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WHO Prequalification Unit (PQT) – Inspection Services Team (INS)
WHO PUBLIC INSPECTION REPORT
Bio-Equivalence Study
WHOPIR

Part 1	**General information**
Organization details	
Company information	
Name and Address of Clinical Research Site	Accutest Research Laboratories (I) Pvt. Ltd., (Satellite) 4th Floor, The Grand Monarch Near Seema Hall, Anand Nagar Road Satellite, Ahmedabad, 380015 India Accutest Research Laboratories (I) Pvt. Ltd., (Vadodara) 1st & 2nd Floor, Synergy Square Complex Krishna Industrial Estate BIDC, Gorwa Vadodara, 390016 India
Name and Address of Bioanalytical Research Site	NA
Name and address Statistical Site	NA
Corporate address of Organization	Accutest Research Laboratories (I) Pvt. Ltd. A-31, M.I.D.C., T.T.C. Industrial Area, Khairane Navi Mumbai – 400 709, Maharashtra India Tel: + 91 22 2778 0718/19/21 Fax: + 91 22 2778 0720
GPS coordinates	Satellite: 23.01307° N 72.52098° E Vadodara: 22.23936° N 73.16612° E

WHO product numbers covered by the inspection/ Product names/ Study numbers/ Study titles	**WHO application no. CV019 (Satellite)** Bioequivalence Study of Molnupiravir 200mg Capsules **WHO application no. HA715 (Satellite)** Bioequivalence Study of Emtricitabine and Tenofovir Disoproxil Fumarate Tablets 200 mg and 300 mg **WHO application no. CV026 (Vadodara)** Bioequivalence Study of Nirmatrelvir 300 mg (2 x 150 mg Film-coated tablets) + Ritonavir 100 mg (1 Film-coated tablet) **WHO application no. CV023 (Vadodara)** Bioequivalence Study of Test Product (T) Molnupiravir 200 mg **WHO application no. TB404 (Vadodara)** Bioequivalence Study of Test Product (T) Bedaquiline Fumarate 100 mg Tablets **WHO application no. MA198 (Vadodara)** Bioequivalence Study of Test Products: Amodiaquine (as hydrochloride) 153 mg Dispersible Tablets + Pyrimethamine/Sulfadoxine 25 mg/500 mg Dispersible Tablets **WHO application no. HA787 (Vadodara)** Bioequivalence Study of Test Product (T) Ritonavir 100 mg Tablets
Inspection details	
Dates of inspection	Satellite site: 20 to 21 May 2024 Vadodara site: 22 to 24 May 2024
Type of inspection	Routine
Introduction	
Summary of the activities	The CRO conducts the following activities: BA/BE Studies (Bioavailability/Bioequivalence): - Phase I studies involving healthy subjects and patients (PK studies) for generics and biosimilars. Clinical Development Services: - Conducting Phase II to IV studies for both small and large molecules. - Providing Post-Marketing Surveillance (PMS) services. - Conducting studies on nutraceuticals and therapeutic equivalence. - Evaluating clinical endpoints.

	- Offering comprehensive services in data management, biostatistics, programming, and medical writing. Biologics Services: - Conducting pre-clinical studies. - Managing Phase I, II, and III clinical trials. - Offering characterization services. - Conducting clinical comparability studies (PK/PD) and immunogenicity studies specifically tailored for biosimilar products.
General information about the company and site	Accutest Research Laboratories was established in 1998 and specializes in providing Bioavailability/Bioequivalence (BA/BE) services to pharmaceutical firms globally, with a focus on India. In response to increased demand, the company expanded its clinical facility in Ahmedabad, Gujarat, in 2006. Additionally, Accutest operates a clinical facility in Vadodara. However, it's noteworthy that their facility in Bodakdev (Unit II) was closed in 2021. The inspection team was informed that the company planned to close the Ahmedabad facility and maintain only the clinical facility in Vadodara, along with their facilities in Navi Mumbai.
History	The following inspections were conducted: **Ahmedabad:** DCGI(01), WHO(08), USFDA(19), EMA(05), ANVISA(03), ISP Chile(01), NPRA-Malaysia(01) **Vadodara:** DCGI(01), WHO(01), USFDA(04), NPRA-Malaysia(01), MoH-Turkey(01)
Brief report of inspection activities undertaken	The review process involved a comprehensive assessment of study-related activities of the clinical part. This included examining the company's historical performance, evaluating the execution of clinical studies, scrutinizing the informed consent process, reviewing ethics committee approvals and related correspondence, assessing IMP accountability, analyzing dispensation and storage practices, evaluating processing and handling protocols for biological (plasma) samples collected during the study, verifying equipment calibration procedures, assessing employee training programs, examining computer control systems, and conducting a facility inspection through a guided tour.
Scope and limitations	
Out of scope	The bioanalytical part of the studies was not in the scope of this inspection.

