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 INSPECTION REPORT
Bio-Equivalence Study

Part 1	**General information**
Organization details	
Company information	
Name and Address of Clinical Research Site	**Macleods Pharmaceuticals Ltd.,** Bioequivalence Department, 1. R and D–I, G-2, Mahakali Caves Road, Shanti Nagar, Andheri (East), Mumbai – 400 093 and 2. R and D– II, Plot number 95, Road Number 16, Opposite Suncity hotel, MIDC area, Andheri (East), Mumbai - 400093
Name and Address of Bioanalytical Research Site	**Macleods Pharmaceuticals Ltd.,** Bioequivalence Department, R and D–I, G-2, Mahakali Caves Road, Shanti Nagar, Andheri (East), Mumbai – 400 093
Name and address Statistical Site (delete if not applicable or if the same as the above)	**Macleods Pharmaceuticals Ltd.,** Bioequivalence Department, R and D–I, G-2, Mahakali Caves Road, Shanti Nagar, Andheri (East), Mumbai – 400 093
Corporate address of Organization	Same as above
WHO product numbers covered by the inspection/ Product names/ Study numbers/ Study titles	1. MA127 2. MA137 3. NT004 4. TB297 5. TB302 6. TB303 7. TB309 8. TB326 9. TB332 10. TB334 11. TB342
Inspection details	
Dates of inspection	10-14 July 2017
Type of inspection	Routine inspection

Introduction	
Brief summary of the activities	The bioequivalence department of Macleods Pharmaceutical Limited commenced in April 2005. Facilities at R and D – I comprising of - Screening area - Clinical section (40 beds) - Bioanalytical section – Instrument lab. – 1 - Quality Assurance - Pharmacokinetic and Statistical section - Pathology department - Bioanalytical laboratory (Instrument lab. -2) - Bioanalytical laboratory (Instrument lab. -3) Facilities at R and D – I extension building - Archival area – 1 at the lower basement - Bioanalytical stores at the lower basement Facilities at R and D – II - Clinical section (-144 beds) - In-vitro analytical laboratory - Archival area – 2
General information about the company and site	Macleods Pharmaceutical Limited, Mumbai, India was incorporated in the year 1986. The company has two finished pharmaceutical product manufacturing facilities located in Daman and Baddi, whereas one active pharmaceutical ingredients facility in Sarigram, India.
History	The bioequivalence department of Macleods Pharmaceutical Limited was approved by Drug Controller of India since 2005. The BE department was inspected by the following regulatory authorities: 1. USFDA inspections: March 2008, October 2009, July 2010, November 2011, June 2014, February 2015, May 2016, June 2016, July 2016 2. World Health Organization inspections: April 2006, May 2006, January 2007, April 2007, September 2007, February 2009, February 2013, March 2016. 3. Approved by ANVISA, March 2008, March 2009 4. MCC, South Africa inspection– November 2010 5. Approved by UAE – October 2011 6. UKMHRA inspection – November 2012, March 2017 7. Thailand GLP inspection – November 2012
Brief report of inspection activities undertaken	
Scope and limitations	
Out of scope	None

Abbreviations

ADR	adverse drug reaction
AE	adverse event
ALCOA	attributable, legible, contemporaneous, original and accurate
BE	bioequivalence
BDL	below detection limit
CAPA	corrective actions and preventive actions
CC	calibration curve
CRA	clinical research associate
CRF	(electronic) case report form
CRO	contract research organization
CTM	clinical trial manager
CoA	certificate of analysis
CSR	clinical study report
DQ	design qualification
ECG	electrocardiogram
GCP	good clinical practice
GLP	good laboratory practice
GMP	good manufacturing practice
HPLC	high-performance liquid chromatograph
HPLC-MS/MS	liquid chromatography–mass spectrometry
IB	investigator's brochure
ICF	informed consent form
ICH	International Conference on Harmonization
IEC	(Independent) Ethics Committee
IMP	investigational medicinal product
IQ	installation qualification
LIMS	laboratory information management system
LLOQ	lowest limit of quantification
LOD	limit of detection
MS	mass spectrophotometer
MVR	monitoring visit report
NRA	national regulatory agency
OQ	operational qualification
PIS	patient information sheet
PQ	performance qualification
QA	quality assurance
QC	quality control
QRM	quality risk management
SAE	serious adverse event
SAR	serious adverse reaction
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
ULOQ	upper limit of quantification
URS	user requirements specifications

Part 2	Brief summary of the findings and comments (where applicable)

1. Organization and management

The bioequivalence department of Macleods Pharmaceuticals Ltd commenced its operations in April 2005 after obtaining approval from the Drug Controller of India. The organization chart as part of the opening meeting was presented which depicted key positions and the names of responsible personnel. The Head, Bioequivalence was supported by the heads of the clinical, bioanalytical lab, and the biostatistician. The head quality assurance directly reports to the Managing Director of the company with administrative reporting to the Head Bioequivalence. The QA staff reports directly to the head of QA. A total of 259 personnel were working in the bioequivalence department.

