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 Team Inspection services
WHO PUBLIC INSPECTION REPORT
(WHOPIR)
Desk Assessment of Active Pharmaceutical Ingredient (API) Manufacturer

Part 1	**General information**
Company information	
Name of Manufacturer	Piramal Healthcare UK Limited
Corporate address of manufacturer	Whalton Road, Morpeth, Northumberland, United Kingdom, NE61 3YA
Inspected site	
Name & address of manufacturing site	Piramal Healthcare UK Limited Whalton Road, Morpeth, Northumberland, United Kingdom, NE61 3YA
Synthetic Unit/Block/ Workshop	Misoprostol is produced in Two Buildings: Chemical 1 & Chemical 3
Desk assessment details	
Date of review	12 September 2019
APIs covered by this desk assessment	Misoprostol Dispersion (1:100 in HPMC), (Stabilized Active Substance) WHOAPI-226
List of documents submitted	- Applicant Section Document: Misoprostol Dispersion/OP/02/Apr-2018 ➢ [APIMF] which contain: General Information, Manufacture, Characterization, Control of drug substance, Reference Materials & Standards, Container closure system, Stability. -EDQM certificate of suitability for Misoprostol (Ref # R1-CEP 2010-121-Rev 01) -Certificate of GMP compliance of manufacturer issued by UK MHRA -Drug Master File Misoprostol, 2018 -Technical Package, 1/2019 -Open Part US DMF, 1/2019 -USFDA compliance documentation -Organization charts [site leadership team & senior management, QO & QC] -Layouts of Chemical Buildings. -Updated APQR for Misoprostol Dispersion API until 31 August 2018. -Updated SMF, Effective date: July 2018. -DMF of Norprostol manufactured for the Piramal Healthcare UK Limited by the Contract Manufacturer Soneas Research Limited (formerly known as Ubichem Research Limited until September 2015), used as intermediate drug substance for Misoprostol manufacture.

	-Complete batch manufacturing record for Tes Norprostol, Misoprostol crude in Toluene, Misoprostol HPMC Dispersion & Misoprostol pure. -Master Batch manufacturing & packaging record for Misoprostol pure, Misoprostol HPMC Dispersion, Tes Norprostol & Misoprostol crude in Toluene -Updated & Authorized List of Drug product & APIs manufactured on site.	
Any documents missing?	None.	
Part 2	**Summary of SRA/NRA inspection evidence considered (from most recent to last) and comments**	
MHRA (UK)	Dates of inspection:	16-19 July 2018
	Type of inspection:	Routine inspection
	Block/Unit/Workshop:	-Chemical 1 & 2 are multiproduct. -Chemical 3 is dedicated to Misoprostol (Pure & Dispersion) -Chemical 4 plant is undergoing reconstruction to become dedicated to a new product Fostemsavir intermediate and API with a dedicated laboratory.
	Type of APIs covered:	Spironolactone, Misoprostol Dispersion (1:100), Misoprostol pure, Parecoxib sodium, Haloperidol, Hydroflumethiazide (HFM), Canrenoate Potassium,
US FDA	Dates of inspection:	9 – 13 January 2017
	Type of inspection:	Routine Inspection
	Block/Unit/Workshop:	Chemical Building 1,2,3 & 4
	APIs covered:	APIs by chemical synthesis
	Physical areas inspected:	API Production areas: Building 1,2,3&4 and ancillary areas

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**

a) Manufacturing authorization and GMP certificate granted by the local authority:

- MHRA Manufacture License no: MIA 29595, Issued: 3/2019
- MHRA GMP certificate: UK API 29595, INS GMP: 29595/18244, Issued:5/11/2018

b) Site master file (SMF):

SMF was assessed and found acceptable (Effective date: July 2018).

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

Updated & Authorized List of Drug product manufactured on site were submitted.

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

NRA	Dates	Outcome
Kenyan	4/2016	Outcome not mentioned in SMF
US FDA	1/2017	GMP compliant
MHRA, UK	7/2018	GMP compliant

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

Updated APQR for Misoprostol Dispersion API and its associated intermediates from 1 September 2017 until 31 August 2018.
Total number of batches produced were 54.
Information contained included summary of all change controls, Deviations, OOS & Rejections for starting & packaging material, intermediates & finished products., review of returns, Complaints & Recalls, review of previous Corrective Actions and Stability Program.
Manufacturing process review & Yield review exist.
All Control Charts & Trends were attached in PQR.

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

Complete Batch manufacturing and Packaging records for Tes Norprostol, Misoprostol crude in Toluene, Misoprostol HPMC Dispersion & Misoprostol pure were submitted and reviewed.

g) Master batch manufacturing and packaging record(s) of the API(s) of interest:
Master Batch manufacturing and packaging records for Misoprostol pure, Misoprostol HPMC Dispersion, Tes Norprostol & Misoprostol crude in Toluene were submitted and reviewed.

h) Recalls in the past three years related to APIs with quality defects:
Declaration was made by qualified person (QP manager) that: No recalls have been made in the last 3 years for any APIs manufactured at this 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:
Declaration was made by qualified person (QP manager) that a full inspection has been performed dedicated to the API manufacturing area.
In addition, the MHRA, UK performed a dedicated inspection of the area on 16 July 2018.

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):
Declaration was made by qualified person (QP manager) that: No warning letter, or equivalent regulatory action, has been issued by any authority for this site.

k) Out-of-stock situations:
Declaration was made by qualified person (QP manager) that: No out-of-stock situations are foreseen in the next year or have taken place in the last three years.

l) Additional documents submitted:

- Data Integrity strategic plan issued on 31/1/2019.
- Declaration for Hormonal products segregation.
- SOP of expiry dating and re-evaluation of purchased and manufactured stock
- SOP for goods receiving
- SOP for Manufacturing record review & batch disposition.
- SOP of PQR
- SOP of vendor approval & revaluation.
- SOP of Deviation reporting.
- SOP of Change control.
- SOP of Self Inspection.
- SOP of Site training.
- SOP of Occupational health arrangement.
- SOP of Goods receiving. [Batch production & date expiry date are not checked on listed item to be checked]
- SOP of creation & life cycle of procedural documents.
- SOP of investigation & reporting of customer complain.
- SOP of customer returns.
- SOP of Market actions.
- Guide line for transportation of pharmaceutical products.
- Periodic review report, information services SQL*LIMS.
- Validation report, Quality operations SQL*LIMS

- List of GMP computerized systems used at Primal healthcare. [Unauthorized]
- Data Integrity policy.
- JD of [QC lead, QP, Manufacturing lead, Quality Manager]

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 ***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.

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 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*. 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/

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. 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

24. 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