

**WHO Prequalification Unit – Inspection Services**  
**WHO PUBLIC INSPECTION REPORT**  
**WHOPIR**  
**Bio-Equivalence Study**

<b>Part 1</b>	<b>General information</b>
<b>Organization details</b>	
Company information	
Name and Address of Clinical Research Site	<b>Accutest Research Laboratories (I) Pvt. Ltd.</b> A-31, MIDC, TTC Industrial Area Khairane Navi Mumbai, 400 709 Maharashtra – India
Name and Address of Bioanalytical Research Site	<b>Accutest Research Laboratories (I) Pvt. Ltd.</b> A-77, MIDC, TTC Industrial Area, Khairane Navi Mumbai, 400 709 Maharashtra – India
Name and address of Statistical Site	<b>Accutest Research Laboratories (I) Pvt. Ltd.</b> A-77, MIDC, TTC Industrial Area, Khairane Navi Mumbai, 400 709 Maharashtra – India
Corporate address of Organization	<b>Accutest Research Laboratories (I) Pvt. Ltd.</b> A-31, MIDC, TTC Industrial Area, Khairane, Navi Mumbai 400709, Maharashtra –India Tel No.:91-22-2778 00718/19/21 Fax: 91-22-2778 0720 Email: <a href="mailto:business@accutestglobal.com">business@accutestglobal.com</a>
GPS coordinates	19.0992° N 73.0175° E
WHO product numbers covered by the inspection/ Product names/ Study numbers/ Study titles	<b>WHO application no. CV020</b> Bioequivalence Study of Ritonavir 100 mg (1 Film-coated Tablet) + Nirmatrelvir 300mg (2 x 150mg Film-coated tablets)  <b>WHO application no. MA193</b> <i>The Bioanalytical portion was performed at the A-77 site in Navi Mumbai; the clinical portion took place at the Satellite site in Ahmedabad.</i> Bioequivalence Study of Sulfadoxine 500 mg and Pyrimethamine 25 mg Tablets
<b>Inspection details</b>	
Dates of inspection	12 - 15 June 2023

Accutest Research Laboratories (I) Pvt. Ltd., Navi Mumbai India - CRO

12 to 15 June 2023

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Contact: [prequalinspection@who.int](mailto:prequalinspection@who.int)

Type of inspection	<p>Follow-up inspection:</p> <p>A notice of concern was raised during the previous inspection in June 2022. This inspection was scheduled to verify the implementation of the suggested corrective and preventive actions, provided on 26 August &amp; 25 November 2022.</p>
<b>Introduction</b>	
Summary of the activities	<p>The facility had the capacity to perform</p> <ul style="list-style-type: none"> <li>- Bioavailability and Bioequivalence Studies</li> <li>- Clinical Development services, including phase I-IV studies for small and large molecules</li> <li>- Clinical Data Management</li> <li>- Biologics services, including pre-clinical, phase I, II &amp; III studies</li> </ul>
General information about the company and site	<p>Accutest Research Laboratories is a CRO based in Navi Mumbai. Accutest Research Laboratories (I) Pvt. Ltd. provides services to the Pharmaceutical, Biotechnological, and Chemical industries in the field of Clinical Research, including Bioavailability and Bioequivalence. The organization has been operational since 1998 and offers services from four centres: Unit I (Head Office: A-31) and Unit IV (A-77) in Navi Mumbai, Unit I-AHD in Ahmedabad, and the Vadodara facility. The company went through an acquisition by new investors in October 2022.</p>
History	<p>The comprehensive list of regulatory inspections and approvals has been appended to the CRO Master File (MF).</p>
A brief report of inspection activities undertaken	<p>The review consisted of the following scope and study-related activities:</p> <ul style="list-style-type: none"> <li>- Evaluation of the company's implementation of the most recent Corrective and Preventive Action (CAPA) plan.</li> <li>- Assessment of the informed consent process.</li> <li>- Review of approvals and correspondence from ethics committees.</li> <li>- Evaluation of test article accountability, including dispensing and storage.</li> <li>- Assessment of the processing and handling of biological (plasma) samples collected during the study.</li> <li>- Verification of equipment calibration.</li> <li>- Examination of employee training procedures.</li> <li>- Evaluation of computer controls.</li> <li>- Tour of the facility to assess overall operations.</li> </ul> <p>Regarding analytical operations, the following areas were covered to ensure adherence to best practices:</p> <ul style="list-style-type: none"> <li>- Confirmation of personnel qualifications involved in analytical testing.</li> </ul>

	<ul style="list-style-type: none"> <li>- Review of procedures utilized during method validations and analytical testing.</li> </ul> <p>Furthermore, a comprehensive review was conducted to scrutinize the following:</p> <ul style="list-style-type: none"> <li>- Clinical study data.</li> <li>- Analytical method validation.</li> <li>- Analytical study data.</li> </ul> <p>This review also involved comparing the source data with the study reports to ensure consistency and accuracy.</p>
<b>Scope and limitations</b>	
Out of scope	<p>This inspection covered the bioanalytical facility located at A-77 and the clinical facility situated at A-31. Our evaluation considered the observations that led to the issuance of the Notice of Concern (NOC) on November 9, 2022.</p> <p>The inspection did not include the assessment of the bioanalytical facility at A-31 or the clinical facility at the Unit-I Ahmedabad (Satellite) site.</p> <p>The Satellite site in Ahmedabad was responsible for conducting the clinical portion of the study related to WHO application no MA193.</p>

Abbreviations	ADR	adverse drug reaction
	AE	adverse event
	ALCOA	attributable, legible, contemporaneous, original and accurate
	ARL	acutest research laboratory
	BA	bioanalytical
	BE	bioequivalence
	BDL	below detection limit
	CAPA	corrective actions and preventive actions
	CC	calibration curve
	CPU	clinical pharmacology unit
	CRA	clinical research associate(e)
	CRF	(electronic) case report form
	CRO	contract research organization
	CTM	clinical trial manager
	CoA	certificate of analysis
	CSR	clinical study report
DQ	design qualification	

