Prequalification Team Inspection services
WHO PUBLIC INSPECTION REPORT
Bio-Equivalence Study

<table>
<thead>
<tr>
<th>Part 1</th>
<th>General information</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Organization details</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Company information</strong></td>
<td></td>
</tr>
<tr>
<td>Name and Address of the Site(s) inspected (Clinical, Bioanalytical and Statistical Site)</td>
<td>Accutest Research Laboratories (I) Pvt. Ltd. (Unit I) A-31/A-77, MIDC, TTC Industrial Area, Khairane Navi Mumbai – 400 709, Maharashtra INDIA</td>
</tr>
<tr>
<td>Corporate address of Organization</td>
<td>Accutest Research Laboratories (I) Pvt. Ltd. (Unit I) A-31, MIDC, TTC Industrial Area, Khairane Navi Mumbai – 400 709, Maharashtra INDIA</td>
</tr>
</tbody>
</table>
| GPS coordinates                             | Latitude: 19.098
|                                             | Longitude: 73.017                                       |
| WHO product numbers covered by the inspection/ Product names/ Study numbers/ Study titles | Study no. ARL/13/487
|                                             | FDC Dispersible Tablets 500 mg and 25 mg                 |
|                                             | Study no. ARL/13/485
|                                             | Dispersible Tablets containing 153 mg                    |
|                                             | Study no. ARL/15/120
|                                             | Tablets 100 mg                                           |
|                                             | Study no. ARL/16/111
|                                             | Tablets 600 mg                                           |
|                                             | Study no. ARL/14/734
|                                             | FDC Film-Coated Tablets 40 mg and 320 mg                 |
|                                             | Study no. ARL/15/709
|                                             | 20 mg + 120 mg Dispersible Tablets                        |
|                                             | Study no. ARL/16/074
|                                             | FDC Film Coated Tablets 40 mg and 320 mg                 |
|                                             | Study no: ARL/16/325                                      |
### Inspection details

<table>
<thead>
<tr>
<th>Dates of inspection</th>
<th>19-23 February 2018</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of inspection</td>
<td>Routine</td>
</tr>
</tbody>
</table>

### Introduction

#### Summary of the activities
The facility had the capacity to perform bioequivalence/bioavailability and in-vitro studies in healthy subjects/patients.

#### General information about the company and site
Accutest Research Laboratories (I) Pvt. Ltd. was contracted as CRO providing services exclusively to the pharmaceutical industry in the field of formulation development and clinical research. The organization was divided in five centers in Mumbai (Unit I and Unit IV), Ahmedabad (Unit I and II) and Vadodara. Unit I of Mumbai is operating as Head office. There was also a Unit III in Mumbai, functioning only as an off-site archive facility.

#### History
The CRO was inspected by various National Medicines Regulatory Authorities. A list of inspections was available was attached to the CRO Master File as appendix-01.

MHRA inspection report dated 23 Dec 2015 was reviewed during the inspection.

#### Brief report of inspection activities undertaken
The following scope and study-related activities were reviewed:

The company’s history, clinical study performance, informed consent process, ethics committee approvals and correspondence, test article accountability, dispensation and storage, processing and handling of biological (plasma) samples collected during the study, equipment calibration, employee training, computer controls, and a tour of the facility.

Regarding the Analytical operations, coverage was provided to confirm practices, qualifications of personnel,
and procedures utilized during the method validations and analytical testing.

A review of the clinical study data, analytical method validation, and analytical study data was accomplished along with comparisons of the source data to study reports.

