



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

**Part 1: General information**

WHO product numbers covered by the inspection	<p><b>HA 417 (BA part of the study)</b> <i>For the product specific information please see Annex I</i></p> <p><b>HA 418 (clinical and BA parts of the study)</b> <i>For the product specific information please see Annex II</i></p>
Study number	<p>US/AHD/07/003 US/06/075</p>
Title of the study	<p><b>HA 417</b> A Randomized, Open Label, Two-Period, Two-Treatment, Two-Sequence Single Dose Crossover Bioequivalence Study in Normal Healthy Male Subjects Under Fasting Condition</p> <p><b>HA 418</b> A Randomized, Single Dose, Open Label, Bioequivalence Study in Normal Healthy Adult Male Subjects Under Fasting Condition.</p>
Clinical Part of the study: Name and address of the organization	<p><u>HA 418</u> 31, M.I.D.C., T.T.C., Industrial Area, Khairane, Navi Mumbai-400 709, India</p>
Bio-analytical laboratory: Name and address	<p><u>HA 417</u> <u>HA 418</u> 31, M.I.D.C., T.T.C., Industrial Area, Khairane, Navi Mumbai-400 709, Maharashtra - India</p>
Name and address of the Sponsors	<p><b>Matrix Laboratories Limited,</b> Clinical Research Center, Saradhi Chambers, Plot no. 4A, Beside Poulomi Hospital, Dr. A.S. Rao Nagar, Hyderabad – 500 062, India</p>

	<b>Cipla Limited</b> Raj Plaza, 3 <sup>rd</sup> Floor, "A" Wing L.B.S. Marg, Vikholi (West) Mumbai - 400083, India
Date of inspection	28 and 29 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**

For information about Accutest Research laboratories (I) Pvt. Ltd., please refer WHO Public Inspection Report (25-26 May 2009), Ahmedabad.

### ***General information about the site***

Accutest Laboratories, located in Mumbai (India) was inspected on the above-mentioned dates. Accutest had one site in Mumbai and separate offsite Archive. The site was located on four floors as following:

- Ground floor - clinical unit I and II, sample collection, dosing, pharmacy and ICU (Intensive care unit)
- Basement - pathological and X rays laboratories
- 1<sup>st</sup> floor - onsite archive, Quality Assurance (QA) department and cafeterias,
- 2<sup>nd</sup> floor - analytical laboratory, statistics department and sample cold storage area.

Offsite archive was located approximately 6 km away from the CRO at Accutest Research Laboratories (I) Pvt. Ltd., Shop no-03, Kadambari Apartment Plot No. 22, Sector –1, Sanpada – Navi Mumbai.400 705, Maharashtra – India.

### ***History of WHO and/or regulatory agency inspections***

WHO conducted six inspections at Accutest Mumbai site previously.

### ***Focus of the inspection***

The inspection focused on the bio-equivalence study conducted for the products HA 417 and HA 418.

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 (morning):

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WHO public inspection report (WHOPIR):  
Accutest Research Laboratories Mumbai, India  
28 and 29 May 2009

Clinical part HA 418

- The site registration, and directors
- Trial Master File contents (Pre-Study Documents & During the Conduct of Trial)
- Form T12 of the India Drug act
- List of signatures of the ethics committee
- List of documents submitted to ethics committee
- Notification to ethics committee
- List of subjects for the screening
- Minutes of the Institutional Review Board meeting, protocol and letters
- Institutional Review Board registration, current registration with the US Office of Human Research Protection (OHRP)
- CV's of the Institutional Review Board members
- Memorandum of association and Articles of association
- Certificate of translation of informed consent form (ICF)
- Consent forms for screening
- Subject information sheets and ICF
- Declaration of financial interest and arrangements of clinical investigators
- Form 1572 - statement of investigator
- CV of Principle Investigator Dr Suhas Khandave
- Volunteers insurance certificate
- Sponsors (Cipla) manufacturing license
- Master sheet for coding of the samples
- Dosing labels
- Formulation dispensing record
- Minutes of pre study meeting
- Letter to the emergency hospital
- Box labels for control plasma and analysis plasma samples
- Protocol deviations
- Custodian records
- Sample transfer to the analytical laboratory
- Contract between sponsor and Accutest (Master service agreement)
- Monitoring and audit reports
- Study protocol and amendment to the protocol
- Screening, and study consent forms
- Master lists for subjects
- Enrolment of subjects
- Subjects drop out records
- Letter of shipment of the products
- Letter of receiving of the products
- Documentation relating to study drugs accountability and dispensing records, and study drug labels
- Randomization schedule and SOP
- Dispensing room line clearance SOP and log book
- Log book for retention samples
- SOP for preparation of labels for the medication
- Registry to enter/exit the pharmacy
- Registry to enter/exit the dispensing room
- Reconciliation of reference and study products

- 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 6, 13, 23, 25, 31 and 42
- Meals menu
- Samples transfer records
- Calibration reports for deep freezers used in clinical and bioanalytical labs
- Log book for deep freezer content
- Temperature log book for deep freezer used in bioanalytical lab
- IQ, OQ, PQ protocols and reports for Zemlog (data logger for central monitoring of cold chambers in pharmacy, deep freezers used in clinical and bioanalytical labs)
- Performance Qualification (PQ) report for alarm system linked to Zemlog system
- ECG use log,
- SOP "Inventory control in Pathology department"
- SOP "Calculation of pharmacokinetic parameters and statistical calculations" in reviewing the process at the Data Processing Centre

After review of mentioned documents inspectors visited:

- Enrollment area
- Medical Examination room
- Consent room
- Samples collection room
- Volunteers room
- Cafeterias
- Sample preparation room
- Intensive care unit
- Archive
- Pharmacy
- Dispensing room

After lunch inspectors visited analytical laboratory, on site and off site archives.

The following documents were reviewed:

- Log book for Working Standards (WS)
- WS receipt and usage log book
- Sample storage
- Log book for achieving documents

The following documents (bioanalytical part HA 418) were reviewed in the morning of day two.:

- Samples inward record
- Procedures for method development and method validation data including specificity, serial dilutions, precision, accuracy, recovery, matrix effect, stability (bench top, auto-sampler, freeze-thaw, long-term for 96 days)
- Subject sample analysis (1 and 2 in one run) - raw data, chromatograms, sample sequence, QCs and CC and back calculation - PI and PII (selected time points)
- Subject sample analysis (7 and 8 in one run) - raw data, chromatograms, sample sequence, QCs and CC and back calculation - PI and PII (selected time points)
- Subject sample analysis (33 and 34 in one run) - raw data, chromatograms, sample sequence, QCs and CC and back calculation - PI and PII (selected time points).

- Calibration record for the LC-MS/MS instrument used

The following documents (bioanalytical part **HA 417**) were reviewed in the afternoon of day two.:

- Samples inward record from Ahmedabad clinical site
- Procedures for method development and method validation data including specificity, serial dilutions, precision, accuracy, recovery, matrix effect, stability (bench top, auto-sampler, freeze-thaw, long-term for 191 days)
- Subject sample analysis (3 and 4 in one run, including the repeat analysis) - raw data, chromatograms, sample sequence, QCs and CC and back calculation - PI and PII (selected time points)
- Subject sample analysis (46 and 47 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, informed consents were within the requirements.

## **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.

Pharmaceutical products were handled appropriately.

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 study Accutest Research Laboratories 31, M.I.D.C.,T.T.C., Industrial Area, Khairane, Navi Mumbai-400 709, 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 unless an inspection outcome is negative prior to the 2 year period.