ECG	electrocardiogram
GAMP	good automated manufacturing practice
GCP	good clinical practice
GLP	good laboratory practice
GMP	good manufacturing practice
HPLC	high-performance liquid chromatography
LC-MS/MS	liquid chromatography–mass spectrometry
IB	investigator’s brochure
ICF	informed consent form
ICH	International Conference on Harmonization
(I)EC	(Independent) Ethics Committee
IMP	investigational medicinal product
ISF	investigator study file
ISR	incurred sample reanalysis
IQ	installation qualification
LIMS	laboratory information management system
LLOQ	lowest limit of quantification
LOD	limit of detection
MS	mass spectrophotometer
MVR	monitoring visit report
NRA	national regulatory agency
OQ	operational qualification
PIS	patient information sheet
PQ	performance qualification
PQS	pharmaceutical quality system
QA	quality assurance
QC	quality control
QRM	quality risk management
SAE	serious adverse event
SAR	serious adverse reaction
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
ULOQ	upper limit of quantification
URS	user requirements specifications

<b>PART 2</b>
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<b>SUMMARY OF THE FINDINGS AND COMMENTS</b>
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<b>General section</b>
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## 1. Organization and management

A comprehensive presentation was delivered, elaborating on the organization's activities in detail, particularly highlighting the significant changes that have occurred since the previous WHO inspection.

The CRO provided an organizational chart that depicted key positions within the company.

A list of signatures from authorized personnel responsible for carrying out tasks during each study was accessible and duly verified.

The management was aware of the necessary measures to ensure the implementation and adherence to appropriate and technically valid SOPs. The maintenance of a well-organized historical file containing all SOPs was duly carried out.

The Master agreement between the sponsor and the CRO was readily available. The agreement was reviewed.

The CRO obtained permission from CDSCO to conduct the Bioequivalence (BE) study, along with the corresponding import license.

An observation related to the Organization and management was adequately addressed in the respective CAPA plan.

## 2. Computer systems

System validations were conducted for various software systems within the organization. The validations were carried out by vendors in accordance with the validation master plan. Vendors performed IQ, OQ, and PQ as part of the validation process. Periodic assessments for computer system validation were conducted by evaluating change control records and identifying any necessary updates. If applicable, necessary updates were implemented. For in-house validation of computer systems, reference was made to the applicable SOP. This procedure was established to ensure that computerized systems were suitable for their intended purpose and underwent validation, operation, and maintenance in compliance with the principles of GCP and GLP, as appropriate.

An inventory of computerized systems on the network was maintained. The design, qualification, management, and control of networks, including the complete client/server architecture and interfaces, were implemented.

An ample number of computers were available to facilitate personnel in conducting data entry and handling tasks that involved calculations and compilation of reports. These computers were equipped with the necessary capacity and memory to support their intended use effectively.

Every computer within the Company was connected to the servers through a local area network (LAN). To ensure system security, data protection agents were installed on all the computers within the premises. These agents were specifically designed to prevent unauthorized access to the system through external storage devices like pen drives, CD/DVD drives, or any other storage medium capable of copying data.

Access to data folders was granted to users solely within their respective departments through the LAN. For instance, the staff members in the Biostatistical department could only access data folders located in the PBS (Pharmacokinetic and Biostatistics) directories via the LAN. To prevent unauthorized access from external networks, a firewall was implemented at the point where the in-house network connected to the internet. Firewall rules were consistently reviewed and promptly modified to mitigate emerging network threats or to provide extended access permissions, as directed by the System Administrator or their designee.

In the event of troubleshooting, vendors were granted access to computer applications through the firewall using remote desktop or internet access. However, access was only permitted for designated desktops/servers, and it required a username/password combination. These credentials were provided by the IT department and were required to be changed after the vendor completed their work. Access authentication was strictly enforced by the firewall. To safeguard against virus attacks, both individual computer systems and the server were equipped with anti-virus software. This software played a crucial role in protecting the data and computers from potential virus threats.

The software programs utilized to execute key tasks were mandated to undergo validation by the vendor to ensure suitability for their intended use. Qualification and/or validation certificates/reports were obtained to verify that the software had undergone proper validation processes and had been developed in compliance with a quality assurance (QA) system. Randomly selected systems' qualifications were reviewed for verification purposes.

Quality risk management was implemented during the process of determining which components required validation. SOPs were established for the usage of each software program employed in conducting activities for a Bioequivalence study. The SOPs included guidelines for the deletion and disabling of software systems, which were specified in the section concerning the deletion and disabling of user accounts. A dedicated form was provided for documenting the creation, modification, transfer, and deletion of user accounts for each software system. To ensure the termination of user access to the chromatography software, the relevant documentation for personnel who had left the company since November 2022 was reviewed. This assessment aimed to confirm that the necessary steps had been taken to revoke the user access rights of individuals who were no longer employed by the company.

The documentation of computer configuration changes in quality systems was mandated according to the SOP for Change Control. Whenever an update or upgrade of a software version was necessary, the respective department or IT department was required to follow a change control procedure. The new software version had to undergo validation to ensure that the applicable process changes were properly addressed.

All relevant activities performed during the update or upgrade process were required to be recorded in the software's history card. The specific procedure for documenting these activities was outlined in the respective SOP. This SOP provided detailed instructions on how to record the necessary information and maintain a comprehensive record of the software's version history.

Data entry procedures, including data validation methodology such as proofreading and double data entry, were specifically designed to prevent errors.

