



WHO PUBLIC INSPECTION REPORT

(WHOPIR)

Contract Research Organization

Part 1: General information

WHO product numbers covered by the inspection	TB231 (Rifampicin/Isoniazid 300mg/150mg tablets) MA091 (Artemether/Lumefantrine 20mg/120mg tablets) HA561 (Emtricitabine/Tenofovir Disoproxil Fumarate 200mg/300mg tablets) HA564 (Emtricitabine/Tenofovir Disoproxil Fumarate 200mg/300mg tablets + Nevirapine 200mg tablets) Other products tested at the site during the period covered by a spot-check (note: may be further verified during the next inspection as well as a thorough check could not be performed due to time constraints): HA465 (Nevirapine 200mg tablets) HA514 (Lamivudine/Tenofovir Disoproxil Fumarate 300mg/300mg tablets) and HA522 (Lamivudine/Tenofovir Disoproxil Fumarate 300mg/300mg and nevirapine 200mg co-packaged tablets) TB259 (Rifampicin 150mg capsules) HA562 (Efavirenz/Emtricitabine/Tenofovir Disoproxil Fumarate 600mg/200mg/300mg tablets) HA574 (Lopinavir/Ritonavir 200mg/50mg tablets)
Study number	BEQ-488-RI(F)-2009 (TB231) BEQ-641-AL(F)-2010 (MA091) BEQ-515-ET(F)-2010 (HA561, HA564) Other studies performed at the site which have not been covered by previous inspections (spot-checks): BEQ-134-NEVI-2007 (HA465) BEQ-514-LT(F)-2010 (HA522, HA514) BEQ-667-RIFA-2011 (TB259) BEQ-701-EET(F)-2011 (HA562) BEQ-806-LR(F)-2011 (HA574)
Title of the study	Study #: BTIF BEQ-488-RI(F)-2009 (TB231) Title: Bioequivalence study of two tablets as single dose fixed dose combination of Rifampicin 300mg and Isoniazid 150mg tablets (each tablet containing rifampicin 300mg and isoniazid 150mg) manufactured by Macleods Pharmaceuticals Ltd., India, comparing with separate formulations of two capsules of Rifadin®

	300mg capsules (each capsule contains 300mg of rifampicin) manufactured by Gruppo Lepetit SpA, Italy and marketed by Sanofi-aventis, UK and three tablets of Isozid® 100mg tablets (each tablet contains 100mg of isoniazid) manufactured by Fatol Arzneimittel GmbH, Germany, in healthy, adult, human subjects under fasting condition. Study #: BTIF BEQ-641-AL(F)-2010 (MA91) Title: Bioequivalence study of four tablets as single dose of fixed dose combination of Artemether 20mg and Lumefantrine 120mg Tablets manufactured by Macleods Pharmaceuticals Ltd, India in comparison with four tablets of Coartem® (artemether/lumefantrine) tablets 20mg/120mg manufactured and distributed by Novartis Pharmaceuticals Corporation, USA in healthy, adult, human subjects under fed condition. Study #: BTIF BEQ-515-ET(F)-2010 (HA561 and HA564) Bioequivalence study of single dose of fixed dose combination of Emtricitabine and Tenofovir disoproxil fumarate tablets 200mg + 300mg (each tablet contains 200mg of emtricitabine and 300mg of tenofovir disoproxil fumarate equivalent to 245mg of tenofovir disoproxil) manufactured by Macleods Pharmaceuticals Ltd, India in comparison with TRUVADA® (emtricitabine and tenofovir disoproxil fumarate) Tablets (each tablet contains 200mg of emtricitabine and 300mg of tenofovir disoproxil fumarate which is equivalent to 245mg of tenofovir disoproxil) manufactured for Gilead Sciences, Inc, USA in healthy, adult, human subjects under fasting condition.
Clinical Part of the study: Name and address of the organization	Macleods Pharmaceuticals Limited , Bioequivalence Department, G-2, Mahakali Caves Road, Shanti Nagar (Andheri East), Mumbai, 400 093
Bio-analytical laboratory: Name and address	Same as above
Date of inspection	8 – 12 February 2013

Part 2: Summary

General information about the site(s)

The bioequivalence department was part of the R&D division of the company.

There were 700 people in R&D of which 200 staff-members were in bioequivalence. There was a total of 6 000 employees in total in the organization. The company performs bioequivalence studies for generic products manufactured by their own company.

