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Prequalification Unit Inspection services
WHO PUBLIC INSPECTION REPORT
DESK ASSESSMENT OF CONTRACT RESEARCH ORGANIZATION (CRO)
WHOPIR

Part 1	**General information**
Company information	
Name of Company	Macleods Pharmaceuticals Limited
Corporate address of Company	Atlanta Arcade, Marol Church Road, Near Leela Hotel Andheri-Kurla Road, Andheri (East) Mumbai-400 059 India
Inspected site	
Name & address of the sites in the scope of desk assessment if different from that given above	Macleods Pharmaceuticals Ltd **R & D: III** Plot No. 18, Street no. 9, MIDC Andheri - (East), Mumbai, 400 093 India Macleods Pharmaceuticals Ltd **R & D: II** Plot no. 95, Road no. 16, Opp. Suncity Hotel MIDC, Andheri - (East) Mumbai 400 093 India Macleods Pharmaceuticals Ltd **R&D-I** G-2, Mahakali caves road, Shanti Nagar, Andheri (E) Mumbai - 400093 India Note: R&D-I site was shut down on 6 July 2019 due to administrative reasons and shifted to the new facility at R&D-III
Desk assessment details	
Date of review	07 September 2020
Product and study information covered by this desk assessment	Study no: BEQ-2216-SuTr (F)-2017 Sulfamethoxazole/Trimethoprim Tablet 800mg/160mg Study no: BEQ-1758-AbLa (F)-2016 Abacavir (sulfate)/Lamivudine Tablet, Film-coated 600mg/300mg Study no: BEQ-2439-SuPy (F)-2018 Pyrimethamine/Sulfadoxine Tablet, Dispersible 25mg/500mg

	Study no: BEQ-2329-AMOD-2017 Pyrimethamine/Sulfadoxine + Amodiaquine (hydrochloride) Tablet, Dispersible 25mg/500mg + 153mg Study no: BEQ-2349-RfIs (F)-2018 Isoniazid/Rifapentine Tablet, Film-coated 300mg/300mg Study no: BEQ-2229-CLOF-2017 Clofazimine Tablet, Film-coated 100mg Study no: BEQ-2092-ISON-2016 Isoniazid Tablet, Dispersible 100mg	
Part 2	**Summary of SRA/NRA inspection evidence considered (from most recent to last)**	
National Pharmaceutical Regulatory Agency (NPRA), Malaysia	Dates of inspection:	15 - 19 July 2019
	Type of inspection:	GCP/GLP Compliance Full Inspection
	Unit:	Clinical & Bioanalytical site at: Bioequivalence Department Plot no 18, Street No.09, MIDC Andheri (East) Mumbai-400093 India
	Type of study covered:	Bioequivalence studies
US FDA, USA	Dates of inspection:	12 - 16 November 2018
	Type of inspection:	Audit of bioanalytical data
	Unit:	Bioanalytical site located at: R&D I G-2, Mahakali Caves Road, Shanti Nagar Andheri- (East) Mumbai 400 093 India
	Type of study covered:	Bioequivalence studies
US FDA, USA	Dates of inspection:	29 October - 2 November 2018
	Type of inspection:	Clinical Phase only CDER's High Priority Premarket Original BIMO inspection
	Unit:	Clinical Units located at: R&D I, II & III With the following registered address: R&D-I

		G-2, Mahakali caves road, Shanti Nagar, Andheri (E), Mumbai - 400093 India. **R&D II** Plot no. 95, Road no. 16, Opp. Suncity Hotel, MIDC, Andheri - (East) Mumbai 400 093, India **R&D III** Plot No. 18, Street no. 9, MIDC Andheri - (East), Mumbai, 400 093, India
	Type of study covered:	Bioequivalence studies
Part 3	**Summary of the last WHO inspection**	
Date and conclusion of most recent WHO inspection	R&D I and II bioanalytical and clinical sites were previously inspected by WHO on 10 – 14 July 2017. The studies in the scope of the inspection were considered to be performed in compliance with WHO GCP/GLP guidelines.	
Brief description of the site's activities	The CRO consists of the three following separate Bioequivalence departments: Bioequivalence Department R&D: II Plot no. 95, Road no. 16 Opp. Suncity Hotel, MIDC Area Andheri - (East), Mumbai 400 093 India Bioequivalence Department R&D: III Plot No. 18, Street no. 9, M.I.D.C Andheri - (East) Mumbai 400 093 India Bioequivalence Department R&D-IV 5th floor, Empire Doctor House Opposite Kargil Petrol Pump Science city road Sola, Ahmedabad- 380060 India	