**Scope and limitations**

| Out of scope | Not applicable |

**Abbreviations**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADR</td>
<td>Adverse drug reaction</td>
</tr>
<tr>
<td>AE</td>
<td>Adverse event</td>
</tr>
<tr>
<td>ALCOA</td>
<td>attributable, legible, contemporaneous, original and accurate</td>
</tr>
<tr>
<td>BE</td>
<td>bioequivalence</td>
</tr>
<tr>
<td>BDL</td>
<td>below detection limit</td>
</tr>
<tr>
<td>CAPA</td>
<td>corrective actions and preventive actions</td>
</tr>
<tr>
<td>CC</td>
<td>calibration curve</td>
</tr>
<tr>
<td>CDISC</td>
<td>clinical data interchange standards consortium</td>
</tr>
<tr>
<td>CPU</td>
<td>clinical pharmacology unit</td>
</tr>
<tr>
<td>CRA</td>
<td>Clinical research associate(e)</td>
</tr>
<tr>
<td>CRF</td>
<td>(electronic)case report form</td>
</tr>
<tr>
<td>CRO</td>
<td>Contract research organization</td>
</tr>
<tr>
<td>CTM</td>
<td>Clinical trial manager</td>
</tr>
<tr>
<td>CoA</td>
<td>certificate of analysis</td>
</tr>
<tr>
<td>CSR</td>
<td>Clinical study report</td>
</tr>
<tr>
<td>DQ</td>
<td>design qualification</td>
</tr>
<tr>
<td>ECG</td>
<td>electrocardiogram</td>
</tr>
<tr>
<td>GAMP</td>
<td>good automated manufacturing practice</td>
</tr>
<tr>
<td>GCP</td>
<td>good clinical practice</td>
</tr>
<tr>
<td>GLP</td>
<td>good laboratory practice</td>
</tr>
<tr>
<td>GMP</td>
<td>good manufacturing practice</td>
</tr>
<tr>
<td>HPLC</td>
<td>high-performance liquid chromatograph</td>
</tr>
<tr>
<td>HPLC-MS/MS</td>
<td>liquid chromatography–mass spectrometry</td>
</tr>
<tr>
<td>IB</td>
<td>investigator’s brochure</td>
</tr>
<tr>
<td>ICF</td>
<td>Informed consent form</td>
</tr>
<tr>
<td>ICH</td>
<td>International Conference on Harmonization</td>
</tr>
<tr>
<td>(I)EC</td>
<td>(Independent)Ethics Committee</td>
</tr>
<tr>
<td>IMP</td>
<td>Investigational medicinal product</td>
</tr>
<tr>
<td>IQ</td>
<td>installation qualification</td>
</tr>
</tbody>
</table>
Part 2 Summary of the findings and comments

General section

1. Organization and management:

At the opening meeting of the inspection, a presentation was provided to explain the structure and operation of the organization. The CRO was founded in 1998 and started the Clinical Development Services to conduct clinical trials for complex and modified release product in 2008.

In 2009, the Brazil office was established. In the same year, the Ahmedabad office was initiated to work on PK patient-based studies. In 2012, the Europe office and in 2014, the US office was inaugurated. Finally, in 2017, the Mumbai facility was expanded.

150 – 200 studies were conducted per year.

The organization’s organogram was provided in their CRO master file as appendix 5.
The following changes were made since the most recent inspection:

- New Clinical Unit III of 42 beds started Jan 2017.
- On-site archiving facility was moved from area A-31 to A-77.
- Templates of clinical and bio-analytical reports were revised as per current regulatory requirements.
- Deep-freezer area at A-31 was expanded.
- Clinical Data Management department was made operational from Feb 2017 to meet recent US FDA requirements related to CDISC activity.
- Dell Nutanix for virtualization of IT infrastructure was introduced.
- Various section i.e. HR, Accounts, Director’s office were moved from area A-31 to A-77 site.
- 100% Quality control check in Clinical and Bioanalytical departments was implemented.
- Graphical presentation of online recording of temperature of deep-freezer and other freezers connected to Eurotherm was added.
- Clinical SOPs were revised.
- Analytical Operation SOPs were revised.
- A fully operational BAL lab at site A-77 on April 2014 was added to the organization.
- All software platforms in the lab such as Analyst, Mass Lynx, etc. were validated to comply with latest regulatory requirements.
- Older platforms i.e. LC-MS/MS systems such as API 3000 and Waters Quattro premier XE were discontinued.
- Complete revamp of all hardware related to LC-MSMS systems to latest configurations was implemented.
- It was attempted to update all instruments on a single, latest software version.
- Critical Excel spreadsheets being used in lab during Method Validation and Subject analysis were validated.

2. **Computerized systems:**
   The CRO had a network of computers which enabled the company to collate data from all operations throughout a project. Bioanalysis of subject sample was done using two types of software. Statistical analysis of project data was done through statistical software. Backup and archival of all data generated at the Unit was done periodically.

   “Validation plan for Excel spreadsheet” dated 23 Mar 2015, signed by third party Anthen GxP Solutions Pvt. Ltd. was available. The roles of validation Agency were described in this documentation to provide design requirement specification, user requirement specification and functional requirement specification for spreadsheets.
The validation plan was detailed including the replacement of critical parts or any major modifications made to the equipment.

Access control to different restricted areas was managed by IT after receipt of an email from HR as soon as a new employee was appointed. In the time of termination of employment, another form was submitted requesting for cancelling of access.