History of WHO and/or regulatory agency inspections

The site has undergone the following compliance inspections:

1. WHO, 6 to 7 April 2006
2. WHO, 25 to 26 May 2006
3. WHO, 22 January 2007
4. WHO, 28 April 2007
5. WHO, 20 September 2007
6. USFDA, 10 to 13 March 2008
7. ANVISA, 24 to 28 March 2008
8. WHO, 25 to 26 February 2009
9. USFDA, 12 to 16 October 2009
10. USFDA, 1 to 7 July 2010
11. MCC, 8 to 13 November 2010
12. CDSCO, 22 June 2011
13. USFDA 7 to 14 November 2011
14. UK MHRA, 29 October to 2 November 2012
15. GLP compliance monitoring authority of Thailand, 28 to 30 November 2012

Focus of the inspection

The inspection focused on the bio-equivalence study conducted for the product TB231, MA91, HA564, HA561. The inspection covered all the sections of the WHO GCP and GLP texts, including the WHO guidance for organizations performing in vivo bioequivalence studies.

Inspected Areas

Day 1

Clinical (TB231)

- Contracts and structure of the company
- Proof of insurance (National Insurance Company Ltd)
- Study protocol, delegation of duties and protocol training attendance form
- Application letter to the independent ethics committee (IEC) on the submission of study protocol and related documents (Informed Consent Form (ICF) version 2 in English, ICF version 1 in Hindi and Marathi, Curriculum Vitae (CV) of the Principal Investigator (PI) and Literature) dated 16 January 2010
- Application letter dated 5 February 2010 to the IEC on the submission of Certificate of Analysis (for which approval was withhold) and amended protocol
- IEC (composition, minutes of meeting, CVs of IEC members, etc.)
- Signed ICF for all subjects

Bioanalytical (HA564/561 and MA91)

- Computer access privileges (Windows and Analyst)
- Audit trails (Instrument, Project and Results)
- Verification of the adequacy integrations
- Verification of acceptance and rejection criteria applied for runs submitted in study dossiers
- Verification of subject sample concentrations vs. values submitted in the bioanalytical report and dossier

Day 2

Clinical (TB231)

- SOP for screening of enrolled volunteers (BEQ/CL/SOP-003-11)
- Monitoring reports (pre-study monitoring, dosing day of Period-I, dosing day of Period-II and Post study visit)
- CRFs for subjects numbers 1, 2, 37, 38 and 39 (general screening, study specific screening for Period-I and II and post study safety assessment)
- Adverse event report of subject number 39
- SOP on dosing
- SAS copy of randomization verified against dosing
- Facility tour of the ground floor 40 bed clinical facility (volunteer registration and screening, debriefing room, examination room, ECGs, X-ray films, enrolment, CPU, alarms, phlebotomy area, centrifugation area, deep and ultra-deep freezers for storage of plasma, ICU (equipment and emergency medicines), oxygen cylinders, calibration of related instruments.)
- Database for volunteers (not shared, including about 11 000 volunteers, including 2 000-3 000 active, not OVIS).
- Biometric system
- Pathology laboratory (used for urine analysis, biochemistry, haematology, accreditation by NABL)
- Pharmacy (reconciliation for the investigational products)

Bioanalytical (MA91)

- Verification of rejected runs and sample reanalysis
- Failure investigations
- Verification of calculation of subject sample concentrations
- In process and retrospective quality assurance audits
- QA training, training program and job descriptions
- Sample preparations and calculations of concentrations (reference standard CofAs, weighing records, stock solutions, dilutions, spikings, processing, cross check against concentrations entered in Analyst for CCs and QCs.)
- Blank plasma matrix (sourcing, pooling and storage)
- Pipette calibration and use

Day 3

- Archives
- Statistical analysis for MA91
- Clinical facility on the 3rd floor
- Process for data transfer from bioanalytical to report writing to statistical
- QA checks on data transfers to statistics and report writing (either one)
- Deep freezer logbooks
- MHRA report
- Bioanalysis for TB231
- Bioanalytical summaries for:
 - BEQ BEQ-488-RI(F)-2009 (TB231)
 - BEQ-641-AL(F)-2010 (MA091)
- Organogram of bio-analytical lab
- SOP for re-integration and chromatography acceptance criteria (BEQ/AL/SOP-014/07)
- CV of Head-BAL, Mr. Mandar Mote
- SOP for procurement, handling and storage of biological matrix
- Review of quality manual version 11
- Signature list of BE staff
- Method validation SOP (BEQ/AL/SOP-012/14)
- Method validation of Rifampicin and desacetyl Rifampicin (started 25/9/2008 and completed on 4/10/2008) on Shimadzu LC2010 HPLC system BEQ-AL-LC-07 and LC-06
- Method validation of Isoniazid started 26/8/2008 and completed on 02/9/2008 BEQ-AL-LC-04 and LC-05
- Inspection of BAL included calibration of auto pipette (BEQ-GN-AP-83) and auto pipette used in RIF-107/01 dated 25/9/2008, balance calibration, reference standards
- Verification of audit trail settings and use of smoothing factor
- Verification of LQC, MQC, HQC, CC, sample analysis and repeats
- ISR analysis
- Transfer of bio-analytical data / result table to excel sheet and checks by QC (100%) and QA (random) before transferred for Pk analysis (SAS9.2)
- Certificate of analysis for rifampicin, desacetyl rifampicin, isoniazid, carbamazepine and metronidazole
- Centrifuges 11 and 12 used for storage of samples
- Sample analysis from subject 1 to 24 on LC-06, subject from 25 to 26 on LC-15 and from 27 to 40 on LC-06

