/0.03mg (Under Assessment) • RH066: Desogestrel/Ethinylestradiol + Placebo Tablet, Film-coated 0.15mg/0.03mg + 0mg (Under Assessment) • RH051: Mifepristone Tablet 200mg (Prequalified (SRA Generic - PQd)

Part 2	**Summary of SRA/NRA inspection evidence considered**	
US Food and Drug Administration (US FDA)	Dates of inspection:	05-07,10-11 June 2019
	Type of inspection:	Pre-approval inspection
	Block/Unit:	Gel/cream manufacturing areas
	Type of products/Dosage forms covered:	Hormonal gel
US Food and Drug Administration (US FDA)	Dates of inspection:	5/21/2018 – 5/25/2018
	Type of inspection:	Pre-approval inspection
	Block/Unit:	Not mentioned
	Type of products/Dosage forms covered:	Hormonal vaginal ring
Spanish Agency-Junta de Castilla y leon	Dates of inspection:	6-8 March 2018
	Type of inspection:	Routine inspection
	Block/Unit:	▪Soft gelatin capsules production line. ▪Tablet production line 1, 2 and 3. ▪Primary and secondary packaging lines. ▪Vaginal rings production line. ▪Semi-solids production line. ▪Liquids production line. ▪Hard capsules production line. ▪Raw material dispensing area. ▪Warehouse and receiving and shipping areas. ▪Sample library. ▪Quality control laboratory.
	Type of products/Dosage forms covered:	▪Hard capsules: hormones or substances with hormonal activity. ▪Soft capsules: hormones or substances with hormonal activity. ▪Liquids for internal use. ▪Other solid pharmaceutical form: hormones or substances with hormonal activity (vaginal rings). ▪ Semi-solid: hormones or substances with hormonal activity. ▪Tablets: hormones or substances with hormonal activity.

Part 3	Summary of the last WHO inspection
Date and conclusion of most recent WHO inspection	Not yet inspected on-site by WHO.
Brief summary of manufacturing activities	According to the SMF, the site is manufacturing medicinal products for human use, under the pharmaceutical forms of soft gelatin capsules, hard capsules, vaginal rings, tablets, film coated tablets, granulates dosified in sachets, oral solutions and semisolids. It also manufactures medicinal products under investigation, in solid pharmaceutical forms such as tablets, film coated tablets, soft gelatin capsules, hard capsules, vaginal delivery system (vaginal rings), oral solutions and semisolids.
General information about the company and manufacturing site	According to the SMF, the production area consists of independent and separate manufacturing lines for granulates, tablets, film coated tablets, soft gelatin capsules, hard capsules, vaginal system (vaginal rings), oral solutions, semisolids to prevent risk of cross-contamination. In addition, the packaging area allows for blister packaging, filling/enveloping of semisolids and primary and secondary packaging.
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
SMF	Site master file
SOP	Standard operating procedure

Part 4	Summary of the assessment of supporting documentation

a) List of all regulatory inspection performed in the last 5 years and their outcomes:

A list of all regulatory inspections performed in the last 5 years was received, including inspections by US FDA, Brazilian Agency (ANVISA), Korean FDA, Belarus Agency, Russian Agency, Turkish Agency, Spanish Agency, Iranian Agency and Ivory Coast Agency. All inspections found the site compliant to GMP.

b) Manufacturing authorization granted by the local authority:

- Manufacturing license, Certificate No. 4208E, Issued on 29/7/ 2019.
- GMP certificate, Certificate No.4208/18, Issued on 11/4/2018

c) Site master file:

Site Master File, Document No.SMF-MT-24, approved date 3/6/2019, was reviewed and found acceptable and in line with the WHO TRS No. 961, Annex 14.

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

A list of all the products and dosage forms manufactured on-site was received, which included tablets, soft gelatin capsules, hard gelatin capsules, vaginal rings, oral solution and semisolid. The facility does not manufacture any beta lactams, penicillin, or cytotoxic products.

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

The APQR report for Levonorgestrel 0.75mg micro tablets/Finished Product, was issued on 24/4/2019. It indicted that there were 2 batches (1.319.391 tablets)/5 Finished Product manufactured during the evaluation period (01/11/2017–30/11/2018). The APQR concluded that the manufacturing process is controlled with no changes to the process or analytical methods recommended.

The APQR report for Levonorgestrel 1. 5mg micro tablets/Packaging, was issued on 11/12/2018. It indicated that 14 batches (2.855.205 tablets)/111 Finished Product batches were manufactured during the evaluation period (01/08/2017–31/07/2018). The APQR concluded that validation is maintained including product specifications. One batch was rejected due to non-conformance analytical results.