The job descriptions of the key personnel were reviewed and found satisfactory.

A list of all studies conducted at the site was obtained and was reviewed. It was noted that a total of 41 and 50 pivotal bioequivalence studies were performed in the year 2015 and 2016 respectively by Macleods.

The issues related to this section have been adequately addressed, and the same shall be verified during future inspections.

2. Computer systems

A list of systems used to perform bioanalytical work was provided to the inspectors. The computer systems were qualified and validated before put on for use. A total of 16 LC-MS/MS were used by the laboratory. The Analyst software was used for these LC-MS/MS.

The issues related to this section have been adequately addressed, and the same shall be verified during future inspections.

3. Quality management

The bioequivalence department has an appropriate quality assurance system with 268 written SOPs in order to conduct bioequivalence studies according to the GCP and GLP requirements. The QA personnel were not directly involved in the BE study related activities, and were responsible to the head QA. The QA was responsible for the verification of various activities during the conduct of the studies such as self-inspections, reliability and traceability.

The issues related to this section have been adequately addressed, and the same shall be verified during future inspections.

4**. Archive facilities**

The document archival room located at the R&D unit II building was visited. The facility was equipped with a fire extinguisher system, smoke detectors, temperature and humidity control. Access to archiving room was restricted and equipped with a fire resistant door. Minimum /maximum thermometer was available and was recorded daily.

The inspectors reviewed the visitor's log, temperature and humidity logs. The logbooks for access to the facility (entry and exit), document storage and documents retrieval were maintained.

The issues related to this section have been adequately addressed, and the same shall be verified during future inspections.

5. Premises

The laboratory premises used to perform bioequivalence studies were generally spacious and adequate for their use. For more details, refer to sections on 7 and 22.

The issues related to this section have been adequately addressed, and the same shall be verified during future inspections.

6. Personnel

Macleods has employed sufficient number of personnel for clinical, bioanalytical, and other areas. Personnel were generally well trained and competent in their respective areas. Training records were reviewed for a few randomly selected staff members and the level of documented training and accreditation was deemed satisfactory.

Clinical section

7. Clinical phase

R&D Unit I consisted of the following facilities:

- Volunteer's Staging Room
- Volunteer's Change Room
- Height/weight and volunteer registration room
- Humidity Chamber and Dispensing Area
- Doctor's Room
- Clinical Pharmacology Unit (40 Beds)
- ECG room
- Volunteer's Rest Room
- Study Coordination Centre
- Phlebotomy and Dosing Area
- Incentive Care Unit (ICU)
- Volunteer's Recreation Room

- Dining Hall
- Food Dispensing area
- Sample Storage Room
- Staff Change Room
- Storage Room
- Waste Segregation area

All the above areas were inspected and were found adequate.

8. Clinical laboratory

The Pathology laboratory located at the R&D unit I was briefly inspected and found to be adequate.

The issues related to this section have been adequately addressed, and the same shall be verified during future inspections.

9. Ethics

Informed consents were acceptable for studies reviewed by the inspectors.

The issues related to this section have been adequately addressed, and the same shall be verified during future inspections.

10. Monitoring

The monitoring of the study reviewed during the inspection was performed by the Sponsor, Macleods.

Monitoring manual was available. The manual requires monitoring to be done during the pre-study, conduct of the study and post-study. Monitoring reports for pre-study visit, dosing day visit, dosing day visit, dosing day visit, dosing day visit for inspected products were available.

11. Investigators

Investigators have appropriate qualifications, trainings and sufficient experience in the conduct of BE studies, as confirmed by their CVs.

The issues related to this section have been adequately addressed, and the same shall be verified during future inspections.

12. Receiving, storage and handling of investigational drug products

Randomization schedule for the selected studies was reviewed and found adequate. The SAS was used for randomization by bio-statistician.

The issues related to this section have been adequately addressed, and the same shall be verified during future inspections.

