



WHO PUBLIC INSPECTION REPORT

(WHOPIR)

Contract Research Organization

Part 1: General information

WHO product numbers covered by the inspection	HA500 (Tenofovir disoproxil fumarate, Emtricitabine and Efavirenz Tablets containing 300 mg Tenofovir disoproxil fumarate, 200 mg Emtricitabine and 600 mg Efavirenz)
Study number	BBRC/US/08/001
Title of the study	A randomized, balanced, open label, single dose, two-treatment, two-period, two-sequence, crossover, truncated bioequivalence study comparing the Fixed Dose Combination (FDC) of Tenofovir disoproxil fumarate, Emtricitabine and Efavirenz Tablets containing 300 mg Tenofovir disoproxil fumarate, 200 mg Emtricitabine and 600 mg Efavirenz of the test product with the reference product (Tenofovir disoproxil fumarate, Emtricitabine and Efavirenz) Tablets containing 300 mg Tenofovir disoproxil fumarate, 200 mg Emtricitabine and 600 mg Efavirenz in 72 healthy adult human subjects under fasting conditions.
Clinical Part of the study: Name and address of the organization	Bombay Bioresearch Centre (BBRC) Plot N° 35, Deonar Ancillary Industrial Plots, Govandi, Mumbai - 400 043, India
Date of inspection	18 - 20 May 2011

Part 2: Summary

General information about the site(s)

BBRC started their clinical and bioanalytical operations for bioavailability / bioequivalence trials in November 2005. The CRO is located in a building built for purpose. There were 51 persons employed by BBRC at the time of the inspection according to the presentation made during the opening meeting. This figure included employees from both the clinical pharmacology unit, the bioanalytical laboratory, data processing and quality assurance. BBRC had completed 141 clinical pharmacology projects for regulatory submissions according to the presentation.

The clinical pharmacology unit was located on the ground floor of the building and the bioanalytical laboratory as well as quality assurance, documentation, data processing cell and the pharmacy were on the 1st floor. There was a total of 72 beds, divided in two units of 36 beds each allowing for two trials to be conducted simultaneously. There was a CCTV network through the



unit. The necessary fire escapes, access controls and alarm systems were present throughout the premises.

History of WHO and/or regulatory agency inspections

This CRO was previously inspected in January and April 2008, in June-July 2009 and in October 2010 by teams of inspectors from WHO. This was the fifth WHO inspection at this site. The inspection in 2009 resulted in a Notice of Concern being issued to the site by the WHO on 21 July 2009. The inspection in 2010 found the site to be compliant for the study inspected.

The site was previously authorized by the Indian regulatory authority and by the following national drug regulatory authorities:

- MCC (South Africa) in 2007 and 2010.
- EMEA in 2007.
- AGES (Austria).
- MEDSAFE (New Zealand).
- ANVISA (Brazil) in 2009.
- FDA (USA) in 2009 and 2010.
- MHRA (UK) in 2010.
- TGA (Australia).

Focus of the inspection

The inspection focused on the bioequivalence study performed on HA500, a product in the WHO prequalification pipeline (study No. BBRC/US/08/001). The study was designed as a balanced, open-label, randomized, two-treatment, two-period, two-sequence, single dose, cross-over truncated bioequivalence study in healthy adult human subjects under fasting conditions.

Inspected Areas

Day 1

After introductions and a brief company presentation, inspectors proceeded to the review of the following documents:

- Contract between the sponsor and BBRC
- Archival and retrieval SOP
- SOP on handling and reporting of adverse events. According to this SOP, the principal investigator is responsible for reporting adverse events within 7 days. This was different from what was reported by the company, that the sponsor was responsible for reporting serious adverse events to the authorities. (No serious adverse events have ever been reported to the DCGI)
- List and signatures of personnel involved in the study for both Period I and Period II, dated 26/04/2008 and 27/04/2008 respectively. There were 43 members of staff participating in the first period (signed 27/04/2008) and 54 in the second period (signed 29/05/2008). There were 10 phlebotomists for Period I and 14 for Period II. All of the staff was declared to be employed full time by the company

- Personal training records for principal investigator
- Duty delegation for screening and period I check-in and dosing
- SOP on Preparation of bioavailability / bioequivalence study protocol
- Agreement between BBRC and independent ethics committee and relevant authorization agreement
- Informed consent form
- Translator qualifications
- Clinical trial liability insurance
- ICF subject information sheets for screening and for the study
- Purchase import license for the reference product
- Questions and queries from subjects
- Subject declarations (willing to participate in study)
- Independent ethics committee (IEC) procedures on "formation and operation of an independent ethics committee"
- Minutes of IEC meetings
- CRF and related communications to the IEC
- Methods of recruitment
- Subject recruitment notice
- Records of payments made to the independent ethics committee
- Case report forms for study subjects
- Case report forms for selected subjects from other studies
- Registration program for biometric identification
- Pre-study calculations for the number of subjects to be included in the study