In accordance with the SOP for Data backup and restoration, the electronic data was regularly backed up. A specific server was utilized for data storage, serving as bidirectional data storage for both the Ahmedabad and Navi Mumbai locations. Additionally, it acted as a disaster recovery (DR) for each other. The data from the Vadodara site was unidirectionally stored at the Ahmedabad site and was also treated as DR for the Vadodara site. The IT department was responsible for performing daily incremental backups of the data stored on the storage/server. Incremental backups were taken daily, and a weekly full backup was conducted on Fridays as depicted in the respective flowchart.

During the inspection, it was found that the regular restoration process was not carried out in accordance with the respective SOP. However, a new template was introduced, and this practice was implemented during the inspection. The restoration of data was supported by screenshots as evidence, and the user department verified the readability of the restored folder.

The user representative prepared an SOP for each respective software, and the relevant study personnel should receive training on the overall operation and usage of the software. To verify the procedure, an application was randomly selected, and the respective documentation was reviewed.

The Bioanalytical department utilized a collection of access-controlled and validated "Raw data Excel sheets" to evaluate the acceptance criteria of analytical runs and instrument performance.

Observations related to the Computerized systems were adequately addressed in the respective CAPA plan.

### **3. Quality management**

The CRO had established QA and QC systems, supported by written SOPs, to ensure the proper conduct of trials and the generation, documentation, and reporting of data in accordance with the protocol, Good Clinical Practice (GCP), Good Laboratory Practice (GLP), and other applicable regulatory requirements. During the inspection, the CRO provided the inspectors with a USB containing the current relevant SOPs for their review. Additionally, upon specific request, the CRO provided the historical versions of the SOPs. It was noted that the company had revised several SOPs since the change of management. To facilitate understanding, the CRO presented a summary of these changes during their presentation at the opening meeting.

The CRO provided a Quality Manual, the purpose of which was:

- Communicate a quality management plan,
- Provide information on quality procedures, control, and assurance,
- Demonstrate conformity to National and International regulatory requirements,
- Share knowledge,
- Serve as evidence of management's commitment to quality.

A QMS was established across all organization sites. The QMS included the implementation of independent QA and QC systems based on in-house SOPs. The QA department operated autonomously and reported directly to the facility management. The purpose of the QMS was to ensure compliance with the GxP requirements, in-house SOPs, relevant study protocols, and applicable regulatory requirements. The quality



management system included management review, root cause analysis, tracking for trends, and the implementation of appropriate CAPA. The procedure for Management review (MR) was revised to organize the MR at least twice per year. The minutes of the meeting for 1 Apr 2023 and 8 Jun 2023 were available and reviewed.

Both in-process and retrospective QA verifications were conducted, including verification during bioanalysis where samples and standards were prepared and tested.

The company outlined the specific audit trail queries or reports to be used for different systems and purposes in the respective SOPs. The SOPs clearly defined the data to be reviewed. During the interview with the QA staff responsible for audit reviews, it was observed that they had a good understanding of how data and any potential modifications were presented in the audit trail, as well as which data changes were deemed acceptable in the routine utilization of the system.

The audit of the Diagnostic laboratory was verified to be handled in accordance with the respective SOP.

The issuance of study templates within the scope of inspection was conducted using the previous manual system, for which an observation was made during the previous inspection. The inspection team noted that a new system had been implemented using a specific software system. Furthermore, the logbook for template issuance and the document for template reconciliation of the study CV020 were present, subject to random verification, and found to be acceptable.

Observations related to the QMS were adequately addressed in the respective CAPA plan.

#### **4. Archive facilities**

The archive facility, located at site A-77, was inspected during the previous inspection and no issues or concerns were noted at that time.

#### **5. Premises**

A facility tour was conducted during the inspection.

On Day 2 of the inspection, the modified areas of the Clinical facility, at Site A-31, were visited. The tour consisted of Unit 1, the pharmacy, the check-in/screening area, the former laboratory area, the server room, and the IT storage room. The sample processing room, sample collection, and dosing area were also visited. The temperature monitoring sensor of a randomly selected freezer was tested, and it triggered an audible alert at 15°C. The temperature records generated by the digital thermometer software application were reviewed. Additionally, the temperature records of the temperature monitoring

application for the stability chamber utilized for the Investigational Medicinal Product (IMP) used for study CV020 were requested and reviewed for the study period, specifically from 1 Oct 2022 to 15 Nov 2022.

The facilities were kept clean and had adequate lighting at the time of inspection.

Clinical trials were conducted in a manner that ensured the safety of the subjects.

The CRO had enough space to accommodate the personnel and activities necessary for conducting the studies. The trial site had suitable facilities and equipment. Access to the facility was restricted and monitored using keycards. Alarm systems were installed, and the doors were appropriately secured. Measures were in place to ensure emergency evacuation procedures. All entries to and exits from the facility were documented and recorded.

The clinical sites included a pharmacy that stored investigational products under suitable conditions. The pharmacy utilized five stability chambers for separate storage of IMPs for ongoing studies, retained samples, and narcotics. Access to the pharmacy was restricted and monitored. Detailed records of each visit to the pharmacy were maintained, including entry and exit logs. The temperature and humidity in the pharmacy were monitored and controlled using the temperature and relative humidity (RH) digital monitoring system.

The laboratory premises (A-77) were designed to accommodate the intended operations. Ample space was provided to prevent mix-ups, contamination, and cross-contamination, facilitated using glass separators. Sufficient storage capacity was available for samples, standards, solvents, reagents, and records.

The laboratory premises were designed with the safety of all employees and authorized external personnel, including inspectors or auditors, in mind. The design aimed to provide adequate protection during the handling or working with chemicals and biological samples.

