



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

Part 1: General information

WHO product numbers covered by the inspection	HA 417 (<i>clinical part of the study</i>) HA 438 <i>Efavirenz (clinical and BA part of the study)</i>
Study numbers	US/AHD/07/003 US/AHD/07/001
Title of the study	HA 417 A Randomized, Open Label, Two-Period, Two-Treatment, Two-Sequence Single Dose Crossover Bioequivalence Study in Normal Healthy Male Subjects Under Fasting Condition HA 438 A Randomized, Single Dose, Open Label, Bioequivalence Study in Normal Healthy Human Subjects Under Fasting Condition
Clinical Part of the studies: Name and address of the organization	<u>HA 417</u> <u>HA 438</u> Accutest Research Laboratories (I) Pvt. Ltd. 4 th floor; The Grand Monarch, Near Seema Hall; Anand Nagar Road, Satellite, Ahmedabad - 380015, India
Bio-analytical laboratory: Name and address	<u>HA 438</u> Accutest Research Laboratories (I) Pvt. Ltd. 4 th floor; The Grand Monarch, Near Seema Hall; Anand Nagar Road, Satellite, Ahmedabad - 380015, India <u>HA 417</u> Accutest Research Laboratories (I) Pvt. Ltd A-31, M.I.D.C., T.T.C., Industrial Area, Khairne,

	Navi Mumbai-400 709, India
Name and address of the Sponsors	Matrix Laboratories Limited Clinical Research Centre, Saradhi Chambers A-4, Rukminipuri, Near Poulomi Hospital, Main Road Dr.A.S.Rao Nagar, Hyderabad - 500062, India Cipla Limited Raj Plaza, 3 rd Floor, "A" Wing L.B.S. Marg, Vikholi (West) Mumbai - 400083, India
Date of inspection	25 and 26 May 2009

Part 2: Summary

The purpose of the inspection was to inspect the clinical and the bioanalytical part of the bioequivalence studies performed at Accutest and to evaluate whether the studies were conducted in compliance with the protocol, Good Clinical Practices (GCP) and Good Laboratory Practices (GLP) where applicable.

General information about the company

Accutest Research Laboratories (I) Pvt. Ltd was established in 1998. The company had 3 clinical and Bionanalytical (BA) centers with totally 254 beds. Company had data bank for more than 16100 volunteers. Analytical laboratories were equipped with 23 LCMC/MS.

Company (Mumbai and Ahmedabad sites) was inspected by:

- US FDA (31 approved studies)
- WHO (16 approved studies)
- MCC South Africa (1 approved study)
- Swedish Regulatory Authority (1 approved study)
- AFSSAPS France (1 approved study)
- MHRA UK (4 approved study)

Center(s) were approved by:

- DCGI
- ANVISA Brazil
- United Arab Emirates

General information about the site

Accutest Laboratories, located in Ahmedabad (India) was inspected on the above-mentioned dates.

Accutest had two units in Ahmedabad:

- Unit I, located on 4th floor; The Grand Monarch, Near Seema Hall; Anand Nagar Road, Satellite, Ahmedabad - 380015, India

- Unit II, located opposite The Grand Bhagwati Hotel, Sarkhej - Gandhinagar Highway, Bodakdev, Ahmedabad - 380054, India

The clinical part of the studies HA 417 and HA 438, as well as the bio-analysis for the study HA 438 were done in Unit I (which was renovated before and after the study).

The study HA 417 was approved by US FDA, though the particular study has not been inspected.

History of WHO and/or regulatory agency inspections

This Prequalification Programme inspection was the second inspection conducted by WHO at Accutest Ahmedabad site.

Focus of the inspection

The inspection focused on the bio-equivalence study conducted for the products HA 417 and HA 438. 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

The following documents were reviewed (clinical part) during the day one and day two (morning):

Clinical part (HA 417)

- Form T12 of the India Drug act
- Trial Master File contents (Pre-Study Documents & During the Conduct of Trial)
- List of subjects for the screening
- Insurance
- Dispensing vial labels
- Shipping records
- Study announcement sheet
- SOP for vitals
 - Respiratory rate
 - Pulse rate
 - Body temperature
 - Blood pressure
- Contract between sponsor and Accutest
- Study protocol
- Project information sheet
- Analytical status record
- Screening, and study consent forms
- Source data and results
- Master lists for subjects
- Documentation and SOPs relating to study drugs accountability and dispensing records, and study drug labels
- Randomization schedule and SOP
- Log for enrolment of subjects
- Training records and duty delegation records of staff present during the study
- SOP for dosing
- Case report forms (CRF) for subjects 07, 13, 21, 38 and 49
- Log for reporting for the study