Day 2

After giving the observations from the previous day, inspectors proceeded with the review of the following documents:

- Screening sheets
- Verification of subject weight relative to inclusion criteria
- Cross-verification of age and weight from the demographic data relative to the report
- Verification of age records
- SOP on measuring and recording the vital signs
- SOP on measurement of blood pressure
- Examination of subject screening physical and laboratory findings
- Randomization printouts
- Sequence of check-in vs. randomization
- Case report forms for study subjects
- Times of sampling
- Test records for screening
- Verification of procedure being used for subject check-in.
- Record of dosing for phase II
- Record of drug tests
- Verification of tests performed post-period II (e.g., measurement of weight)

Inspectors then proceeded to visit the CPUs on the ground floor. This included a visit of the registration room, the room where informed consent was obtained, the vital signs room and



equipment. Sample processing rooms and the deep freezer areas were visited. The two adjacent rooms were verified to contain 36 beds each and were adequately segregated from each other.

The system which was used to register each subject and to perform biometric identification was verified. Validation/qualification of the system's ability to identify subjects by fingerprint could not be shown to inspectors.

The intensive care unit was visited. The list of medicines was verified to be up to date. The company had a system in place to ensure that medicines were discarded when expired.

Day 3

After giving the observations from the previous day, inspectors proceeded to the review of the following documents:

- Verification of clinical diagnostic reports for subjects
- CRFs
- ECGs.
- Custody of subject belongings sheet and subject check-in and check-out
- SOP on subject check in and check-out
- Logbooks for the deep-freezers
- Calibration records for the PT sensors for the deep freezers
- Instruction sheet for portable alcohol breath tester
- Deep freezer plasma transfer records
- SOP on transport of plasma samples to outside laboratory or to the sponsor.
- QA audit report
- QA note regarding accountability of investigational product.
- Monitor report.

After lunch, inspectors also performed a visit of the following areas on the 2nd floor:

-Pharmacy (included entrance procedures and logbooks, line clearance and dispensing, temperature monitoring logbooks for investigational product refrigerators - and verified the number of reference tablets remaining in stock against the records).

-Archive facilities (associated procedures and logbooks were consulted.)

2.1. PROVISIONS AND PREREQUISITES FOR A CLINICAL TRIAL

All of the necessary prerequisites were considered to be fulfilled.

2.2. THE PROTOCOL

The protocol contained all of the necessary details except for minor issues which will be resolved for future studies according to the company's corrective and preventive actions.

2.3. PROTECTION OF TRIAL SUBJECTS

The protocol contained all of the necessary details except for minor issues which were resolved in the company's corrective and preventive actions.



2.4. RESPONSIBILITIES OF THE INVESTIGATOR

Responsibilities of the investigator covered all of the elements prescribed by the WHO GCPs.

2.5. RESPONSIBILITIES OF THE SPONSOR

The sponsor fulfilled all of its necessary responsibilities.

2.6. RESPONSIBILITIES OF THE MONITOR

Monitoring activities were undertaken by the sponsor. Monitoring reports from both before and during the study were presented.

2.7. MONITORING OF SAFETY

The CRO handled and recorded adverse events. The study sponsor was responsible for the reporting of adverse events. Observations were raised in this regard. According to the company's CAPAs, now both the sponsor and BBRC will be responsible for the reporting of adverse events.

2.8. RECORD-KEEPING AND HANDLING OF DATA

Data was archived in a fire-proof air-conditioned area for periods defined by the study protocols and applicable regulations (e.g., 5 years for BBRC/US/008/01). There was no monitoring of temperature and humidity.

2.9. STATISTICS AND CALCULATIONS

Statistical analyses were performed by an outside contractor and were therefore not the object of this inspection.

2.10. HANDLING OF AND ACCOUNTABILITY FOR PHARMACEUTICAL PRODUCTS

The sponsor was responsible for providing both the test and reference product to BBRC. BBRC performed accountability of the product after the study.



2.11. ROLE OF THE DRUG REGULATORY AUTHORITY

Not examined during this inspection.

2.12. QUALITY ASSURANCE FOR THE CONDUCT OF A CLINICAL TRIAL

Quality assurance fulfilled its responsibilities. Minor issues were nevertheless noted regarding records of the performance of its functions in some cases. Acceptable preventive actions were taken for future studies performed at this site.

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 clinical part of study No. BBRC/US/08/01 was considered to have been conducted at an acceptable level of compliance with WHO GCP at *Bombay Bioresearch Center (BBRC), Plot N° 35, Deonar Ancillary Industrial Plots, Govandi 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.