Safety data sheets were available to staff before testing was carried out. Staff working in the laboratory were familiar with and knowledgeable about the material safety data sheets for the chemicals and solvents they were handling. Firefighting equipment, including fire extinguishers and fire blankets, was readily available. Staff were instructed to wear laboratory coats. Highly toxic and/or genotoxic samples were handled in a safety cabinet to avoid the risk of contamination. Containers of chemicals were fully labelled and included prominent warnings (e.g., “poison”, “flammable”) whenever appropriate. Staff members were well-informed about the importance of not working alone in the laboratory. First-aid materials were easily available, and the staff received comprehensive training in first-aid techniques, emergency care, and the use of antidotes. The inspectors

lacked the necessary qualifications to verify the insulation and adequacy of the wires and electrical infrastructure used throughout the facility, primarily due to the facility's substandard condition.

Containers containing volatile organic solvents, such as mobile phases or liquid/liquid extraction solvents, were closed with an appropriate seal. Volatile organic chemicals were handled under certified fume hoods or air extractors, and safety and eye showers were available in the laboratory.

Premises had suitable systems in place to dispose of waste, treat fumes, and protect the environment in conformance with local or national regulations.

Observations related to the Premises were adequately addressed in the respective CAPA plan.

## **6. Personnel**

The company underwent significant personnel changes and management transition since the previous WHO inspection, which was introduced during the opening meeting.

A sufficient number of qualified and experienced medical, paramedical, technical, and clerical staff were present to support the trial and effectively respond to foreseeable emergencies. The total staff count for the company was 380 individuals, at the time of inspection. Throughout all stages of the trial, including nighttime, adequately trained personnel were available to ensure the protection of subject rights, safety, and well-being, as well as provide emergency care. Contract workers were also employed for specific activities.

To verify compliance, a review was conducted on randomly selected current curricula vitae and training records of both full-time and contract workers involved in trial activities. Specifically, the verification was performed on the completion of yearly GLP training, data integrity training, and emergency training conducted in 2022.

Observations related to the Personnel were adequately addressed in the respective CAPA plan.

**Clinical section****7. Clinical phase**

The clinical phase of the studies was performed on the premises of the CRO.

The CPU at Site A-31 had a total of 122 beds, with an additional three beds in the ICU. Accommodation facilities were equipped with systems that allowed subjects to notify CRO staff if assistance was needed. The facilities for changing and storing clothes, as well as for washing and using the restroom, were clean, easily accessible, and suitable for the number of users. To better accommodate the female subjects, extra toilets were added to Unit 1 at A-31. These toilets were lockable, alarmed, and designed to be opened from the outside in case of a medical emergency.

The clinical site consisted of:

- subjects' registration and screening; obtaining informed consent of individual subjects without compromising privacy. The area also served as a check-in area prior to study initiation;
- CPU;
- subjects' recreation;
- Pharmacy;
- Room for the administration of the investigational products and sample collection;
- sample processing (e.g., plasma separation) and storage (freezer);
- Archive facility;
- Preparation of standardized meals and a dining hall;
- ICU

Provisions were made for the urgent transportation of subjects to the hospital. An acknowledgement from the hospital was received and documented.

Access to the randomization list was limited. The pharmacist would submit a request to the statistician via email, and upon generation, the statistician would send the list to the pharmacy's email address. To ensure security, the list was password protected. The relevant emails were available and verified for this purpose.

The equipment used was appropriately calibrated at predefined intervals. During the previous inspection, the ECG machine was inspected, specifically for its capability to store patient data and ECG records used for screening volunteers. No remarks were raised.

## 8. Clinical laboratory

The CRO employed an accredited external clinical laboratory for sample analysis. The laboratory held a valid certificate of accreditation issued by NABL, in accordance with ISO 15189:2012, until the 12<sup>th</sup> of April 2024.

To close the in-house pathology laboratory, a change control process was initiated. The initiation of the change control was documented on a specific form., and the verification of change implementation was recorded on another form. Partial verification of implementation was confirmed on 30 Dec 2022, while verification for all points mentioned in the change control dated 29 Nov 2022 was completed on 10 Mar 2023.

Hematological tests, urine analysis, and other tests were performed during the clinical trial as specified in the study protocol.

The sample labeling process utilized the barcode system integrated with a specific cloud system. This ensured complete traceability and maintained the integrity of the samples throughout their receipt, storage, and chain of custody. The process of sample collection at the screening area and check-in area was thoroughly reviewed. Each volunteer/subject was assigned a unique barcode generated in the respective database for identification purposes. The phlebotomist verified the volunteer's identification and entered the corresponding data into the cloud system, along with the selection of tests required as per the protocol. Automatically generated barcodes were affixed to the vacutainer/container used for sample collection. Additionally, a Test Requisition Form was completed for each volunteer, and a copy was sent to the Laboratory along with the samples. The Laboratory custodians were then contacted to facilitate the transfer of samples to the laboratory for testing. The test results were subsequently exported by the study physicians who had access to the cloud system and securely stored with the Case Report Forms (CRFs) for further analysis and record-keeping.

During the inspection, the current and signed curriculum vitae (CV) of the Head of the Clinical Laboratory, was reviewed.

Appendix B of the protocol contained an inclusive compilation of reference ranges and clinically acceptable values for the clinical laboratory tests performed at the study site. These reference ranges were also documented in the TMF. The reference ranges in the laboratory reports issued by the Laboratory were different from the normal ranges recorded on form Appendix B. Consequently, in preparation and extrapolation of the acceptable ranges, different normal values were considered. During the protocol preparation stage, the CRO utilized an in-house laboratory, resulting in different normal values. However, by the time the study commenced, the CRO had made the decision to outsource the service to the external Laboratory, which operated with different values. The CRO was aware of this transition and conducted an evaluation to assess whether the

difference in values had any impact on the safety of the study participants. As a result, the reference list was revised for future studies to align with the updated laboratory service provider. Additionally, a note to file was generated to address this issue, providing an explanation of the discrepancy, and including a safety evaluation.