Daily, weekly and monthly backups were provided. Daily incremental backup and weekly full backup were carried out through Networker VTL. Monthly backup was a full backup which would be carried out on the last day of each month on a magnetic tape at the Mumbai Site. The Monthly full backup was stored in the in-house archiving facility.

EMC VNXe 3100 storage was used as bidirectional data storage for both location in Ahmedabad and Navi Mumbai. The system was also functioning as a Disaster Recovery. There was a connection between Navi Mumbai and Ahmedabad site, over the WAN and through the software to execute the backup from both sites.

The data generated by the analytical software system was primarily stored on the D: Drive of computer and then transferred to the EMC backup system. Administrator of the software (IT-personnel) had the “copy, paste and delete” rights of the electronic folders.

The SOP for backup was reviewed. It was mentioned that a backup would be stored on a tape in case the possibility for taking a backup on the server was not available.

SOP for Access control, system security and user roles for operation of MassLynx and Analyst was reviewed, and the roles were confirmed.

The Administrator of Analyst® software system (IT-personnel) had the right to disable, enable and clear audit trail, as defined in the respective SOP. In this context, a meeting was set up, inviting the representative from AB Sciex to clarify the following issues:

1. Why did the rights to disable, enable and clear audit trail exist in the security setting of Quantitation tab “Disable Enable and clear audit trail”? The representative from AB Sciex demonstrated that these options were deactivated. Nevertheless, the options existed by default from earlier versions.

2. Is it possible to revoke the option to delete the files from D: Drive (rights by administrator)? The service provider was asked to investigate the possibility of revoking the options.
3. The consequence of disabling of “Check sum functionality” was described. It was also explained that the function would be enabled by default from the next upgrade of Analyst®.

4. According to the representative explanation, a notification would be generated in Analyst®, notifying the operator whenever the files were changed and/or any file in the software was modified when the check sum was enabled.

A list of all computer systems operated by outdated XP windows operator was provided.

Software Analyst® 1.6.3 was reviewed to verify the security configuration.

The computer system used for registration of volunteers (CTMS) was customized for the Navi Mumbai facility in 2016 after retirement of previous system “Biometrix”. Data on the old software was migrated to the new system with new identification numbers.

The QA-designee had only reading rights to verify the changes made to the parameters. The organization kept a log of changes in a logbook, authorized by PI or investigator. Observations made in relation to the computerized system were addressed adequately in the CAPA provided by the CRO.

Observations made in relation to the computerized systems were addressed adequately.

3. **Quality management:**

The organization’s Quality manual described the company’s Quality Management System. Organization’s new CRO Master File was drafted after the recent recommendation from WHO-inspection team to organize the Master File according to the WHO TRS No. 957, Annex 7. The finalization procedure was in process.

The templates required for each study, could only be issued QA. An electronic system was to be implemented where the templates could only be requested electronically for the respective activity. Hence, it indicated that, for each study, the number of the templates used, were strictly controlled and only limited to the exact number of activities performed.

An electronic system for document management and training was under implementation.

A list of SOPs was reviewed, in addition to number of SOPs related to various activities. Furthermore, there were 9 policies implemented in the company’s QMS to set up the principles of different activities.

SOPs for internal audit and vendor audit were reviewed.
Organization’s internal audit consists of two types of audit:
- Study specific audit (The plan was reviewed for 2014 and 2015)
- Retrospective audit (The plan was reviewed for 2015)

SOP for Preventive maintenance and handling breakdown of instrument effective 19 March 2016 was reviewed. The actions required to be taken during the break down of the instrument was described. It was required to complete a service report by the engineer.

SOP for Obtaining of ICF was reviewed. The SOP stipulated that the medical related queries or comments should be answered or explained by medical personnel only.

SOP for training and the annual training schedule as per the Annexure 07 were reviewed.

SOP for Segregation, transfer, retention and disposal of biological sample and SOP for Transport of biological samples outside the study center were verified.

The QA-team was committed to carry out a complete QA of ongoing activities, 20 % QA-check including all repeats, complete TMF verification, and randomly selected subjects’ data confirmation, in addition to a complete AE check.

SOP for Quality Assurance Audit for the Pharmacokinetics and Biostatistics was reviewed. Audit report for study code ARL/17/128 was found as per Annexure 1 of the respective SOP.

Observations made in relation to the QMS were addressed adequately.

4. Archive facilities:
The study related documentation was stored in the CRO’s archiving facilities. The archive facility was located at plot A-77. The access by key card was authorized for four archivists and QA-Head.