Day 4

- Review of clinical data for TB231 study (Protocol, IEC meeting minutes, Certificates of analyses for IPs, Line clearance forms, etc.)
- Review of bioanalytical summaries of the order of sequences performed for:
 - BEQ-134-NEVI-2007 (HA465)
 - BEQ-514-LT(F)-2010 (HA522, HA514)
 - BEQ-515-ET(F)-2010 (HA561, HA564)

- BEQ-641-AL(F)-2010 (MA091)
- BEQ-667-RIFA-2011 (TB259)
- BEQ-701-EET(F)-2011 (HA562)
- BEQ-806-LR(F)-2011 (HA574)
- Review of instrument logbooks for selected portions of the above studies
- SOP on incurred bioanalytical samples reanalysis
- Verification of calibration concentrations and quality controls for desacetyl rifampicin and rifampicin
- Preparation of spiked calibration curve standards and QCs
- Matrix (plasma) sourced from six sources
- SOP on blood collection for blank plasma/serum study
- Slope verification from calibration curve to Table 1A
- Long term stability at -50°C for 70 days and 243 days
- Auto sampler stability study
- Closing meeting

2.1. PROVISIONS AND PREREQUISITES FOR A CLINICAL TRIAL

All of the provisions and prerequisites for a clinical trial were met in general for the studies that were seen (TB231 and MA91).

Clinical studies were conducted in 2 different clinics for the 2 studies reviewed. The company had a total of 184 available beds, some of which were at another facility but were not inspected as they had not been used for the studies under inspection. The clinics were found to be in generally acceptable condition.

2.2. THE PROTOCOL

Protocols were found to be acceptable in general for the studies reviewed (TB231 and MA91).

2.3. PROTECTION OF TRIAL SUBJECTS

The clauses from the Declaration of Helsinki were given during informed consent according to the documentation that was seen however a recommendation was made to clearly display it in the screening and informed consent areas.

The Independent Ethics Committee composition and organization followed the necessary requirements. However, issues were noted with regards to the amount of time given to the ethics committee for review.

The clinical pharmacology units were found to be adequate in general for the subjects.

Beds and toilets were verified to be equipped with alarms for the clinic on the ground floor. The alarms were linked to a panel which allowed to retrace to which area the alarm came from.

Issues were raised with regards to the potential for blood-borne pathogen transmission, but were resolved in the company CAPAs. This area was considered to be acceptable overall.

2.4. RESPONSIBILITIES OF THE INVESTIGATOR

The responsibilities of the investigator were considered to be fulfilled in general.

2.5. RESPONSIBILITIES OF THE SPONSOR

The sponsor was Macleods and hence the sponsor was the same commercial entity as the investigator. The applicable responsibilities were in general fulfilled.

2.6. RESPONSIBILITIES OF THE MONITOR

Monitoring could not be performed independently since the BE site was part of the same commercial entity as the Applicant for the products under study. The monitoring of the studies were done by the staff of the medical department of BE centre. In general, these were found acceptable.

2.7. MONITORING OF SAFETY

No issues were found regarding the handling, recording and reporting of adverse events.

2.8. RECORD-KEEPING AND HANDLING OF DATA

Responsibilities of the investigator and sponsor were generally fulfilled with regards to record keeping and data handling. The on-site archive, although dated, was equipped with a fire extinguishing system and a steel door. Documents were tracked using a logbook for the removal and return of documents and personnel entry was also entered in a logbook. The documents were found to be in adequate order.

2.9. STATISTICS AND CALCULATIONS

Statistical analyses were performed using the SAS program. No issues of concern were found upon examination of the statistical data for MA91 and TB231.

2.10. HANDLING OF AND ACCOUNTABILITY FOR PHARMACEUTICAL PRODUCTS

This area was considered to be acceptable overall.