13. Case report forms (CRFs)

The CRFs for the subjects randomized in selected studies were verified by the inspector, and no issues were found.

The issues related to this section have been adequately addressed, and the same shall be verified during future inspections.

14. Volunteers, recruitment methods

During the inspection, the following recruitment process for a running study was observed in both R&D unit I and R&D unit II location: the volunteers are entering the volunteer staging room after being registered in the visiting log book and received a screening slip. Identity of the eligible volunteers is checked by ID card, volunteer registration number or by fingerprint. The finger print recognition of volunteers has been implemented in 2016. For new volunteers, a unique registration number is created. Verification for eligibility in the washout period or concomitant trials in OVIS database is performed. If no issues identified the ICF is distributed. All volunteers are provided with a general description of the ICF followed by a one to one discussion with the medical doctors and ICF signature. An ICF copy is provided to the subject. The ICF process is video and audio recorded as per the local regulatory requirements.

Drug abuse and pregnancy tests for female subjects are performed. Breath alcohol test and medical examination including vital signs, inclusion/exclusion criteria evaluation follows. After having the volunteers registered in the ECG log book and the ECG testing is performed. A hard copy of ECG results for archiving purposes is created. One subject was chosen randomly by the inspector and verified in the ECG log book vs the visitors log book at the main entrance.

The volunteers received a batch with the study number and his/her photo. Lockers were available in the changing room for the volunteers to store personal belongings. A meal is provided as per protocol requirements and the volunteers are invited for an overnight stay. The next morning, the investigational drug was administrated followed by a mouth check. The blood sample collection and other study procedures were performed as per protocol requirements. The study personnel were well trained and qualified.

The issues related to this section have been adequately addressed, and the same shall be verified during future inspections.

15. Food and fluids

Volunteers were not allowed to have meals and fluids other than those served by the study team. Meals were administered according to the study schedule and were identical in all study periods.

16. Safety, adverse events, adverse event reporting

One SAE reported for subject enrolled in the selected study. Initial and follow-up reports were present and considered to be satisfactory. Adverse events reporting procedures were followed, no issues identified.

17. Method development

The bioanalytical laboratory had a procedure in place which described how bioanalytical methods were developed. The laboratory kept the copies of the publications which were used in developing the bioanalytical methods. Method development was stated to be recorded in a logbook. Method development and method validation were reviewed and were found satisfactory.

The issues related to this section have been adequately addressed, and the same shall be verified during future inspections.

18. Method validation

The laboratory referred EMA guideline on bioanalytical method validation. The laboratory had procedure and protocol in place which described validation requirements for the bioanalytical methods.

The issues related to this section have been adequately addressed, and the same shall be verified during future inspections.

19. Sample collection, storage and handling of biological material

There was a procedure in place for the collection, preparation, transport or shipping and storage of samples. Records of the storage and retrieval of samples were maintained.

The deep freezers and freezers used for storage of plasma samples were inspected and found as acceptable overall. The room where they were located (third floor) had controlled access and entry and exits were recorded.

The issues related to this section have been adequately addressed, and the same shall be verified during future inspections.

20. Analysis of study samples

The results of the method validation were available before the initiation of study sample analysis except long-term stability of the analyte in matrix. Each analytical run included calibration curve (CC), QC samples and subject samples. Minimum of 6 different sources of plasma were used as blank plasma for the preparation of CCs and QCs.

The issues related to this section have been adequately addressed, and the same shall be verified during future inspections.

21. Data processing and documentation

The integration settings for the chromatograms inspected were justifiable as base to base integration method was applied. Also, smoothing was kept 3 for all of the chromatograms inspected for selected studies.

The bioanalytical laboratory has a procedure on the user rights management for Analyst software.

The issues related to this section have been adequately addressed, and the same shall be verified during future inspections.

22. Good laboratory practices

The inspectors visited the bioanalytical laboratories which was located on two different floors. In general, the laboratory was well equipped with modern equipment and instruments.

There were 16 HPLC-MS/MS systems at the time of the inspection.

The issues related to this section have been adequately addressed, and the same shall be verified during future inspections.

Pharmacokinetic, statistical calculations and reporting section

23. Pharmacokinetic, statistical calculations

For pharmacokinetic and statistical analysis, SAS was used by the bioequivalence department. The procedure was in place to double check data values input to the system.

This section was not inspected in detail due to time constraints.

24. Study report

This area was not covered due to time constraints.

