World Health Organization

20, AVENUE APPIA – CH-1211 GENEVA 27 – SWITZERLAND – TEL CENTRAL +41 22 791 2111 – FAX CENTRAL +41 22 791 3111 – WWW.WHO.INT

**Prequalification Unit Inspection services**
**WHO PUBLIC INSPECTION REPORT**

**Desk Assessment of Active Pharmaceutical Ingredient (API) Manufacturer**

| Part 1 | General information |
|---|---|
| Company information | |
| Name of Manufacturer | Farmabios S.p.A |
| Corporate address of manufacturer | Via Pavia, 1 -27027 Gropello Cairoli – Pavia, Italy |
| Inspected site | |
| Name & address of manufacturing site | Farmabios S.p.A<br>Via Pavia, 1 -27027 Gropello Cairoli – Pavia, Italy<br>GPS: N45°10.161` E09°00.198`<br>DUNS: 428680078<br>CFB: 9610268<br>FEI: 3002806965 |
| Synthetic Unit/Block/Work shop | Oral steroid department: RS10, RS03 and RS04 |
| Manufacturing license number | Manufacturing authorization No API-171/2020 |
| Desk assessment details | |
| Start and end dates of review | 02 – 05 November 2020 |
| Inspection record number | INSP-2018-0210 |
| APIs covered by this desk assessment | Medroxyprogesterone monoacetate sterile |
| List of documents submitted | 1. AIFA (Italian Medicines Agency) Distant assessment report June 2020<br>2. GMP certificate No IT-API/112/H/2020<br>3. AIFA Inspection report September 2019, CAPA plans 1st and 2nd parts<br>4. Farmabios statement – AIFA inspection September 2019<br>5. GMP certificate No IT-API/206/H/2019<br>6. AIFA Inspection report June 2018 and response dated June 2018, November 2018. Note: all documents submitted in Italian language therefore not reviewed<br>7. GMP certificate No IT-API/201/H/2018<br>8. AIFA Inspection report May 2017 and CAPA plans dated April 2017, July 2017 and September 2017. Note: all documents submitted in Italian language therefore not reviewed.<br>9. GMP certificate No IT-API/111/H/2017<br>10. Ministry of Industry and Trade of Russian Federation Distant assessment report August 2020<br>11. Ministry of Industry and Trade of Russian Federation Inspection report February 2019 |

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| | 12. Ministry of Industry and Trade of Russian Federation Inspection report March 2018 and response dated September 2018. GMP certificate<br>13. US FDA EIR and response dated 15 June 2017<br>14. US FDA letter dated 4 August 2020<br>15. List of regulatory inspections from 2015<br>16. Manufacturing authorization No API-171/2020<br>17. SMF, version 2, approved 27.07.2020 with appendices<br>18. Veterinary products GMP certificate No NBF/40/2020/V<br>19. PQR Medroxyprogesterone acetate Jan – Dec 2019<br>20. Executed BMR, 6-Metilene-Acetossiprogesterone, Medroxyprogesterone acetate<br>21. Master BMR: 6-Metilene-Acetossiprogesterone, Medroxyprogesterone acetate<br>22. Lonza Pharma & Biotech (contract manufacturer – micronization) Batch release verdict – BMR micronization Medroxyprogesterone acetate<br>23. Lonza Pharma & Biotech (contract manufacturer – micronization) Batch release verdict – master BMR<br>24. Lonza Pharma & Biotech (contract manufacturer – micronization) certificate of compliance - micronization<br>25. CoA Medroxyprogesterone acetate and analytical raw data<br>26. Gammtom CoA for Medroxyprogesterone acetate micronized sterilization<br>27. Declaration – external audit<br>28. Declaration – internal audit | |
| Any documents missing? | N/A | |
| Part 2 | Summary of SRA/NRA inspection evidence considered (from most recent to last) and comments | |
| *AIFA (Italian Medicines Agency), Italy* | Dates of inspection: | 12 June 2020 |
| | Type of inspection: | Distant assessment (remote inspection) with final meeting in video- conference in June 12, 2020.<br><br>The distant assessment has been focused on the verification of the CAPA sent for the resolutions of the deviations found during the inspection from 16 to 20 September 2019. |
| *AIFA (Italian Medicines Agency), Italy* | Dates of inspection: | 16-20 September 2019 |
| | Type of inspection: | Evaluation of the suitability to produce active pharmaceutical substances according to the Good Manufacturing Practices |
| | Block/Unit/Workshop: | Steroids department |
| | APIs covered: | Not mentioned – general GMP inspection<br>WHO API under PQ was not specifically covered |
| Part 3 | Summary of the last WHO inspection | |
| Date and conclusion of most recent WHO inspection | The site has not been inspected by the WHO | |
| Abbreviations | Meaning | |
| BMR | Batch manufacturing record | |
| BPR | Batch production record | |
| CAPA | Corrective and preventive action | |

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|---|---|
| CC | Change control |
| CoA | Certificate of analysis |
| GMP | Good manufacturing practices |
| OOS | Out of specifications |
| OOT | Out of trends |
| PQR | Product quality review |
| 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:**