The archive facility was equipped by numbered shelves in metal, fire proof door, chemical extinguisher and smoke detectors. Pest control was carried out every 15 days. The pest control visits were recorded on a visit card provided by ULTIC Pest Control as a service report, kept by HR-department. The pest control was regularly executed on mosquitos, rodents and GD. The respective agreement was reviewed valid from June 2017 to June 2018.
The location of documents was kept indexed on an Excel sheet which was backed up on the server. Request for handling of inspection documentation was reviewed to verify the process of handling of retrieval of documentation. The process of timely return of documentation was ensured.

The retention period of storage of documentation was managed by agreements and requirements, whichever longer.

5. Premises:
   During the inspection, a tour of facility was provided.

   In addition to two facilities in Navi Mumbai for clinical and bioanalytical activities, there was also an off-site archiving facility only for storage of documentation.

   The building located at A-77 (Unit IV) consisted of bioanalytical and biological laboratory and administration offices. The other facility located at A-31 (Unit I) consisted of clinical units, bioanalytical laboratory, pharmacy, kitchen for preparation of food and clinical laboratory.

   X-ray procedure was outsourced to an external X-ray facility. A pregnancy test was required prior to the X-ray procedures for fertile female subjects.

   The facilities were accessed by key cards. There were four master access-cards to be used in emergency situations; one for access to the whole facility and three others for access to specific areas. QA was responsible to ensure and oversee the use of master cards by non-authorized personnel by review of the respective audit trail in timely manner.

   The access to the pharmacy was authorized for four pharmacists. Monitoring of temperature was managed by Eurotherm digital thermometer. Synchronized clocks were located throughout the facility to document the exact time study activities occurred.

   One 500 KVA diesel generator was installed for power failure backup purpose. During discussions, the site confirmed to have power cut off every Friday as per the municipality requirements. The maintenance logbook for generator was verified. 7 UPS devices providing a total of 216 KVA were available on the site. Maintenance services for diesel generator and UPS devices were provided every three months by an external vendor.

   Disposal of waste and other environment-friendly measures was properly done and outsourced.
Screening area
The clinical facility at Plot A-31 was visited. Volunteers were only recruited for specific studies, and no general screening of volunteers would take place. Hence, the name of subjects was already recorded on the visit-log. Subjects were led to the screening area where the study details were explained. ICFs were available in three languages. The subjects could be given the opportunity to consult with their family regarding the participation in the study.

Clinical Pharmacology Unit
Once a subject was verified to be eligible, an ID-card was generated with a registration number and study code. Lockers assigned to the volunteers for their belonging were supervised by the CRO’s CRA. Each volunteer was given a kit to accommodate the volunteers’ need during their stay.

The CPU units were visited. CPU unit II had a capacity of 30 beds. 30 portable-bells were available to be distributed to the subjects at bedtime. The alarms were tested randomly.

Female and male subjects could be kept together in case of lack of capacity.

The emergency exit was kept open when the CPU was staffed by subjects. In order to supervise the Emergency Exit, a sensor was installed at the external door, to monitor any possible exit and entry of unauthorized visitors.

ICU
The record of the medications used in the ICU and their accountability were carried out appropriately. The logbooks for “Emergency medication usage record” available at the facility was reviewed.

Pharmacy
Entry/exit records for each visit were noted in the logbook.

The Pharmacy was kept in good hygienic conditions, consisting of receipt area, dispensing area and storage area with four stability chambers. Logbooks were well-organized.

The retention documentation for both studies in the scope of inspection was requested and reviewed.

Temperature and humidity measurement was tested during the inspection.

Observations made during the inspection were addressed adequately.
6. **Personnel:**
Randomly Selected CVs and JDs were reviewed.

According to the training SOP, all personnel joining the organization were given induction training and briefed on the organization and its activities. Employees were also trained on study specific procedures such as protocols, method SOPs etc. GCP/ GLP /cGMP as applicable training were offered to all the applicable personnel as required by their job description.

Employees were trained in emergency and fire evacuation, as well as policy for environment, health and safety (EMS), within their induction program. The documentation was reviewed and verified.

### Clinical section

7. **Clinical phase:**
The clinical facility was visited during the dosing process. Labelling of study medication, monitoring checklist and blood sample collection form, verification of vital signs, subjects’ well-being and hygienic condition of restrooms were verified.

Delegation log for study site personnel was verified.