PART 3

Conclusion

Based on the areas inspected, the people met and the documents reviewed, and considering the findings of the inspection, including the observations listed in the Inspection Report, as well as the corrective actions taken and planned, the studies

- BEQ-1254-AA (F)-2013
- BEQ-2008-ArLu(F)-2016
- BEQ-1531-PRAZ-2015
- BEQ-448-LINE-2009
- BEQ-1680-RiIs (F)-2015
- BEQ-1290-TERI-2014
- BEQ-2039-RIP (F)-2016
- BEQ-1535-LEVO-2015

- BEQ-1949-RIFA-2016
- BEQ-1612-ETHA-2015
- BEQ-2055-MOXI-2016

were considered to have been conducted at an acceptable level of compliance with WHO GCP and GLP at *Macleods Pharmaceuticals Ltd, Bioequivalence Department, Mumbai, India*.

All the non-compliances observed during the inspection that were listed in the full report as well as those reflected in the WHOPIR, were addressed by the CRO, to a satisfactory level, prior to the publication of the WHOPIR

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

PART 4

List of guidelines referenced in the inspection report

1. Guidance for organizations performing in vivo bioequivalence studies. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifties Report* Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 9
   Short name: WHO TRS No. 996, Annex 9
   http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex09.pdf
2. Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability. In: *Expert Committee on Specifications for Pharmaceutical Preparations. Forty-ninth report*. World Health Organization, Geneva. WHO Technical Report Series, No. 992, Annex 7, 2015, pp. 347–390
   Short name: WHO TRS No. 992, Annex 7
   http://apps.who.int/prequal/info_general/documents/TRS937/WHO_TRS_937__annex7_eng.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 TRS No. 850
   http://apps.who.int/medicinedocs/en/d/Js5516e/19.11.html
4. WHO guidance on good data and record management practices. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifties 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
5. WHO Handbook on Good Laboratory Practice/OECD Series on Principles of Good Laboratory Practice and Compliance Monitoring, Number 1: OECD Principles on Good Laboratory Practice (as revised in 1997). Organization for Economic Co-operation and Development. ENV/MC/CHEM(98)17. 26.Jan, 1998.
   http://www.who.int/tdr/publications/documents/glp-handbook.pdf
6. The Good Automated Manufacturing Practice (GAMP) Guide – A risk-based approach to compliant GxP computerized systems (GAMP5). ISPE – International Society for Pharmaceutical Engineering, December 2009.
   http://www.ispe.org/gamp-5

7. Guidelines on Bioanalytical Method Validation EMEA/CHMP/EWP/192217/2009 Rev.1 Corr.* Committee for Medicinal Products for Human Use (CHMP), 1 February 2012. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/08/WC500109686.pdf
8. WHO Operational guidelines for Ethics Committees that review biomedical research (7). WHO, TDR/PRD/ETHICS/2000.1 http://www.who.int/entity/tdr/publications/documents/ethics.pdf?ua=1
9. Good Practices for Computerised Systems in Regulated "GXP" Environments, PIC/S Guidance, Pharmaceutical Inspection Convention Pharmaceutical Inspection Co-operation Scheme, PI 011–3, 25 September 2007. http://www.picscheme.org/pdf/27_pi-011-3-recommendation-on-computerised-systems.pdf
10. US FDA Code of Federal Regulations Part 11 http://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=11&showFR=1
11. EU guidelines to Good Manufacturing Practice and Medicinal Products for Human and Veterinary Use Annex 11, Computerized systems http://ec.europa.eu/health/files/eudralex/vol-4/annex11_01-2011_en.pdf
12. Handbook – Good Laboratory Practice (GLP): quality practices for regulated non-clinical research and development – Annex I: The OECD Principles on GLP, 2nd ed., 2009. This document will be referred to as "GLP". http://www.who.int/tdr/publications/documents/glp-handbook.pdf
13. 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://apps.who.int/prequal/info_general/documents/TRS961/TRS961_Annex9.pdf
14. Guidelines for the preparation of a contract research organization master file, WHO Technical Report Series, No. 957, 2010, Annex 7 **Short name: WHO TRS No. 957, Annex 7** http://www.who.int/medicines/publications/TRS957_2010.pdf
15. Glove use information leaflet, Patient Safety, Save lives clean your hands, WHO, revised August 2009 http://www.who.int/gpsc/5may/Glove_Use_Information_Leaflet.pdf
16. WHO Good Clinical Laboratory Practices (GCLP) http://www.who.int/tdr/publications/documents/gclp-web.pdf