In response to the inspection team's request, the CRO supplied a list of volunteers with discrepancies in their safety sample analysis. The affected volunteers were identified, and their inclusion was thoroughly discussed during the inspection.

An observation related to the Clinical Laboratory was adequately addressed in the respective CAPA plan.

## 9. Ethics

Trials were approved by the Independent Ethics Committee (IEC) before any study was conducted. The Committee's independence from the sponsor, the investigator, and the CRO was verified through the respective member list. IEC's decisions, recommendations, and decisions of the IEC meetings were well documented. The IEC was given sufficient time to review protocols, informed consent forms (ICFs), and related documentation based on the letter available in the TMF. The BE study was also authorized by CDSCO.

An Insurance Company provided insurance coverage for the period from 16 Apr 2022 to 15 Apr 2023. Details regarding insurance coverage and compensation or treatment procedures in the event of injury or disability resulting from participation in the trial were made available through the insurance policy.

### Informed consent form

Information was provided to study participants in either Marathi or Hindi languages, ensuring that it was communicated at a level of complexity suitable for their understanding. The information was conveyed both orally and in writing.

Prior to commencing any trial-related activities, informed consent was obtained from each subject and documented in writing. The provided information was clear, emphasizing that participation in the study was voluntary and that subjects had the right to withdraw from the study at any time without the need to provide a reason. Any reasons for withdrawal were duly recorded in the study documentation.

Volunteers or subjects were given the opportunity to discuss any concerns they might have had regarding potential side effects or reactions from the investigational products with a physician before deciding to participate in the trial. This information was adequately explained in the Informed Consent Form (ICF).

The certificates of in-house translation for the informed consent forms were reviewed as part of the process.

## 10. Monitoring

The study was subject to monitoring conducted by third-party monitors acting on behalf of the sponsor. These monitors visited the study site to ensure compliance with the protocol, GCP, and relevant ethical and regulatory requirements. Their responsibilities included verifying the correct completion of Case Report Forms (CRFs) and ensuring the accuracy of collected data. The scope of the monitoring was specified in the report. Monitoring visits were conducted during each phase of the trial. After each site visit, the monitor prepared a written report detailing their findings and communicated any issues to the CRO and the sponsor in a timely manner. This allowed for swift corrective action, even while the study was ongoing. All relevant communications and subsequent corrective actions were documented accordingly.

Monitors from the third party were assigned to study CV020. The monitoring reports for this study were signed by the assigned monitor as well as other designated individuals involved in the monitoring process.

## 11. Investigators

The principal investigator (PI) was responsible for the clinical conduct of the study, including clinical aspects of study design, administration of the products under investigation, contacts with local authorities and the ethics committee, and signing of the protocol and the final study report. The agreement was electronically signed.

## 12. Receiving, storage and handling of investigational drug products

Comprehensive records were maintained regarding the receipt, storage, handling, and accountability of investigational products throughout the entirety of the trial. Additionally, the shipment, delivery, receipt, description, storage conditions, dispensing, administration, reconciliation, and return of any remaining pharmaceutical products were thoroughly verified. Pertinent details of the pharmaceutical products used, including dosage form, strength, lot number, and expiry date, were documented. The shipment of investigational products was equipped with a data logger, and the relevant documentation contained the ID number and temperature records associated with it.

All procedures related to the management of investigational medicinal products were clearly defined in the respective SOPs, such as SOP for the Handling of Investigational Medicinal Products. This SOP also outlined the specified retention time for investigational medicinal products.

Pharmaceutical products were stored according to the appropriate conditions specified in the official product information provided by the sponsor. The storage conditions were monitored using the digital temperature and humidity monitoring system. In the case of alarm logs, investigations were initiated using a designated form. Although the forms documenting humidity excursions during the study CV020 were not classified as controlled documents, the integrity of these forms was confirmed by the verification of the presence of the individuals who had signed them.

Randomization was carried out following the SOP for the randomization of treatment, and proper documentation was maintained, including the randomization list and seed. The randomization list was created by utilizing the appropriate template in the randomization program (using the PROC PLAN procedure) in SAS. Access to the randomization list was restricted to the individual responsible for its generation, a dispensing pharmacist, and the statistician, who could access it via email. The list was securely kept in the pharmacy.

The investigational products were appropriately labelled, and their conformity with the randomization list was verified after printing and before labelling the containers. Labels were affixed to the containers to prevent loss of information when the lid was opened. The labels were created using Excel sheets.

Adequate routines for labelling and documenting the administration of the IP were established to verify that each subject received the product dispensed for them by using labels with a tear-off portion. Labels were designed to have two identical labels, one portion to be pasted onto the container and the second label pasted onto the CRF at the time of dosing.

The empty containers were labelled separately for the test and the reference investigational products. They remained segregated in the stability chambers under lock and key to avoid the risk of any potential mix-ups until the dispensing stage.

Dispensing and packaging procedures were performed following the applicable requirements. Dosing was performed in accordance with the respective SOP.

The surface on which the product was handled was thoroughly cleaned. A second person verified that the surface area/line was clear and clean before bringing in and opening containers of the product. The IMPs were handled with appropriate utensils. Tablets were distributed into each container in accordance with the randomization list for the comparator or the test product as appropriate. The two products, i.e., Test & Reference, were handled at different times. This also applied to the labelled containers. Every step was recorded sequentially in detail.



Investigational product accountability and dispensing records were maintained. Every activity was documented at the moment it occurred, encompassing details such as administered doses, returned or destroyed doses, and verification by a second person for each step.

Dosing was carried out in accordance with the respective SOP under the supervision of the investigator and qualified staff member to whom this task was explicitly delegated in writing. Since there was no activity during the inspection, dosing administration was not observed. However, it was checked that dosing was directly documented in the CRFs.

