



Prequalification of Medicines Programme

WHO PUBLIC INSPECTION REPORT

Bio-Equivalence Study

Part 1: General information

WHO product numbers covered by the inspection	Efavirenz / Lamivudine / Tenofovir Disoproxil Fumarate 600/300/300mg tablets
Study number	650/08
Title of the study	An Open Label, Balanced, Randomized, Two-treatment, Two-period, Two-sequence, Single Dose, Crossover, Bioequivalence Study of Fixed Dose Combination of Tenofovir Disoproxil Fumarate 300mg, Lamivudine 300mg and Efavirenz 600mg Tablets of [REDACTED] comparing with that of Viread [®] (containing Tenofovir Disoproxil Fumarate) 300 mg tablets of Gilead Sciences, Inc. Foster City, CA 94404, Made in Canada, EPIVIR [®] (containing Lamivudine) 300 mg tablets of GlaxoSmithKline Research Triangle Park, NC 27709, Made in England, manufactured under agreement from Shire pharmaceuticals Group Plc, Basingstoke, UK and SUSTIVA [®] (containing Efavirenz) 600 mg tablets of Bristol-Myers Squibb Company, Princeton, NJ 08543 USA in Healthy, Adult, Human Subjects under Fasting Conditions
Clinical Part of the study: Name and address of the organization	Bioserve Clinical Research (P) Ltd 6-56/6/1A, Opp.IDPL Factory, Balanagar, Hyderabad 500 037, A.P. India
Name and email address of contact person (Clinical part)	Dr VVS Shiv Prasad info@bioserve.co.in
Date of inspection	19 May 2010

Part 2: Summary

The purpose of the inspection was to inspect the clinical part of the abovementioned bioequivalence study performed at Bioserve Clinical Research (P) Ltd (hereafter referred to as Bioserve), including the examination of related source data for Efavirenz / Lamivudine / Tenofovir Disoproxil Fumarate 600/300/300mg tablets, and to evaluate whether the study was conducted in compliance with the protocol and Good Clinical Practices (GCP).

General information about the site

Bioserve, located in 6-56/6/1A, Opp.IDPL Factory, Balanagar, Hyderabad 500 037, A.P. India was inspected on the above-mentioned date. See below for more information.

History of WHO and/or regulatory agency inspections

This was the first inspection conducted by WHO at this site. It was however previously inspected by:

- Indian FDA 2009
- US FDA - 2008 and 2009
- UK MHRA - 2010

Focus of the inspection

The inspection focused on the bio-equivalence study conducted for the product Efavirenz / Lamivudine / Tenofovir Disoproxil Fumarate 600/300/300mg tablets. The inspection covered the relevant sections of the WHO GCP related texts, including the WHO guidance for organizations performing in vivo bioequivalence studies.

Inspected Areas

After arrival, the inspectors exchanged business cards and introduced the PQ program and themselves to the company representatives. The personnel of the CRO introduced themselves and provided a presentation on the activities of the site. They informed the inspectors that Bioserve was established in December 2004 and that it started operations in 2005. Key personnel included:

- SS Redy - Managing Director
- VVS Shiv Prasad - Executive Director
- C Joshi - Head QA and RA
- R Radjagobal - Study director

Services offered by Bioserve included BE studies, food effect studies, Drug-drug interactions, multi dose state studies and pharmacoscintographic imaging. The bioanalytical services included method development, method validation and bio analysis.

It also provided services including medical writing, PK and statistical analysis and report preparation.

The clinical area was provided with 92 beds (spread over 3 floors). One unit was equipped with 58 beds and one with 34 beds. There was a 4 bed emergency room, a pharmacy, sample collection and processing area and a storage area.

The admin offices, pharmacy, QA, screening and enrollment, clinical laboratory and PK and statistical analysis areas were located on the ground floor, with clinical unit I and the emergency room on the first floor. The second floor housed clinical unit II, sample storage areas and the bio-analytical laboratory.

Chest X-rays and ECGs were taken on site. A radiologist was contracted to review the films.

More than a hundred people were employed by the CRO at the time of the inspection. The pharmacy was under the control of the PK unit at the time of the study. There were three units reporting to the study director at the time. These were clinical, bioanalytical and PK. The QA unit was separate. (QC was introduced in July 2009).

The CRO performed about 60 to 70 studies per year. Sponsors were mainly from India (75%), USA and Europe. The CRO and inspectors discussed volunteer recruitment. There were about 7000 volunteers in the data bank. Informed consent (IC) was obtained for general screening (which was valid for 28 days), and study specific IC was obtained before enrollment to a study.

The inspectors were informed that the CRO used WinNonlin and SAS for pharmacokinetic analysis. This as well as the bio-analytical laboratory was not inspected.