The clinical phase started with the ICF process and signature, obtaining demographic information, medical history and followed by physical exam based on a pre-populated checklist. The volunteers were receiving an individual barcode that was later scanned for identification purposes during the study conduct.

After subjects’ registration, their eligibility was verified using the OVIS database to avoid cross-participation, followed by alcohol test and ECG exam.

The ECG process was inspected. Subjects were invited for ECG procedure after site personnel scanned the barcode provided during the registration. Printout of the ECG was sent to the responsible physicians for evaluation. Following evaluation, the scanned ECG was uploaded to the study specific folder where restricted access was granted for the PI and ECG technician. The ECG device used was a simple one which only recorded and printed out the results, without having the possibility to connect the machine to a computer and save the record.

The next assessment performed was the physical examination to verify the pertaining inclusion criteria. If the results failed, the volunteer would be recorded as “screen failure”. The blood and urine samples collection of the screening process were verified.
The screening area was generally well maintained.

Medical skills of the ICU personnel were investigated, followed by discussion conducted with the medical personnel.

The medication available for medical emergencies was verified for expiry date, and none of them was found to be close to expiry date or expired. Medical emergencies equipment: oxygen cylinder, defibrillator, ECG machine, suction machine, laryngoscope was inspected. Logbooks for emergency medication, maintenance of defibrillator and oxygen cylinder were verified. The defibrillator was checked before every study start. Water in the oxygen cylinder was changed every 7 days.

The calibration certificates for defibrillator and laryngoscope were verified. No calibration certificate was provided for pulse-oximeters. The site confirmed that there was no possibility to calibrate the pulse-oximeters. Hence, a decision was made to replace them once a year.

The dosing area was visited while subjects were receiving their respective study drugs. The dosing was performed according to the protocol and respective procedures.

The next area visited was the blood sample processing area. Process and pertaining equipment were investigated, and the data recorded in the centrifuge usage logbook was verified. Samples were centrifuged according to the time, speed and temperature established in the respective protocol.

The process for investigation of hemolyzed blood samples was reviewed. If any of the samples was hemolyzed, the sample would be identified by respective chart, coded from A to D, and recorded in the corresponding form. The missing samples were also documented accordingly. After blood samples-collection at each time point in pre-labelled tubes, samples were sent to the sample processing room for centrifugation and freezer-storage.

Freezers’ temperature was monitored by Eurotherm digital thermometer which generated notification to the sample storage custodian and the security through automated phone call in case of temperature excursions out of acceptable range.

During the facility tour, it was observed that two subjects participated in ARL/16/557 study were employees of Accutest. The study was performed for blank plasma collection.

The contract and Master Agreement between the sponsor and CRO were reviewed.
A hospital was contracted to handle the emergency situations. Agreement starting 18 Mar 2014 and valid for 1 year, applied to all studies performed in this period was verified.

Observation made related to clinical phase were adequately addressed in the provided CAPA, by the CRO.

8. **Clinical laboratory:**
   The Head of clinical laboratory was interviewed.

   It was verified that the date and time of laboratory results available in the computer was not possible to be changed. Clinical samples were barcoded for use in clinical laboratory. The samples receipt logbook was verified. The Clinical/Pathology laboratory department was generally spacious and adequate for the purpose.

9. **Ethics:**
   The subject’s insurance during the conducting of the studies ARL/13/487 and ARL/13/485 was verified.

   **ARL/13/485**
   All 56 ICFs signed by the subjects were verified.

   **ARL/13/487**
   All 32 ICFs signed by the subjects were verified.

10. **Monitoring:**
    Studies ARL/13/487 and ARL/13/485 were not monitored.

11. **Investigators:**
    CV and training log, as well as the job descriptions of PI and sub-investigators were verified.

    Investigators had appropriate qualifications, training and sufficient experience in the conduct of BE studies, as confirmed by their CVs.

12. **Receiving, storage and handling of investigational drug products:**
    Information concerning the receipt, storage, handling and accountability of IMP at every stage of the trial was properly recorded in applicable logbooks.

    Upon receipt of shipment of IMP, respective documentation such as certificate of analysis (CoA), purchase order and packaging condition was verified. In case of discrepancy, the project manager would be notified. As soon as the shipment was accepted, physically and
quantity check of the shipment was initiated by verifying the IMP content of a randomly selected package. Data-logger readings were reviewed.

Temperature was monitored by hygro-thermometer twice a day and recorded in a logbook. Digital thermometer (Eurotherm) connected to the security room was in use for stability chambers and storage area.