Investigational product reconciliation was verified after dosing by a second individual. Original container samples were kept for potential confirmatory testing for at least one year beyond the expiration date of the newest product. The sample retention time was outlined in the applicable SOP and specified in the sponsor-CRO contract. Additionally, unused dispensed products were retained. The IMP documentation for the MA193 study was accessible and underwent a spot check by the CDSCO observer.

### **13. Case report forms**

Randomly selected CRFs from the study CV020 were reviewed.

The data collected on each volunteer was specified in the trial protocol.

Copies of the clinical laboratory reports and all ECGs certified copies were included in the CRFs for each subject. Information about ICFs (screening and study specific), drug and alcohol tests, screening activities, inclusion/exclusion criteria, study participation, IMP administration, blood sample collection procedure, vital sign and physical examination measurement, and ambulatory sample visit details, was recorded in the CRFs. A selective cross-verification was conducted by comparing the corresponding information in the respective database.

An observation related to the CRFs was adequately addressed in the respective CAPA plan.

### **14. Volunteers, recruitment methods**

A database was maintained on volunteers to avoid cross-participation and specify a minimum time that should elapse between a volunteer's participation in one study and the next. Access to the database was password controlled to secure confidential information on volunteers or subjects.

Identification of volunteers and subjects was ensured through a biometric system, and the information was captured by the audit trail.

The informed consent of potential subjects was obtained for any screening procedures required to determine eligibility for the study, in addition to informed consent for participation in the research portion of the study. The clinical trial protocol described criteria for subject selection (inclusion and exclusion criteria) and screening procedures. A software system, i.e., OVIS was used to determine whether any of the subjects had participated in a previous trial. Participation data was uploaded to this central repository to prevent over-volunteering.

## **15. Food and fluids**

Meals were standardized, adequately controlled and scheduled during the study days. The CRO was able to arrange standardized meals, snacks, and drinks for the study subjects as described in the clinical trial protocol and according to the list of meal details, using the in-house kitchen.

Timing, duration, and amount of food and fluids consumed were recorded. Before samples were obtained from ambulatory subjects, they were asked about their food and drink consumption. A dietitian with appropriate qualifications, training, and experience designed standardized meals for the facilities within Accutest. The CV was signed on 6 June 2023 in the respective software application. The dietitian was based in Ahmedabad.

## **16. Safety, adverse events, adverse event reporting**

The study was planned, organized, performed, and monitored so that the safety profile was acceptable, including to the volunteers. A medical doctor was responsible for medical decisions in the case of adverse events and notifying the relevant health authorities, the sponsor, and, when applicable, the ethics committee, specifically in the case of a serious adverse event.

First-aid equipment and appropriate rescue medication were available in the ICU. Any treatment given to a subject was documented and included in the CRF and the supporting documentation in the ICU. It was discussed to clearly link the logbook for the use of medication in an emergency with the respective ICU, during the inspection.

The CRO had adverse event registration and reporting forms as part of the CRF.

**Bioanalytical section**

The inspection primarily focused on study CV020, including the associated validation projects, with additional spot checks performed for study MA193. The investigation encompassed the following records and activities:

- Source documentation and raw data pertaining to the validation of the bioanalytical methods were examined.
- The analysis of subject plasma samples and their corresponding electronic data was scrutinized.
- Audit trails related to the electronic data capture and handling procedures concerning the bioequivalence (BE) studies were reviewed.
- Results obtained from calibration standards, quality control samples (QCs), and subject plasma samples in analytical runs were assessed. Additionally, the chromatograms generated from the analytical runs were thoroughly examined.
- The preparation process for analyte stock solutions, calibration standards, QCs, internal standards, and reagents was investigated.

Furthermore, chromatograms and their integration, the absence of signals in the blank samples, and the absence of any unexplained interruptions in the injected sequences were investigated. The reason for the study sample repeat analyses and all instrument failures was reviewed. The provisions and the documentation of the ISRs were confirmed. The documentation and justification for the reinjection of the analytical runs were verified and compared to the provisions.

For a review of the study documentation, the inspection team received adequate support from well-informed and transparent personnel.

**17. Method development, Method validation & Analysis of study samples**

The method development process was adequately described and documented, and the usage of IS was justified based on the relevant literature. A copy of the literature was available. After method development, an analytical plan was provided as a basis for the method validation. In the MS methods, a stable isotope-labelled internal standard was consistently utilized. Study CV020 employed Sodium Heparin as the anticoagulant, whereas study MA193 employed K<sub>3</sub>EDTA.

During the method validation, in accordance with the respective SOP, a run was conducted to determine the suitability of batch size for study CV020 and study MA193. The runs consisted of 155 samples for study CV020 and 131 samples for study MA193, using quality control (QC) samples and calibration curves (CCs). This run aimed to establish a batch size that was comparable in length to the batches expected to be used for the subsequent analysis.

The sample processing was documented in the respective forms. A note to file was also provided to record any unexpected activity during sample processing, when applicable.

Data to support the stability of the samples under the stated conditions and period of storage was available before the start of the studies, except for the long-term stability, which was performed before the issuance of the study reports.

The review of the entire method validation included precision and accuracy testing (P&A), sensitivity, selectivity, matrix effect, calibration curve, autosampler carry-over, dilution integrity, stability (including freeze-thaw stability, stock solution stability, and reference standard storage stability), haemolytic effect, recovery, and reinjection reproducibility. Partial validation was performed according to the requirements. The matrix used for the analytical method validation was the same as the matrix of the study samples, including anticoagulants and additives. The documentation pertaining to the plasma obtained from the in-house clinic of Accutest was reviewed and discussed. This included the examination of records related to the receipt, storage, retrieval, preparation, and consumption of the pooled plasma.