- Manufacturing authorization No API-171/2020
- GMP certificate No IT-API/112/H/2020
- Veterinary products GMP certificate No NBF/40/2020/V

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

SMF with appendices submitted and reviewed. SMF written according to the WHO TRS No. 961, Annex 14

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

Total number of APIs manufactured on site: 77

Therapeutic groups: hormones (oral grade and sterile), anticancer, cholic acid derivatives, high potent substances

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

| Authority | Dates of inspection | Scope | Outcome |
|---|---|---|---|
| Italian Health Authority (AIFA, Italy) | 26 – 30 January 2015 | General GMP inspection | GMP compliant |
| US FDA, USA | 19 - 23 October 2015 | Pre-approval inspection (on sterile steroid product) | GMP compliant |
| Italian Health Authority (AIFA), Italy | 14 – 18 March 2016 | GMP inspection | GMP compliant |
| Italian Health Authority (AIFA), Italy | 4 – 7 April 2017 | GMP inspection | GMP compliant |
| US FDA, USA | 22 – 26 May 2017 | Pre-approval inspection (on sterile steroid product) | EIR issued |
| Ministry of Industry and Trade of the Russian Federation, Russia | 5 – 8 March 2018 | GMP inspection | CAPA plan implemented in Sept 2018 |
| Italian Health Authority (AIFA), Italy | 28 May – 1 June 2018 | Authorization of a new Warehouse – general GMP inspection | GMP compliant |
| Ministry of Industry and Trade of the Russian Federation, Russia | 19 – 21 February 2019 | GMP inspection | GMP compliant |
| Italian Health Authority (AIFA), Italy | 16 – 20 September 2019 | Authorization of a new Micronization Plant – general GMP inspection | GMP compliant |

| Authority | Dates of inspection | Scope | Outcome |
|---|---|---|---|
| Italian Health Authority (AIFA), Italy | 12 June 2020 | Distant assessment (due to COVID 19 emergency) | GMP compliant |
| Ministry of Industry and Trade of the Russian Federation, Russia | 03 – 07 August 2020 | Distant assessment (due to COVID 19 emergency) | GMP compliant |

**e) Most recent product quality review (PQR) of the concerned WHO API:**
Submitted and reviewed:
PQR Medroxyprogesterone acetate Jan – Dec 2019

**f) Batch manufacturing and packaging records, including the analytical part, for the most recently released batch of relevant API:**
Submitted and reviewed:
- BMR, 6-Metilene-Acetossiprogesterone
- Medroxyprogesterone acetate lot XX
- Medroxyprogesterone acetate lot XY
- CoA Medroxyprogesterone acetate and analytical raw data
- Gammtom CoA for Medroxyprogesterone acetate micronized sterilization

**g) Master batch manufacturing and packaging record of the API of interest:**
Submitted and reviewed:
- 6-Metilene-Acetossiprogesterone
- Medroxyprogesterone acetate
- Medroxyprogesterone acetate
- Lonza Pharma & Biotech Batch release verdict – master BMR

**h) Recalls in the past three years related to APIs with quality defects:**
Declaration submitted – no recalls in past three years

**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:**
Declaration submitted – external audit performed
Declaration submitted - internal audit dedicated to the API has been performed and all matters dealt with

**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:**
AIFA inspection report, dated September 2019 submitted and reviewed

**k) Out-of-stock situations:**
Declaration submitted – no out-of-stock situations

**l) Additional documents submitted:**
N/A

| Part 5 | Conclusion – Desk assessment outcome |
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Based on the previous WHO inspections and 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 ***Farmabios S.p.A (Oral steroid department: RS10, RS03 and RS04),*** located at ***Via Pavia 1, Gropello Cairoli, Pavia, 27027, Italy*** 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 WHO 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 TRS 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.
   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. 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

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.
Short name: WHO TRS No. 961, 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 3.
Short name: WHO TRS No. 957, Annex 3
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.
Short name: WHO TRS 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.
Short name: WHO TRS 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. Short name: WHO TRS 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.
Short name: WHO TRS 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.
Short name: WHO TRS 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. Short name: WHO TRS 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. Short name: WHO TRS 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. Short name: WHO TRS 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. 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

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. 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

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. 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

20. WHO Recommendations for quality requirements when plant – derived artemisin is used as a starting material in the production 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

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 guidance 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 Multisource guidance or 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

24. Production of water for injection by means other than distillation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fourth Report. Geneva, World Health Organization, 2020 (WHO Technical Report Series, No. 1015), Annex 3.
Short name: WHO TRS No. 1025, Annex 3
https://www.who.int/publications-detail/978-92-4-000182-4

25. Good chromatography practice. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fourth Report. Geneva, World Health Organization, 2020 (WHO Technical Report Series, No. 1025), Annex 4.
Short name: WHO TRS No. 1025, Annex 4
https://www.who.int/publications-detail/978-92-4-000182-4

26. Points to consider for manufacturers and inspectors: environmental aspects of manufacturing for the prevention of antimicrobial resistance. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fourth Report. Geneva, World Health Organization, 2020 (WHO Technical Report Series, No. 1025), Annex 6.
Short name: WHO TRS No. 1025, Annex 6
https://www.who.int/publications-detail/978-92-4-000182-4

27. 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