Randomization list was provided in a password protected email, by statistician upon request from PI. Password was submitted by a separate email. Labels were then generated accordingly, which were also quality controlled by QA.

The randomization list was confirmed versus IP labels for studies pertaining to applications MA117 and MA068.

The process for dispensing of solid and liquid form drugs was reviewed.

Reconciliation of the study drug was carried out after completion of study and the drug was retained for a period, defined by sponsor. Retention and destruction documentation for study ARL/13/487 was reviewed.

The retention documentation for studies pertained to the application number MA117 and the respective logbook for IMP log were reviewed. Samples of the products were properly retained in the storage and according to the contract with sponsor. Retention time was recorded as 5 years.

Observations made related to this section were adequately addressed in the provided CAPA, by the CRO.

13. Case report forms:
This section was not inspected due to time constraint.

14. Volunteers, recruitment methods:
   Recruitment
   Approximately, 15000 volunteers were registered in the CRO’s volunteer registration database. Volunteers were contacted by volunteer coordinator / registration officer to inform them about the upcoming studies. Recruitment could also take place by visiting the area with possible volunteers by Company’s registration officer.

   Registration
   Volunteers were registered and identified biometrically in the database CTMS customized for Navi Mumbai facility. For more details, see section for Computer systems.
Observation made related to inclusion of the volunteers was adequately addressed in the provided CAPA, by the CRO.

**Screening procedures**

Volunteers were led to the ICF room to go through the ICF process by either the medical personnel or the CRA. Any medical question was addressed by qualified medical personnel. Video recording was only carried out for volunteers in vulnerable populations.

After obtaining the ICF form, the study specific processes were explained to the volunteers by using a checklist prepared for this purpose.

After registration, the subject was provided a study specific barcode for next procedures. The screening activities at the clinical site consisted of OVIS-verification, Alcohol breath analysis test, urine test for drug and final physical examination including ECG.

Physical examination was conducted in the presence of the inspectors. The medical personnel performing the procedures was qualified and experienced. No observation raised during physical examination, medical history and vital signs measurements activities.

Sample collection process was inspected. Once the ECG was performed, subject was led to the sample collection room to be identified by barcode to ensure that the prevalent activities performed, were not flagged for any medical or other relevant reasons.

Test requisition form was already completed, including five barcodes:

- Serum
- Hematology
- Fluorine
- Urine
- TRF

The respective labels were generated by database SUFLAM once the time of collection was entered. The samples were kept in a box with ice provided by custodian. Logbook was completed by lab-technician and signed by custodian.

SOP for Collection of biological samples for pathological investigations was available.

Acceptable range for at least five parameters recommended by WHO was established and the medical assessment of inclusion/exclusion criteria was made based on the lab-results within the established range.

Observations made related to this section were adequately addressed in the provided CAPA, by the CRO.
15. Food and fluids:
   The food menu was prepared by the di etician according to the protocol based on the total number of subjects. All ingredients of the food were measured and handed over to the chef who was responsible for preparation of meals.

   The preparation of the food took place in the CRO’s kitchen and by CRO’s employees.

   Observations made related to hygienic condition of kitchen and preparation of meals were adequately addressed in the provided CAPA, by the CRO.

16. Safety, adverse events, adverse event reporting:
   ARL/15/120
   No adverse events or SAEs were reported during the entire course of the study.

   ARL/13/485
   One adverse event was reported during the clinical phase of the study which was assessed as expected and probably related to the study drug. Outcome of the adverse event was recorded as resolved. No serious adverse event was reported during entire course of the study.

Bioanalytical section

   The inspection included auditing of source documentation and raw data for validation of bioanalytical methods, and analysis of subject plasma samples as well as audit of the electronic data, audit trails for electronic data capture and handling related to the PK study. Results of calibration standards, quality control samples (QCs), subject plasma samples in analytical runs were verified along with the chromatograms generated from analytical runs. The preparation of analyte stock solutions, calibration standards, QCs and internal standards, and reagents were also audited.