	The Bioequivalence Department has been operational since 2005 to carry out bioavailability and bioequivalence studies. The studies are guided by the World Medical Association's, Declaration of Helsinki (October 2013), and as per regulatory GCP/GLP guidelines. The CRO is licensed to conduct bioavailability, bioequivalence and invitro studies.
Areas inspected during the last WHO inspection	Both clinical and bioanalytical activities of the studies were inspected during the last WHO inspection.
WHO product(s) and clinical trial(s) covered by the last WHO inspection	• Artesunate and Amodiaquine Tablets 100mg/270mg • Artemether and Lumefantrine Dispersible Tablets 20mg/120mg • Praziquantel Tablets USP 600mg • Linezolid Tablets 600mg • Rifampicin 75mg and Isoniazid 50mg Dispersible Tablets • Terizidone Capsules 250mg • Rifampicin 75mg, Isoniazid 50mg and Pyrazinamide 150mg Dispersible Tablets • Levofloxacin Dispersible Tablets 100mg • Rifampicin Capsules 300mg • Ethambutol Dispersible Tablets 100mg • Moxifloxacin Hydrochloride Dispersible Tablets 100mg
Abbreviations	**Meaning**
CCs	Calibration Curve standards
CAPA	Corrective and preventive action
CROMF	CRO master file
GCP	Good clinical practices
GLP	Good laboratory practices
NC	Non-conformity
NRA	National regulatory agency
QA	Quality assurance
QC	Quality control
SOP	Standard operating procedure
SRA	Stringent regulatory authority

Part 4	Summary of the assessment of supporting documentation

a) Clinical trial license granted by the local authority:
A clinical trial license was issued and submitted for the following studies:
- BEQ-2439-SuPy (F)-2018, dated 29 Aug 2018
- BEQ-2329-AMOD-2017, dated 31 Aug 2018
- BEQ-2349-RfIs (F)-2018, dated 19 Jul 2018
- BEQ-2092-ISON-2016, dated 6 Feb 2017

For the rest of the trials in the scope of this desk-review assessment, a license was not applicable since either a monograph was published for the respective molecule, or the drug was previously approved by CDSCO.

b) CRO Master File:
An organization Master File with version no 1 authorized by Dr Ashish Mungantiwar on 29 Aug 2020, was submitted. The Master File was arranged in accordance with WHO Technical Report Series, No. 957, 2010 Annex 7 for Guidelines for the preparation of a contract research organization master file.

c) List of all regulatory inspections performed in the last 3 years and their outcome:
A list of all regulatory inspection performed in the last 3 years was provided. For more details, refer to Part 2 of this report.

d) Copy of any warning letter, or equivalent regulatory action, issued by any authority for the site:
There was no warning letter, or any equivalent regulatory action issued by any authority.

e) Confirmation by the senior quality assurance representative that a full self-inspection or external audit dedicated to the studies conducted for WHO product(s) has been performed and all matters dealt with:
A Quality Assurance statement was issued and signed by QA-Head on 29 Aug 2020 to confirm the compliance of studies with WHO guidelines and the regular monitoring by way of periodic audits.

It was also verified that all audits, data reviews and the report audit were reported in writing to the Principal Investigator, study director and to management. The final reports of the studies were audited by the Quality Assurance Unit. It was considered to be an accurate description of the procedures and practices followed during the course of the study and an accurate presentation of the findings.

f) IRB/IEC clinical trial approval (including the approved protocol, the amended protocol and consent form):

The following approval letters and the respective study specific documentation were provided:
- Approval letter from HumanCare IEC, dated 19 Jul 2018 for protocol no BEQ-1758-AbLa (F)-2016
- Approval letter from Ethicare EC, dated 31 Aug 2017 for protocol no BEQ-2092-ISON-2016
- Approval letter from Ethicare EC, dated 21 Aug 2018 for protocol no BEQ-2216-SuTr (F)-2017
- Approval letter from HumanCare IEC, dated 26 Nov 2017 for protocol no BEQ-2229-CLOF-20 17
- Approval letter from CBP IEC, dated 27 Jun 2019 for protocol no BEQ-2329-AMOD-2017
- Approval letter from Samiksha Institutional Ethics Committee, dated 30 Aug 2018 for protocol no BEQ-2349-Rfls (f)-2018
- Approval letter from HumanCare IEC, dated 20 Jan 2019 for protocol no BEQ-2439-SuPy (F)-2018

g) Additional documents submitted:

