



**WHO PUBLIC INSPECTION REPORT
(WHOPIR)
Bio-Equivalence Study (CRO)**

Part 1: General information

WHO product numbers covered by the inspection	HA430
Study number	081-06
Title of the study	A randomized, open label, two-treatment, two-period, two-sequence, single-dose, crossover oral bioequivalence study in normal, healthy, adult, human subjects under fasting condition.
Clinical Part of the study: Name and address of the organization	GVK Biosciences Pvt.Ltd Clinical Research and Development 7th Floor, Swarna Jayanthi Commercial Complex Ameerpret 500 038 Hyderabad India
Bio-analytical laboratory: Name and address	GVK Biosciences Pvt.Ltd Clinical Research and Development 7th Floor, Swarna Jayanthi Commercial Complex Ameerpret 500 038 Hyderabad India
Name and address of the Sponsor	Emcure Pharmaceuticals Limited Plot No P-2, IT-BT Park Phase II MIDC, Hinjwadi Pune 411 057 India
Date of inspection	21-23 April 2009

Part 2: Summary

The purpose of the inspection was to inspect the clinical and the bioanalytical part of the bioequivalence study performed at GVK Biosciences Pvt.Ltd, including the examination of related source data for the product Efavirenz 600 mg tablet, and to evaluate whether the study was conducted in compliance with the protocol, Good Clinical Practices (GCP) and Good Laboratory Practices (GLP) where applicable.

General information about the site

GVK Biosciences Pvt.Ltd (GVK), located in Hyderabad (India) was inspected on the above-mentioned dates.

GVK started its activity as a Contract Research Organization in November 2003 and was conducting different types of bioavailability and bioequivalence studies.

The premises were situated on the seventh floor of the building located in Hyderabad and consisted of:

- four independent access controlled clinics with 144 beds
- 8 station phlebotomy rooms, clinical examination rooms, emergency room and equipment, entertainment room, dining area with separate access for caterers, separate men's and women's toilets
- Sample handling and storage facilities, including sample separation and interim storage as well as a bioanalytical laboratory with the following instruments:
 - 13 LC/MS/MS instruments
 - 2 API 2000
 - 3 API 3000
 - 3 API 3200
 - 4 API 4000
 - One Waters- Quattro premier XE
 - HPLCs with Fluorescence, UV detectors

The CRO employed 228 employees from which 117 were permanent staff and 111 on contract basis.

History of WHO and/or regulatory agency inspections

This Prequalification Programme inspection was the third inspection conducted by WHO at GVK site. The GVK site was also previously inspected by:

- USFDA (USA)
- ANVISA (Brasil)
- AFSSAPS (France)
- MoH (Turkey)

The Clinical Laboratory was ISO 15189:2007 certified.

Focus of the inspection

The inspection focused on the bio-equivalence study conducted for the product HA430 Efavirenz 600 mg tablet. 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

A tour was made to visit the bioanalytical facility and clinical facilities which included:

- Archive
- Pre screening area
- Enrolment room
- Clinical laboratory
- Clinic No 3
 - Change room
 - Intensive Care Unit (ICU)
 - Ward
 - Entertainment room
 - Phlebotomy room
 - Sample separation room
 - Dining room
 - Drug store pharmacy

Documents related to the clinical and bioanalytical parts of the study were reviewed during the inspection, for example:

- Ethics committee approval
- ICF
- Protocol agreement
- Insurance
- List of volunteers signatures
- Monitor's report
- Protocol training
- GCP training file for Mr. Shekhar
- CRF for subjects 33 to 37, including the laboratory results, sample analyses, chromatograms, back calculations, x rays, ECGs and dosing
- Documents related to the method validation and study analysis (preparation of stock solution, chromatograms, logbooks and forms).

2.1 PROVISIONS AND PREREQUISITES FOR A CLINICAL TRIAL

There was no evidence that the sponsor requested GVK to design the protocol.

2.2 THE PROTOCOL

The Protocol was found in general to be acceptable. The protocol was designed and approved by the EC after being formally approved by the sponsor.

2.3 PROTECTION OF TRIAL SUBJECTS

Protection of the volunteers in general was found to be acceptable, Helsinki declaration was followed.

The information on the pro rata temporis compensation given in the consent form was ambiguous. The term pro rata was used in the ICF but followed by the indication "after study completed" which was contradictory.

The copy of ICF given to the subjects masked the name of the sponsor . The language and level of complexity was not adequate for the volunteers, for example increased ALT, GGT, AST etc. There was no proof that the time given to the subjects for the review of the ICF was sufficient.

2.4 RESPONSIBILITIES OF THE INVESTIGATOR

The delegation of responsibilities from the investigator to the CRO was not detailed enough. Selection of subjects was done in accordance with defined procedures. ICFs were signed by the volunteers. The study protocol was reviewed and approved by the ethics committee. Adverse reactions were recorded.

Pharmaceutical products were handled appropriately.

The trial site in general had adequate premises. However the change room in clinic No 3 was not adequate. The room was used for storage of log books used to record the access of people to the facility.

2.5. 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.

2.6. RESPONSIBILITIES OF THE MONITOR

There was only one monitoring visit performed (see observations below). Case report forms were appropriate.

2.7. MONITORING OF SAFETY

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

2.8. RECORD-KEEPING AND HANDLING OF DATA

Handling of data was considered acceptable. Study records were stored accordingly. Security related log books were not properly archived. (They were stored in the changing room).

2.9. STATISTICS AND CALCULATIONS

Statistics and calculations inspected were found in general to be acceptable in order to guarantee data integrity.

2.10. 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 clear evidence and records that the dispensing had been done under conditions avoiding possible mix ups.

2.11. ROLE OF THE DRUG REGULATORY AUTHORITY

Not inspected.

2.12. QUALITY ASSURANCE FOR THE CONDUCT OF A CLINICAL TRIAL

The quality assurance was consistent and comprehensive.

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 study conducted by GVK Biosciences Pvt. Ltd Clinical Research and Development, 7th Floor, Swarna Jayanthi Commercial Complex Ameerpet 500 038 Hyderabad India was considered to have been conducted at an acceptable level of compliance with WHO GCP and GLP.

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 2 years, provided that the outcome of any inspection conducted during this period is positive.