   Personnel assisting the inspection team with review of study-documents were knowledgeable, transparent and helpful.
### 17. Method development, Method validation & Analysis of study samples:

<table>
<thead>
<tr>
<th>Study Code: ARL/13/485</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Method development</strong></td>
</tr>
<tr>
<td>There was no SOP for method development. However, some of the steps to be taken were described in other SOPs such as SOP for preparation of standard solutions, calibration curve standards and quality control samples. The chemist notebook was reviewed. The notebook was indexed and properly organized. The cone voltage optimization, optimized MS spectrum, collision energy optimization, optimized daughter spectrum and other necessary information was recorded in the method development report.</td>
</tr>
<tr>
<td>Method of detection: LC-MS/MS Matrix Anticoagulant: NA Heparin Details were presented in a study specific presentation as requested by inspection team.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Method validation</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>CoAs were reviewed for both analytes and the respective Internal Standards (IS). Pipette calibration documentation for pipette thermal used in the study was reviewed and verified. Training record for method dated 30 Dec 2013, was verified to ensure that the activities were performed by delegated trained personnel. Preparation of master stock solution of all analytes and pertaining IS, together with intermediate stock solution, and spiking working solution made on 30 Dec 2013 were reviewed.</td>
</tr>
<tr>
<td>Matrix effect The results for the matrix effect and preparation of plasma lots on 30 Dec 2013 was provided and reviewed. The database used for the run was reviewed to verify the process. Selectivity Date: 30 Dec 2013 Preparation of solutions and the generated data by the database and the results on Excel sheet was reviewed and confirmed. Dilution integrity Date 6 Jan 2014 Preparation of ULOQ, diluted solutions and generated data, together with the results of the</td>
</tr>
</tbody>
</table>
Solutions were made according to the analytical data sheet provided for method validation for different solutions.

The logbook for handling of pooled matrix used in method validation and subject analysis was reviewed. The observation made was addressed adequately.

### Precison and Accuracy
Independent preparation of QC and CC stock solutions was verified. Stock solutions were made on 30 Dec 2013 and the spiking solutions were made on 2 Jan 2014.

### Stability
Freeze/Thaw
5 freezing/thawing cycles were verified starting from 2 Jan 2014 to 6 Jan 2014. Logbook for the respective freezer was reviewed.

FT3 and Auto-sample stability run was performed on 4 Jan 2014. FT5 and hemolyzed effect run was performed on 7 Jan 2014.

### Analysis of Samples
Sample retrieval documentation from Deep freezer dated 21 May 2014 for three subjects, relevant QC and CCs were reviewed and verified.

Dilution integrity was performed for $\frac{1}{2}$ and $\frac{1}{4}$ dilution factor.

One subject was excluded from the analytical statistics according to the protocol since he was not present for period II of the study.
The audit trail pertaining to LC/MS-MS instrument was reviewed and verified for the period of sample analysis from 14 May 2014 to 1 Jul 2014.

Randomly selected analytical runs were reviewed including the required calibration curve and QC samples in the same run and all were adequately documented.

<table>
<thead>
<tr>
<th>Repeat analysis</th>
<th>All the repeat analyses were done according to the applicable procedure, documenting the pertaining investigation for the reason for the repeats.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Re-integrated chromatograms</td>
<td>Not applicable</td>
</tr>
<tr>
<td>ISR</td>
<td>The ISR runs were carried out according to the applicable SOP.</td>
</tr>
<tr>
<td></td>
<td>The Excel sheet used for calculation of acceptance criteria was requested.</td>
</tr>
<tr>
<td></td>
<td>The observation made was adequately addressed.</td>
</tr>
<tr>
<td>Back calculations</td>
<td>Back calculation was performed for randomly selected subjects for ARL/13/485 study.</td>
</tr>
<tr>
<td>Acceptable ranges fulfilled</td>
<td>It was verified for randomly selected runs.</td>
</tr>
</tbody>
</table>

**Study: ARL/13/487**

**Method development**

The Precision and Accuracy runs to determine the LLOQ and ULOQ of the method, was reviewed.

**Method validation**

This activity was not inspected.

**Analysis of samples**

Preparation and sample processing of randomly selected subject samples was reviewed.
The internal standard solution which was added to the samples was prepared in two batches, one in 6 May and the other on 13 May 2014. The preparation was documented on the form for “Preparation of intermediate stock solution” with specific ID as “Intermediate stock solution ID”. Two stock solutions were made, for two analytes, with two different final concentrations. The use of the solution in aliquots was documented on the “sample processing form” in volume used as 25 µl to each sample.

The use of specific batches was documented in the chemist notebook, together with the information about the storage conditions. The refrigerator logbook was also randomly reviewed, to verify the proper storage.

18. Sample collection, storage and handling of biological material:

Specification of the samples, sampling method, volume and number of samples were stated in the clinical trial protocol and the information provided to the volunteers.

The procedures for the collection, preparation, transport/shipping and storage of samples were documented and the respective SOP was available.