- Log for presentation of study ICF
- Subjects drop out records
- Adverse reaction summary sheet
- Compensation list
- Letter of shipment of the products
- Letter of receiving of the products
- SOP Handling of Pharmacy
- SOP handling of investigational product
- SOP for preparation of labels for the medication
- Dispensing room line clearance SOP and log book
- Registry to enter/exit the pharmacy
- Registry to enter/exit the dispensing room
- Reconciliation of reference and study products
- Log book for retention samples
- Temperature log for sample incubators
- Archiving procedure (SOP for Retrieval, Retention and Destruction of documents)
- SOP Archiving for the documents
- Log book for archiving
- Records retrieval log book
- Documents transfer note for study
- Log book for deep freezer content
- SOP Processing, Storage, Distribution & Retention of Biological Samples
- Samples transfer records
- Data logger calibration certificate
- Deviation reporting form
- RIA and Vacutainer master labels
- IQ, OQ, PQ protocols and reports for Mack Pharmatech system (data logger for central monitoring of deep freezers used in clinical and bioanalytical labs in Unit I)
- Performance Qualification (PQ) report for alarm system linked to Mack system
- Performance Qualification (PQ) report for cold chamber (pharmacy)
- Calibration reports for deep freezers used in clinical and bioanalytical laboratories
- Audit schedule index for study based audit (Clinical phase)
- QA audit report (Clinical phase)

On the afternoon of the day one, the inspectors visited Unit I where the particular studies had been performed. The visit included:

- Enrollment area
- Medical Examination rooms
- Consent rooms
- Samples collection room
- Volunteers room
- Canteen
- Sample preparation room
- Intensive care unit
- Archives
- Pharmacy
- Dispensing room

The following documents were reviewed during the second day (morning):

Clinical part (HA 438)

- Form T12 of the India Drug act
- Trial Master File
- Master services agreement
- List of signatures of the ethics committee
- List of documents submitted to ethics committee
- Notification to ethics committee
- Ethics committee notice of the meeting
- Agenda of the ethics committee meeting
- Minutes of ethics committee meeting
- Certificate of translation of informed consent form (ICF)
- Volunteers insurance certificate
- Site qualification report by the sponsor
- Monitor visits and audit reports
- Study protocol
- Container label for transfer to dosing
- Dispensing vials label
- Formulation storage boxes labels for the pharmacy
- Dispensing and accountability record
- Log book for the pharmacy
- Log book for retention samples
- Randomization schedule
- Lists of signatures of staff present during the study and training records of staff present during the study
- QA audit report
- QA compliance statement
- Case report forms (CRF) for subjects 03, 19, 24, 41 and 55 (including Screening, and study consent forms)
- Meals menu
- Letters of shipment of the investigational and reference products
- Import license
- Project information sheet
- Study announcement sheet
- Letter to emergency hospital
- Letter to EC regarding study reports
- RIA and Vacutainer labels
- CoA's for investigational and reference products
- Batch packaging record for investigational product
- Invoice for the reference product
- Audit schedule index for study based audit (Clinical and BA phases)
- QA audit report (Clinical and BA phases)
- SOP "Auditing clinical phase"
- Subjects drop out records

Before lunch inspectors visited the analytical laboratory.

The following documents (bioanalytical part HA 438) were reviewed after lunch during day two.:

- Samples inward record

- Procedures for method development and method validation data (*performed in Accutest lab in Navi Mumbai*) including specificity, serial dilutions, precision, accuracy, recovery, matrix effect, stability (bench top, auto-sampler, freeze-thaw, long-term for 67 days)
- Partial validation data (*performed in Accutest lab in Ahmedabad*) for precision, accuracy (3 batches), selectivity, recovery, matrix effect, dilution integrity
- Subject sample analysis (19 and 20 in one run) - raw data, chromatograms, sample sequence, QCs and CC and back calculation - PI and PII (selected time points)
- Subject sample analysis (24 and 25 in one run) - raw data, chromatograms, sample sequence, QCs and CC and back calculation - PI and PII (selected time points)
- Subject sample analysis (58 and 59 in one run) - raw data, chromatograms, sample sequence, QCs and CC and back calculation - PI and PII (selected time points)

2.1 PROVISIONS AND PREREQUISITES FOR A CLINICAL TRIAL

Sponsors request for the trial, supporting data and available literature.

2.2 THE PROTOCOL

The Protocol was found in general to be acceptable.

2.3 PROTECTION OF TRIAL SUBJECTS

Protection of the volunteers was found to be acceptable, Helsinki declaration was followed, and informed consents were obtained.

2.4 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. Local drug authority was accordingly informed about the study. The study protocol was reviewed and approved by the ethics committee. Adverse reactions were recorded.

The trial site had adequate premises.

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. Subjects received compensation in accordance with the protocol. Quality audits were performed; audit reports were available for inspection.

2.6 RESPONSIBILITIES OF THE MONITOR

Responsibilities of the monitor were specified in the contract between sponsor and CRO. 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. Some findings were made regarding appropriateness of the archiving activities. Study records were stored accordingly for 5 years in the CRO archive.

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 up.

2.11. ROLE OF THE DRUG REGULATORY AUTHORITY

Acceptable

2.12. QUALITY ASSURANCE FOR THE CONDUCT OF A CLINICAL TRIAL

The quality assurance was consistent and comprehensive. Quality audits of clinical and bioanalytical part were performed, audit reports were available for inspection,

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 studies conducted by the Accutest Research Laboratories (I) Pvt. Ltd. 4th floor; the Grand Monarch, Near Seema Hall; Anand Nagar Road, Satellite, Ahmedabad - 380015, 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.