2.11. ROLE OF THE DRUG REGULATORY AUTHORITY

The trials under inspection had been authorized by the CDSCO. A CDSCO inspector was present during the WHO inspection. The sites of the company had been previously inspected.

2.12. QUALITY ASSURANCE FOR THE CONDUCT OF A CLINICAL TRIAL

This area was considered to be satisfactory overall.

II. BIOANALYTICAL PART

1. SUMMARY OF BIOANALYSES

a. BEQ 515 ET(F) 2010 Study (HA564/ HA561)

The bioanalytical portion of the study was done in 2 separate portions, one for emtricitabine, and one for tenofovir due to the differences in solubility and hydrophobicity of the 2 APIs and detector saturation issues.

For emtricitabine: abacavir internal standard was used (mother ion was 287.200 Da and daughter ion was 191.200 Da, while emtricitabine was set to a mother ion of 248.200 Da and a daughter ion of 130.100 Da respectively). The emtricitabine study data was verified on the API 3200 HPLC-MS/MS 06 system. Another system was used for tenofovir.

b. BEQ-488-RI(F)-2009 (TB231)

The bioanalytical portion of the study was done for Rifampicin using internal standard carbamazepine. The subject sample analysis was performed on two separate HPLC systems (06 and 15) due to the non-availability of the first HPLC system.

The inspector verified the HPLC MS/MS system used for the study sample analysis. Issues were raised with regards to the smoothing factor used but in general, this was not seen to have a significant impact on test results and the bioanalysis of Rifampicin was found acceptable.

2. OVERALL HANDLING AND PROTECTION OF ELECTRONIC TRIAL DATA

Electronic data was stored in a central server used by the entire company. Analyst software was used for HPLC MS/MS.

User access privileges were defined for both Windows and Analyst software. Time and date was locked and was accessible only to the IT Administrator. Only 2 persons at the site had administrator password privileges.

User access rights in Analyst software were set on a similar basis. Supervisors were only able to review data (most restrictive).

3. AUDIT TRAILS

HA561/HA564: Instrument, project and results audit trails were reviewed in detail.

Instrument audit trails were complete. There were no gaps in the audit trails seen (approximately 2 year period seen).

Project audit trail checks were performed in detail.

Conclusion: project audit trail files were available without any gaps for the entire time period spanning from 10 June to 22 June 2011.

Similar checks were performed for TB231. The audit trail files for the project TB231 were available without any gaps or entries of concern.

4. INSTRUMENT CALIBRATION

Calibration of the instrument which was used for MA91 and HA561/HA564, was reviewed in detail.

Software validation was last performed in September 2010. Results were compared to SAS output. This was acceptable in general.

5. PREPARATIONS AND THEIR STORAGE

Stock solutions

Stock solution for artemether standard used in the MA91 study could be stored up to 8 days on the refrigerator according to the CRO. The refrigerator stability was supported with adequate analysis.

Blank plasma matrix

The blank plasma was seen to be collected from volunteers at the Macleods clinical facilities and was stored in 15 volumes of 10 mL each per volunteer, as documented by the matrix received consumption logbooks. The nature of the anticoagulant and its concentration was documented and was collected in house. Pooling was documented in the preparations specific to the study and completed by another set of Matrix received/consumption log book records which showed the quantity consumed for a particular study. Blank plasma was stored in the -20°C deep freezer.

6. CORRECTNESS OF DATA SUBMITTED IN WHO DOSSIER AND RELIABILITY OF BIOANALYTICAL DATA

Apart from minor differences in subject plasma concentrations due to the smoothing factor, which are deemed to be cancelled out as these are applied to both periods, the data submitted was found to be correct and reliable overall.

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-488-RI(F)-2009 (TB231), BEQ-641-AL(F)-2010 (MA091) and BEQ-515-ET(F)-2010 (HJA561, HA564) were considered to have been conducted at an acceptable level of compliance with WHO GCP and GLP at Macleods Pharmaceuticals Limited, Bioequivalence Department, G-2, Mahakali Caves Road, Shanti Nagar (Andheri East), Mumbai, 400 093.

Furthermore, according to the spot-checks that were made, no issues of significant concern were found with regards to the following studies:

BEQ-134-NEVI-2007 (HA465)

BEQ-514-LT(F)-2010 (HA522, HA514)

BEQ-667-RIFA-2011 (TB259)

BEQ-701-EET(F)-2011 (HA562)
BEQ-806-LR(F)-2011 (HA574)

However, if warranted, a further check may be performed during the next inspections.

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.