Each analytical run included calibration curve (CC) standards, QC samples interspersed throughout the run, and subject samples, all processed simultaneously. The exact sequence of processing was defined and documented. All samples collected from a given subject during all trial periods were analyzed in the same run. The acceptance criteria for the analytical runs were confirmed by a review of the analytes' retention time, the accuracy of calibration standard and quality control samples, peak integration, and IS peak areas, as per the applicable SOPs. A system suitability and a stabilization test were done prior to the start of runs on each day.

Of the first 1000 samples, 10% were used to run Incurred Sample Reanalysis (ISR), and of the subsequent samples, 5% were used for the same purpose. The samples were selected with a concentration around  $C_{max}$  and in the elimination phase. The acceptance criteria were clearly defined in the respective SOP.

The system audit trail review was carried out at the time of the studies in the scope of the inspection, and adequate training was provided to the responsible personnel through documentation.

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

The specification of samples (blood plasma), sampling method, volume, and number of samples were stated in the clinical trial protocol and the information provided to the volunteers. The collection, preparation, transport, or shipping and storage of samples took place in accordance with the applicable SOPs.

Actual sampling times and deviations from the prespecified sampling times were recorded, and the respective deviations were considered when calculating the pharmacokinetic parameters.

The labelling of collected samples was clear to ensure each sample's correct identification and traceability. All storage conditions (e.g., freezer temperature) were controlled, monitored, and recorded throughout the storage period and during transportation. Records of the storage and retrieval of samples were maintained. Samples were duplicated in aliquots, shipped, and stored separately.

The study samples, QC samples, and pooled matrix were discarded in accordance with SOP for Segregation, transfer, retention, and disposal of biological samples. The retention of samples was defined in the agreement between the sponsor and the CRO.

An observation related to the Handling of biological samples was adequately addressed in the respective CAPA plan.

## 19. Data processing and documentation

Integration settings were based on scientific principles and could be justified. The smoothing factor was kept low enough not to mask possible interferences and changes in peak geometry.

The criteria for acceptance and exclusion of CC standards and QC samples, as well as batch acceptance, were clearly defined in the applicable SOP. The source data for all the analytical runs contained all information about the original first evaluation of runs (containing all calibration samples) when the analysis was repeated. The calibration range was adequately truncated. Internal standard variations were trended and used as part of the verifications of result validity.

Full audit trails were always activated on all analytical instruments before, during, and after the method validation and the studies of interest.

All original analytical raw data, including calculations, chromatograms, and associated audit trails, were documented in a manner that ensured traceability. This documentation

encompassed essential information such as the sample number, equipment used, date and time of analysis, as well as the name(s) of the technician(s) involved. All audit trail files were retained (e.g., results table audit trail, project audit trail, and instrument audit trail).

Each data point was traceable to a specific sample, including sample number, time of collection of the sample, time of centrifugation, time when the sample was placed in the freezer, and time of sample analysis, to be able to determine whether any aberrant results might have been caused by sample mishandling.

## **20. Good laboratory practices**

On Day 3, a facility tour of Site A-77 was conducted to assess its suitability in terms of arrangement and safety. Throughout the bioanalytical part of the bioequivalence studies, the general principles of Good Laboratory Practice (GLP) were diligently followed.

The deep freezers designated for sample storage and the refrigerators allocated for Reference standards storage underwent qualification, calibration, and regular maintenance procedures. An alarm system was installed in conjunction with the respective digital thermometer to generate buzzing sounds, alerting the responsible custodians in charge of facility maintenance. During the inspection, the automatic alarm system was tested to ensure its proper functionality and records of daily monitoring and alarm checks were diligently documented.

For the purposes of qualification verification, the temperature mapping of a randomly selected Deep Freezer was reviewed to verify the hotspot and the location of the respective sensor. The temperature mapping process was carried out at the time of inspection. Transfer of samples to equivalent storage units was considered under maintenance and repair.

Balances, other measuring devices, and equipment and instruments used during the conduct of a trial were periodically calibrated and verified before use to be fit for their intended purpose.

The operation, use, calibration, checks, and preventive maintenance of equipment were described in the respective SOPs. Records were maintained in accordance with applicable requirements. These activities were verified by random review of the equipment used in study-related activities. Equipment and its components were labelled with the respective ID number, date of calibration, and date of next calibration. The equipment usage was adequately documented in the analytical sheets, as well as the respective logbooks for the instrument usage. The use of columns was recorded in the logbook for the usage of columns. The daily, quarterly, and yearly calibration records of randomly selected analytical balance, as well as the daily and yearly calibration records of micropipettes were verified.

Chemicals, reference substances, reagents, solvents, and solutions were labelled to indicate identity, purity, concentration when appropriate, expiry date, and specific storage instructions. Information concerning the source, preparation date, and stability was available on the label or the CoA.

## Pharmacokinetic, statistical calculations, and reporting section

### 21. Pharmacokinetic, statistical calculations

A comprehensive presentation was delivered by the Biostatistician on Day 4 to provide a detailed explanation of the randomization list generation process and the planning of pharmacokinetic (PK) and statistical analysis for the bioequivalence studies. The statistical model underlying the primary BE analysis was stated in the protocol.

The statistician’s qualification was verified.

The study protocol provided explicit details on how pharmacokinetic and statistical calculations were to be conducted, specifying the software and scripts to be used.

Calculations and PK analysis were performed utilizing the SAS application. To ensure data integrity, the raw data underwent both a QC check and a 100% QA check throughout the data flow process. Additionally, a second qualified individual performed a double-check of the data values input, in accordance with relevant SOPs. This approach ensured the accuracy and adherence to established protocols during the analysis phase.

### 22. Study report

The process of study report writing was verified during the inspection. Procedures were established to ensure the quality and integrity of the study report. No discrepancies were identified between the results stated in the report and the original (raw) data.

The study report included a report on the bioanalytical part of the trial, including a description of the bioanalytical method used and a report on the validation of this method. The Principal Investigator approved the clinical study reports. The responsible staff and management also approved the bioanalytical reports. Monitoring and audit reports were available before the release of the final study report.