The inspection plan was presented to the organization and agreed upon. The following documents were reviewed and / or the activity was explained:

- Current organization chart and responsibilities
- Job descriptions
- SOP: Training of personnel (Induction, job specific, refreshment and study specific)
- List of delegation of tasks for the study, and study specific training
- Employee files with Curriculum vitae, job descriptions and training records
- Material used in providing training to employees (GCP)
- SOP for deviations
- Trial master file
- Study Protocol P-650/08 Revision 00 (dated and signed 22 August 2008)
- CRF for the study
- Request for IRB decision sent on 25 August located in Hyderabad
- Minutes of the meeting of the IRB on 28 August 2008

- SOPs for IRB
- Agreement between the sponsor and CRO
- Correspondence between the sponsor and CRO (study specific)
- IMP COAs
- Drug receipt record
- T licences (number T-558/06 and T-2598/06)
- Drug dispensing record
- Drug reconciliation
- Insurance
- Randomization schedule (against dosing forms for all subjects)
- CRFs for selected subjects
- Dosing sheets for all PI and P II
- ICFs
- Allotment (subject number allocation) details list for subjects
- Chest X ray films for selected subjects
- Tests for drug abuse for selected subjects
- Tests for HIV for selected subjects
- Dosing plan
- Test kits for HIV and drug abuse including import license
- Blood sample collection times / sheets for selected subjects
- Monitor report P I and P II by the sponsor representative
- SOP for deviations (protocol and procedures) and summary of deviations
- Deviation BA/001/08 and related temperature records for the deep freezer CU/FZ02, as well as daily logs (data logger and display)
- Dispatch record for samples of P I and P II (aliquot 1 and 2). (It was noted that the one data logger (box 3 of 4) was not started, therefore the temperature monitoring of the samples in this box was not done).
- Dispatch record for samples of P I and P II (aliquot 3)

In the afternoon, the clinical unit, pharmacy, archives and related areas were inspected. These included:

- Pharmacy and pharmacy records and procedures including SOPs, line clearance, dispensing record, temperature monitoring records
- Screening area
- Area for obtaining informed consent
- Medical examination
- Sample collection
- CPU areas including rest area, dosing, sample collection and processing area
- Dining area
- Wash rooms and toilet facilities.

THE PROTOCOL

The Protocol was found in general to be acceptable.

PROTECTION OF TRIAL SUBJECTS

Protection of the volunteers was found to be acceptable, Helsinki declaration was followed, informed consents were within the requirements. Follow-up could be improved (see observations below).

RESPONSIBILITIES OF THE INVESTIGATOR

Responsibilities of the investigator were defined, selection of subjects were done in accordance with defined procedures. Subjects were properly informed, ICFs were signed by the volunteers. The study protocol was reviewed and approved by the ethics committee. Adverse reactions were recorded. The Monitor performed a site audit prior to using the CRO and monitoring reports during were available for period I and period II.

Pharmaceutical products were handled appropriately.

The trial site had adequate premises.

RESPONSIBILITIES OF THE SPONSOR

The activity inspected was found to be in general, acceptable. The trial was performed in accordance with the protocol. Trial management and handling of data was properly carried out. Required standard procedures were available. Subjects received compensation in accordance with the protocol.

RESPONSIBILITIES OF THE MONITOR

Case report forms were appropriate.

MONITORING OF SAFETY

Subject safety was monitored, adverse events were reported and subjects received necessary treatment.

RECORD-KEEPING AND HANDLING OF DATA

Handling of data was considered acceptable. Study records were stored in the CRO archive.

HANDLING OF AND ACCOUNTABILITY FOR PHARMACEUTICAL PRODUCTS

Supply of products and storage of products as well as labeling and packaging were found in general to be acceptable. Dispensing was done in accordance with GMP principles.

There was evidence and records that the dispensing had been done under conditions avoiding possible mix up.

QUALITY ASSURANCE FOR THE CONDUCT OF A CLINICAL TRIAL

The quality assurance was consistent and acceptable.

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, the clinical part of study 650/08 "An open label, balanced, randomized, two treatment, two sequence, single dose, crossover, bioequivalence study of fixed dose combination of Tenofovir Disoproxil Fumarate 300mg, Lamivudine 300mg and Efavirenz 600mg tablets of [REDACTED] comparing with that of Viread 300mg tablets of Gilead Sciences Inc Foster City CA 94404, made in Canada, Epivir 300mg tablets of GSK, England, manufactured under agreement from Shire Pharmaceuticals, UK and Sustiva 600mg tablets of BMS, USA in healthy, adult, human subjects under fasting conditions", conducted Bioserve Clinical Research (P) Ltd, 6-56/6/1A, Opp. IDPL Factory, Balanagar, Hyderabad 500 037, A.P., India was considered to have been conducted at an acceptable level of compliance with WHO GCP.

Part 4: Reference documents

1. Guidelines for good clinical practice (GCP) for trials on pharmaceutical products. *WHO Expert Committee on the Use of Essential Drugs. Sixth Report.* Geneva, World Health Organization, 1995 (WHO Technical Report Series, No. 850), Annex 3
http://whqlibdoc.who.int/trs/WHO_TRS_850.pdf
2. OECD Principles of Good Laboratory Practice (GLP). [C(97)186/Final], 1997
http://www.oecd.org/document/63/0,2340,en_2649_34381_2346175_1_1_1_1,00.html
3. Additional guidance for organizations performing in vivo bioequivalence studies. WHO Technical Report Series, No. 937, 2006, Annex 9 www.who.int/prequal