Following additional documentation was submitted and reviewed:
- Approval letter related to the manufacture of new drug formulation under Rules 122-B of the Drugs and Cosmetics Rules1945, namely Vardenafil film coated tablets, dated 6 Feb 2019
- DCGI Approval Letter R&D-III, dated 05 Sep 2018
- DCGI Approval Letter R&D-II, dated 13 Jan 2020
- DCGI Approval Letter R&D-III, dated 03 Mar 2020
- DCGI Query letter related to the site R&D 2 and 3
- Response to DCGI
- Response to Malaysia (NPRA) inspection report

Part 5	**Conclusion – Desk assessment outcome**

Based on the previous WHO inspections and on the GCP/GLP/BE evidence received and reviewed, it is considered that a desk assessment is acceptable in lieu of a WHO onsite inspection. The ***Macleods Pharmaceuticals Limited*** sites located at the following addresses are considered to have performed the studies submitted to WHO PQT under an acceptable level of compliance with WHO guidelines.

Macleods Pharmaceuticals Ltd
R & D: III
Plot No. 18, Street no. 9, MIDC
Andheri - (East), Mumbai, 400 093
India

Macleods Pharmaceuticals Ltd
R & D: II
Plot no. 95, Road no. 16, Opp. Suncity Hotel
MIDC, Andheri - (East),
Mumbai 400 093
India

Macleods Pharmaceuticals Ltd
R&D-I
G-2, Mahakali caves road, Shanti Nagar, Andheri (E)
Mumbai - 400093
India
Note: R&D-I site was shut down on 6 July 2019 due to administrative reasons and shifted to the new facility at R&D-III

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. Guidance for organizations performing in vivo bioequivalence studies. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fiftieth Report Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 9.
   Short name: WHO BE guidance or ***TRS996 Annex 9***
   http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex09.pdf

2. Good clinical laboratory practice (GCLP), WHO on behalf of the Special Programme for Research and Training in Tropical Diseases. Geneva, 2009
   Short name: WHO GCLP
   https://www.who.int/tdr/publications/documents/gclp-web.pdf

3. Guidelines for good clinical practice for trials on pharmaceutical products. WHO Technical Report Series, No. 850, 1995 (pp. 97–137). ***Short name: WHO GCP***
   http://apps.who.int/medicinedocs/en/d/Js5516e/19.11.html

4. Handbook – Good Laboratory Practice (GLP): quality practices for regulated non-clinical research and development – Annex I: The OECD Principles on GLP, 2nd ed., 2009. ***Short name: OECD GLP***
   http://www.who.int/tdr/publications/documents/glp-handbook.pdf

5. Standards and operational guidance for ethics review of health-related research with human participants. Guidance Document. Geneva, World Health Organization, 2011. ***Short name: WHO Ethics Committee Guidance***
   https://www.who.int/ethics/publications/9789241502948/en/

6. 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 storage and transport guidance*** or ***TRS 961 Annex 9***
http://apps.who.int/medicinedocs/documents/s18683en/s18683en.pdf

7. Guidelines for the preparation of a contract research organization master file, WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957), Annex 7.
Short name: WHO CROMF Guidelines or ***TRS No. 957, Annex 7***
http://www.who.int/medicines/publications/44threport/en/

8. Glove use information leaflet, Patient Safety, Save lives clean your hands. Geneva, World Health Organization, 2009 (revised). ***Short name: Glove use information leaflet***
http://www.who.int/gpsc/5may/Glove_Use_Information_Leaflet.pdf

9. WHO 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: TRS 996 Annex 5 or ***WHO GDRMP guidance***
http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex05.pdf

10. Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability. Republication of multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability. WHO Technical Report Series No. 992, Annex 7 with a new appendix 2. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-first Report Geneva, World Health Organization, 2017 (WHO Technical Report Series, No. 1003), Annex 6. ***Short name: TRS 1003 Annex 6***
http://apps.who.int/medicinedocs/documents/s23245en/s23245en.pdf

11. 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

12. 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