An observation related to the Study report was adequately addressed in the respective CAPA plan.

Miscellaneous	
<i>Samples taken</i>	N/A
<i>Assessment of the CRO master file</i>	The current CROMF was submitted and reviewed.

<b>Part 3</b>	<b>Conclusion – inspection outcome</b>
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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 studies were considered to have been conducted at an acceptable level of compliance with WHO GCP/GLP/BE guidelines at **Accutest Research Laboratories (I) Pvt. Ltd.** located at the following addresses:

**Clinical site**

**A-31, MIDC, TTC Industrial Area  
Khairane  
Navi Mumbai, 400 709  
Maharashtra – India**

**Bioanalytical site**

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

<b>Part 4</b>	<b>List of guidelines referenced in the inspection report</b>
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1. Guidance for organizations performing in vivo bioequivalence studies. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fiftieth Report Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 9.  
**Short name: WHO BE guidance or TRS996 Annex 9**  
<https://apps.who.int/iris/bitstream/handle/10665/255338/9789241209960-eng.pdf?sequence=1&isAllowed=y>
2. Good clinical laboratory practice (GCLP), WHO on behalf of the Special Programme for Research and Training in Tropical Diseases. Geneva, 2009  
**Short name: WHO GCLP**  
<https://apps.who.int/iris/handle/10665/44092>



3. Guidelines for good clinical practice for trials on pharmaceutical products. WHO Technical Report Series, No. 850, 1995 (pp. 97–137).  
**Short name: WHO GCP**  
<https://www.who.int/publications/i/item/9241208503>
4. Handbook – Good Laboratory Practice (GLP): quality practices for regulated non-clinical research and development – Annex I: The OECD Principles on GLP, 2nd ed., 2009. **Short name: OECD GLP**  
<http://www.who.int/tdr/publications/documents/glp-handbook.pdf>
5. Standards and operational guidance for ethics review of health-related research with human participants. Guidance Document. Geneva, World Health Organization, 2011.  
**Short name: WHO Ethics Committee Guidance**  
<https://www.who.int/publications/i/item/9789241502948>
6. Guidelines for the preparation of a contract research organization master file, WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957), Annex 7.  
**Short name: WHO CROMF Guidelines or TRS No. 957, Annex 7**  
[https://www.who.int/publications/i/item/WHO\\_TRS\\_957](https://www.who.int/publications/i/item/WHO_TRS_957)
7. Model guidance for the storage and transport of time-and temperature-sensitive pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth Report. Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 9.  
**Short name: WHO storage and transport guidance or TRS 961 Annex 9**  
[https://apps.who.int/iris/bitstream/handle/10665/44079/WHO\\_TRS\\_961\\_eng.pdf?sequence=1&isAllowed=y](https://apps.who.int/iris/bitstream/handle/10665/44079/WHO_TRS_961_eng.pdf?sequence=1&isAllowed=y)
8. Glove use information leaflet, Patient Safety, Save lives clean your hands. Geneva, World Health Organization, 2009 (revised).  
**Short name: Glove use information leaflet**  
[https://www.who.int/publications/m/item/glove-use-information-leaflet-\(revised-august-2009\)](https://www.who.int/publications/m/item/glove-use-information-leaflet-(revised-august-2009))
9. Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability. Republication of multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability. WHO Technical Report Series No. 992, Annex 7 with a new appendix 2. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-first Report Geneva, World Health Organization, 2017 (WHO Technical Report Series, No. 1003), Annex 6.  
**Short name: TRS 1003 Annex 6**  
<chrome-extension://efaidnbnmnibpcjpcglclefindmkaj/https://www.who.int/docs/default-source/medicines/norms-and-standards/guidelines/regulatory-standards/trs1003-annex6-who-multisource-pharmaceutical-products-interchangeability.pdf>

10. Good chromatography practice. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fourth Report. Geneva, World Health Organization, 2020 (WHO Technical Report Series, No. 1025), Annex 4.  
**Short name: WHO TRS No. 1025, Annex 4**  
<https://apps.who.int/iris/handle/10665/331814>
11. Guideline on data integrity. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fifth Report. Geneva, World Health Organization, 2021 (WHO Technical Report Series, No. 1033), Annex 4.  
**Short name: WHO TRS 1033, Annex 4**  
<https://apps.who.int/iris/handle/10665/340323>
12. Declaration of Helsinki, World Medical Association Declaration of Helsinki, Ethical principles for medical research involving human subjects, Bulletin of the World Health Organization, 2001 (79(4)).  
**Short name: Declaration of Helsinki**  
<https://apps.who.int/iris/handle/10665/268312>
13. Bioanalytical Method Validation and Study Sample Analysis M10, ICH Harmonised Guideline, Final version, Adopted on 24 May 2022  
**Short name: ICH M10**  
[https://database.ich.org/sites/default/files/M10\\_Guideline\\_Step4\\_2022\\_0524.pdf](https://database.ich.org/sites/default/files/M10_Guideline_Step4_2022_0524.pdf)
14. Good Manufacturing Practices: Guidelines on validation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-third Report Geneva, World Health Organization, 2019 (WHO Technical Report Series, No. 1019), Annex 3.  
**Short name: WHO TRS No. 1019, Annex 3**  
<https://www.who.int/publications/m/item/trs-1019---annex-3-good-manufacturing-practices-guidelines-on-validation>
15. Supplementary guidelines on good manufacturing practices: validation, WHO Expert Committee on Specifications for Pharmaceutical Preparations, Fortieth report, World Health Organization, 2006 (Technical Report Series, No. 937), Annex 4.  
**Short name: WHO No. 937, Annex 4**  
<https://apps.who.int/iris/handle/10665/43443>  
[ring-practices-guidelines-on-validation](#)