Two separate forms were in use for record of the missing and hemolyzed samples. The form for missing samples pertaining to the last shipment received, was reviewed.

The deep freezer room located at A-31 was visited. Freezers with temperature conditions -70 and -20 °C were available. Forms for sample transfer records were completed with study code, study period, drug name, type of matrix, ID-number of subject, anticoagulant use, together with total number of samples, storage temperature, counted number of samples per subject, data logger ID number, deep freezer ID number and time of storage.

Transfer of subject samples from Clinical site to Bioanalytical site process was also reviewed. Applicable information was recorded in the respective logbook.

The temperature monitoring log for the refrigerator used for storage of solutions used in selected studies was reviewed for period of 30 Dec 2013 to 31 Jan 2014.

The retention time of blood samples was agreed between the CRO and the sponsor. The bio-samples were discarded after the completion of the study according to the agreement. Discard of samples pertaining to study no. ARL/13/487 and study no. ARL/13/485 was properly documented. The control samples for both studies were discarded on March 2015 recorded on the freezer logbook.
19. Data processing and documentation:
The general documents included SOPs, Forms, Formats and Log Formats. The SOPs described and standardized all the important study-related and general procedures to be followed across the CRO.

Study Protocols, Study plans, Informed Consent Documents, Case Report Forms, Analytical Plans/Procedures and other documents that provided guidance in conduct of clinical, bioanalytical, statistical and other phases of study were available.

Observations made in relation to this section were addressed sufficiently.

20. Good laboratory practices:
The new laboratory at the facility located at A-77 started in April 2014 was visited.

The laboratory was equipped with LC-MS/MS instruments. Lab equipment was labelled with calibration date and validity, as well as a unique ID number. Cross contamination of samples on the working benches was prevented adequately. Two operators were simultaneously present to ensure the cross-check of the sample processing.

Balance room was also visited. Four balances were in the room, in addition to two new balances under installation.

Material safety data sheet was available at the laboratory visited.

Standard Operating procedure for calibration was provided. The process for calibration of the micropipette was observed to ensure proper calibration procedure.

Observations made in relation to this section were addressed sufficiently.

Pharmacokinetic, statistical calculations and reporting section

21. Pharmacokinetic, statistical calculations:
The pharmacokinetic and statistical department consisted of five biostatisticians, working for both Accutest sites (Ahmedabad and Mumbai).

Randomization
Generation of the randomization list was performed by SAS version 9.2.

The sample size was determined based on the molecule, past studies and the available literature.
PK analysis was performed using software system Enterprise Guide 4.3.

The clinical and bioanalytical results were submitted to the statisticians via e-mail by QA department. Collection times and the time deviations reported by the CRA were recorded by the statisticians manually once the data was reviewed by QA.

Results were provided by Enterprise Guide 4.3 software and stored on a public folder for QA review. It was explained that only statisticians had access to the corresponding server. Inspectors attempted to access the server via the login-account of the Head of QA department. It was confirmed that the respective server was neither accessed by Head of QA nor by any other QA-department members. Only the statisticians had access to the study specific folder on server where the results were stored.

The performance qualification of SAS database was carried out once a year.

Observations made in relation to this section were addressed adequately.

22. Study report:
This section was not inspected.

<table>
<thead>
<tr>
<th>Miscellaneous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Samples taken</td>
</tr>
<tr>
<td>Assessment of the CRO master file</td>
</tr>
<tr>
<td>Annexes attached</td>
</tr>
</tbody>
</table>

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 study was considered to have been conducted at an acceptable level of compliance with WHO GCP and GLP at the CRO:

**Accutest Research Laboratories (I) Pvt. Ltd. (Unit I)**
A-31, MIDC, TTC Industrial Area, Khairane
Navi Mumbai – 400 709, Maharashtra
INDIA

**Accutest Research Laboratories (I) Pvt. Ltd. (Unit IV)**
A-77, MIDC, TTC Industrial Area, Khairane
Navi Mumbai – 400 709, Maharashtra
INDIA
All the non-compliances observed during the inspection that were listed in the complete 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.

### Part 4

**List of guidelines referenced in the inspection report**

   **Short name:** WHO BE guidance  

   **Short name:** WHO multisource guidance  

   **Short name:** WHO GCP  
   http://apps.who.int/medicinedocs/en/d/Js5516e/19.11.html

   **Short name:** WHO TRS No. 996, Annex 5 WHO GDRMP guidance  
   http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex05.pdf


   http://www.ispe.org/gamp-5