The APQR report for Levonorgestrel 0.150mg-Ethinylestradiol 0.03mg tablets/Finished Product, was issued in 2018. It indicated that 125 batches (168.463.889 film coated tablets)/156 Finished Product were manufactured during the evaluation period (01/01/2017–31/12/2017). The APQR concluded that validation is maintained including product specifications. OOS assay test results were identified which was followed up with a root cause analysis.

The APQR report for Desogestrel 0.150mg/Ethinyl Estradiol 0.03mg Film Coated Tablets/Finished Product, was issued on 5/2019. It indicated that 19 batches (3.653.928 tablets)/23 Finished Product were manufactured during the evaluation period (01/01/2017–28/02/2018). The APQR concluded that validation is maintained including product specifications. Two OOS were identified resulting in the rejection of the batches.

The APQR report for Mifepristone 200mg Tablets /Finished Product, was issued on 4/2019. It indicated that 12 batches (481.487 tablets)/30 Finished Product were manufactured during the evaluation period (01/12/2017–30/12/2018). The APQR concluded that validation is maintained including product specifications.

The APQR report for Levonorgestrel 0.150mg - Ethinylestradiol 0.03mg MICRO film coated tablets /Finished Product, was issued on 6/2019. It indicated that 147 batches (226.149.886 film coated tablets)/213 Finished Product were manufactured during the evaluation period (01/01/2018–31/12/2018). The APQR concluded that validation is maintained including product specifications.

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

- Levonorgestrel 0.75mg tablets Batch Records (Executed, Batch No. LF16857C).
- Levonorgestrel 1. 5mg tablets Batch Records (Executed, Batch No. LF14236A).
- Levonorgestrel 0.150mg-Ethinylestradiol 0.03mg tablets Batch Records (Executed, Batch No. LF16949C).
- Desogestrel 0.150mg/Ethinyl Estradiol 0.03mg Film Coated Tablets Batch Records (Executed, Batch No. LF15429A).
- Mifepristone 200mg Tablets /Finished Product Batch Records (Executed, Batch No. LF16809A).

g) If any of the products are sterile, the completed batch records for the most recent media fill validation that is relevant to the product(s) of the interest and report on its outcome:

None.

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

List of recalls in the past three years was submitted.

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:

Self-inspection declares: That during the year, it receives around 30 external audits from clients and authorities, which covered the site and related products. In addition an annual self-inspection plan, covering all areas of the site has been established.

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 product(s):

None.

k) Out-of-stock situations:

Not applicable seeing that Leon Farma is a Third-Party manufacturer with orders executed on a "make to order" basis.

l) Additional documents submitted:
A declaration on an upcoming inspection by the competent national regulatory authority of the Colombia Health Authority, INVIMA.

Part 5	Conclusion – Desk assessment outcome

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 ***Laboratorios Leon Farma*** located at ***C/La Vallina s/n, Polígono Industrial Navatejera, Villaquilambre, León,24008, Spain*** is considered to be operating at an acceptable level of compliance with WHO GMP guidelines.

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

Part 6	List of guidelines referenced in this inspection report

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 TRS No. 986, Annex 2***
   http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_986/en/

2. 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

3. WHO Good Manufacturing Practices: water for pharmaceutical use. *WHO Expert Committee on Specifications for Pharmaceutical Preparations*. Forty-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/

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.
Short name: WHO TRS No. 929, Annex 4
http://whqlibdoc.who.int/trs/WHO_TRS_929_eng.pdf?ua=1

5. 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/

6. Guidelines on heating, ventilation and air-conditioning systems for non-sterile pharmaceutical products. Part 2: Interpretation of Guidelines on heating, ventilation and air-conditioning systems for non-sterile pharmaceutical products. *WHO Expert Committee on Specifications for Pharmaceutical Preparations*. Fifty-third Report Geneva, World Health Organization, 2019 (WHO Technical Report Series, No. 1019), Annex 2. **Short name: WHO TRS No. 1019, Annex 2**
https://apps.who.int/iris/bitstream/handle/10665/312316/9789241210287-eng.pdf?ua=1

7. Good manufacturing practices: guidelines on validation. *WHO Expert Committee on Specifications for Pharmaceutical Preparations*. Fifty-third Report Geneva, World Health Organization, 2019 (WHO Technical Report Series, No. 1019), Annex 3. **Short name: WHO TRS No. 1019, Annex 3**
https://apps.who.int/iris/bitstream/handle/10665/312316/9789241210287-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. 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 3.
Short name: WHO TRS No. 957, Annex 3
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. 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

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.
Short name: WHO TRS No. 996, Annex 10
http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex10.pdf