World Health Organization

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**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 | Piramal Healthcare UK Ltd |
| Corporate address of manufacturer | As below |
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| Name & address of manufacturing site | Piramal Healthcare UK Ltd<br>Whalton Road, Morpeth, Northumberland, NE61 3YA,<br>United Kingdom of Great Britain and Northern Ireland<br>GPS:<br>Latitude: 55.151641N<br>Longitude: 1.7139463W<br>D-U-N-S: No 345609965 |
| Manufacturing buildings | Buildings 1 and 3 (Misoprostol)<br>Building 3 (Misoprostol Dispersion) |
| Manufacturing license number | API 29595, version 11, dated 10/06/2021 |
| | |
| Start and end dates of review | 12 – 16 June 2021 |
| APIs covered by this desk assessment | Misoprostol Dispersion |
| List of documents submitted | 1. List of SRA inspections<br>2. Medicines & Healthcare products Regulatory Agency (MHRA) inspection report, dates of inspection 31.03 – 9.04.2020<br>3. MHRA Post inspection letter<br>4. MHRA Post inspection response CAPAs<br>5. MHRA GMP certificate No UK API 29595 Insp GMP/GDP 29595/18244-0040<br>6. MHRA manufacturing license API 29595, version 11, dated 10/06/2021<br>7. SMF and 8 Appendixes<br>8. Misoprostol Dispersion PQR<br>9. Manufacturing records/analytical reports:<br>a) Misoprostol Dispersion analytical report<br>b) Misoprostol Dispersion manufacturing record<br>c) Misoprostol Pure analytical report<br>d) Misoprostol Pure Crude manufacturing record<br>e) Misoprostol Dispersion Crude in Toluene manufacturing record<br>f) TES Norprostol analytical report<br>g) TES Norprostol manufacturing record<br>h) TES Norprostol analytical report |

| | | |
|---|---|---|
| | i) TES Norprostol manufacturing record<br>10. Master batch documents<br>a. Misoprostol: HPMC Dispersion<br>b. Misoprostol: HPMC Dispersion<br>c. Misoprostol: Pure<br>d. Misoprostol Dispersion Crude in Toluene<br>e. Misoprostol Crude in Toluene<br>f. TES Norprostol<br>g. TES Norprostol<br>11. Declarations: self-inspection, recalls, warning letters, out-of-stock situation | |
| Any documents missing? | N/A | |
| **Part 2** | **Summary of SRA/NRA inspection evidence considered and comments** | |
| Medicines & Healthcare products Regulatory Agency (MHRA) | Dates of inspection: | 31.03 – 9.04.2020 |
| | Type of inspection: | Remote inspection during COVID-19 travel restrictions |
| | Building: | N/A - Remote inspection |
| | APIs covered: | Fostemsavir |
| **Part 3** | **Summary of the last WHO desk assessment** | |
| Date and conclusion of most recent WHO desk assessment | On-site inspection has never been performed by the WHO PQ Team.<br><br>Last WHO Desk assessment was performed September 2019 and was based on MHRA inspection report, dates of inspection 16-19 July 2018.<br><br><u>Conclusion – Desk assessment outcome</u><br>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 ***Piramal Healthcare UK Limited*** located at ***Whalton Road, Morpeth, Northumberland, United Kingdom, NE61 3YA*** is considered to be operating at an acceptable level of compliance with WHO GMP guidelines for APIs.<br><br>This compliance status shall be valid until 19/7/2021 or when another inspection is conducted by WHO or by a stringent regulatory authority. It remains the prerogative of WHO to carry out an inspection any time prior to that. | |
| Brief summary of manufacturing activities according to the SMF MISC-000049 | Manufacturing and quality control of:<br>• APIs<br>• Uncoated tablets<br>• Film coated tablets, including enteric coated<br>• Compression coated tablets<br>• Hard gelatin capsules<br>• Pharmaceutical granules | |
| Focus of the last WHO Desk Assessment | Misoprostol Dispersion | |
| WHO API covered by the | Misoprostol Dispersion | |

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|---|---|
| last WHO Desk Assessment | |
| **Abbreviations** | **Meaning** |
| 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:**
MHRA manufacturing license API 29595, version 11, dated 10/06/2021
MHRA GMP certificate No UK API 29595 Insp GMP/GDP 29595/18244-0040

**b) Site master file (SMF):**
SMF and 8 Appendixes 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 8 APIs are manufactured on-site:

| **Class of Drug** |
|---|
| Prostaglandin / Gastrointestinal Agent |
| Aldosterone Receptor Antagonist |
| HIV Attachment Inhibitor |
| Mineralocorticoid Receptor Antagonist |
| Diuretic |
| Iron Product |
| Antipsychotic |
| COX-2 Inhibitor and NSAID |

Total 48 FPPs are manufactured on-site:

| **Class of Drug** |
|---|
| Anti-mineral corticoid, Steroidal antiandrogen |
| Aldosterone Receptor Antagonist |
| Nonsteroidal anti-inflammatory drug |
| Prostaglandin / Gastrointestinal Agent |
| Antihistamine |
| Adenosine triphosphate-citrate lyase (ACL) inhibitor |
| Uricosuric agent |
| Hormone replacement therapy |
| Progestins |
| Progestin used for contraception |
| Iron Product |
| Peripherally acting mu-opioid receptor antagonist |
| Farnesoid X receptor agonist |
| Glucocorticoid |
| Tetracycline antibiotic |
| Anticoagulant |

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

| Agency Name | Inspection date | Outcome |
|---|---|---|
| **UK MHRA** | Pharmaceutical and IMP:<br>14 Dec 2020<br><br>API: 31 Mar 2020 (Onsite inspection planned 14-17 Jun 2021) | GMP Certificate No:<br>UK MIA 29595 Insp GMP/IMP 29595/18244-0041<br>UK MIA(IMP) 29595 Insp GMP/IMP 29595/18244-0041<br>UK ManA 29595 Insp GMP/IMP 29595/18244-0041<br>UK API 29595 Insp GMP/GDP 29595/18244-0040 |
| **US FDA** | Desktop Review: 09 Aug 2019<br>On-site Inspection: 09-13 Jan 2017 | EIR issued |
| **Bahrain NHRA** | Desktop Compliance Review: Valid from 15 Jan 2020 for 5 years | Registration Certificate of a Pharmaceutical Manufacturing Site (non-sterile: products: capsules hard shell, tablets, other solid dosage forms) Number: MSRN-0220/14 |

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|---|---|---|
| **Japan PMDA** | Desktop Compliance Review: Valid from 19 Dec 2016 to 18 Dec 2021 | Accreditation Certificate of foreign drug manufacturer (non-sterile drugs) Number: AG20500021 |

**e) Most recent product quality review (PQR) of the concerned WHO API:**
Submitted and reviewed:
Misoprostol Dispersion PQR, review period 1 February 2019 to 21 January 2020

**f) Batch manufacturing and packaging records, including the analytical part, for the most recently released batch of relevant API:**
Submitted and briefly reviewed:

a) Misoprostol Dispersion analytical report
b) Misoprostol Dispersion manufacturing record
c) Misoprostol Pure analytical report
d) Misoprostol Pure Crude manufacturing record
e) Misoprostol Dispersion Crude in Toluene manufacturing record
f) TES Norprostol analytical report
g) TES Norprostol manufacturing record
h) TES Norprostol analytical report
i) TES Norprostol manufacturing record

**g) Master batch manufacturing and packaging records of the APIs of interest:**
Submitted and checked:

a. Misoprostol: HPMC Dispersion
b. Misoprostol: HPMC Dispersion
c. Misoprostol: Pure
d. Misoprostol Dispersion Crude in Toluene
e. Misoprostol Crude in Toluene
f. TES Norprostol
g. TES Norprostol

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

**i) Confirmation by the senior quality assurance representative that a full self-inspection or external audit dedicated to the API has been performed and all matters dealt with:**
Declaration submitted: a full self-inspection or external 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:**
Declaration submitted: no warning letter, or equivalent regulatory action, issued by any authority

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

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

| Part 5 | Conclusion – Desk assessment outcome |
|---|---|

Based on the previous WHO desk assessment 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 **Piramal Healthcare UK Ltd buildings 1 and 3**, located at **Whalton Road, Morpeth, Northumberland, NE61 3YA, United Kingdom of Great Britain and Northern Ireland** 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 |
|---|---|

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 TRS 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. ***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 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

4. 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

5. 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

6. 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/

7. 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/

8. 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

9. 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

10. 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

11. 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

12. 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

13. 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/

14. 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/

15. 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

16. 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

17. 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

18. 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

19. 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/

20. 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

21. 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

22. 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. 1025), Annex 3.
***Short name: WHO TRS No. 1025, Annex 3***
https://www.who.int/publications-detail/978-92-4-000182-4

23. 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

24. 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

25. Points to consider when including Health-Based Exposure Limits (HBELs) in cleaning validation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fifth Report. Geneva, World Health Organization, 2021 (WHO Technical Report Series, No. 1033), Annex 2. ***Short name: WHO TRS 1033, Annex 2***
https://www.who.int/publications/i/item/55th-report-of-the-who-expert-committee-on-specifications-for-pharmaceutical-preparations¨

26. WHO good manufacturing practices: water for pharmaceutical use. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fifth Report. Geneva, World Health Organization, 2021 (WHO Technical Report Series, No. 1033), Annex 3. ***Short name: WHO TRS 1033, Annex 3***
https://www.who.int/publications/i/item/55th-report-of-the-who-expert-committee-on-specifications-for-pharmaceutical-preparations

27. Guideline on data integrity. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fifth Report. Geneva, World Health Organization, 2021 (WHO Technical Report Series, No. 1033), Annex 4. ***Short name: WHO TRS 1033, Annex 4***
https://www.who.int/publications/i/item/55th-report-of-the-who-expert-committee-on-specifications-for-pharmaceutical-preparations