Abbreviations	ADR	adverse drug reaction
	AE	adverse event
	ALCOA	attributable, legible, contemporaneous, original and accurate
	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 chromatograph
	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
	PD	Pharmacodynamics

PK	Pharmacokinetics
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

PART 2	**Summary of the findings and comments**

General Section

1. Organization and management

A detailed presentation was provided explaining the organization's activities at the opening meeting.

The CRO had an organizational chart depicting key positions and the names of responsible persons. The organizational chart was dated April 20, 2024, and was authorized. It was updated during the inspection, as a new Corporate QA Head had joined the company a few days prior to the inspection and was not yet reflected on the chart. The CRO was accredited by the national regulatory authority, as mentioned in the respective CROMF. The registration certificate of the Ahmedabad site, along with the license to import (for WHO application no. HA715) and the license for examination, testing, and analysis, and the details of the respective notification were available and reviewed.

There was a job description for each employee, including their responsibilities. It was randomly verified that every job description was signed and dated by the staff member to whom it applied.

A list of signatures of the authorized personnel performing tasks during each study was available and verified.

The CRO management acknowledged that, as the investigator was a CRO employee, certain responsibilities typically assigned to investigators also fell under CRO management's purview. Management ensured the implementation and adherence to appropriate and technically valid SOPs, maintaining an organized historical file of all SOPs.

Working hours for a 5-day week were from 9:00 AM to 5:30 PM, including work scheduled for every 2nd and 4th Saturday.

2. Computer systems

A list of software and computer systems utilized in the studies was provided.

Procedures for Computer System Validation were established to ensure that computerized systems were suitable for their intended purpose and validated, operated, and maintained in accordance with the principles of GCP and GLP, as appropriate.

An inventory of all computerized systems on the network was available, identifying those regulated by GxP. Any changes to the network, including the temporary addition or removal of systems, were documented.

There were an adequate number of computers to facilitate personnel in performing data entry and handling calculations for report compilation. Computers possessed sufficient capacity and memory for their intended use.

Access to software systems containing trial-related information was controlled. The method of access control was specified, and a list of individuals with database access was maintained. Secure and unique, individual-specific identifiers and passwords were employed.

The software programs utilized for critical processes were deemed appropriate for their intended purposes. Qualification and/or validation certificates were provided under the user’s supervision. The qualification of the randomly selected systems was reviewed for verification, such as the document management system, subject registration software, and temperature record software.

The specific user requirements, regulatory/guideline requirements for BE studies, and the operating environment in which the system was used were considered in the Performance Qualification. Quality risk management was applied to decide which components needed to be validated. SOPs for the usage of each software program used to perform activities of a BE study were available.

Whenever required, key software programs were regularly updated following an appropriate risk assessment of the potential impact on current data and qualification or validation status. These updates were conducted in accordance with the respective SOP.

The software programs used, the frequency of virus testing, the storage of data, and the procedure for backing up and archiving all relevant electronic data, including the frequency of backups were specified in an SOP. Backups were periodically rewritten as part of the procedure, and the data from previous backups were archived. The reliability and completeness of these backups were verified.

Data entry procedures, including data validation methodologies such as proofreading and double data entry, were designed to prevent errors. These procedures were detailed in the applicable SOP.

Observations related to the computerized systems were sufficiently addressed in the respective CAPA plan.

3. Quality management

The CRO had appropriate QA and QC systems, with written SOPs, to ensure that trials were conducted, and data were generated, documented, and reported in compliance with the protocol, GCP, GLP, GMP, and applicable regulatory requirements. A Quality Manual (version 2, dated 12 Feb 2024) was provided. QA personnel were not directly involved in trial-related activities.

The QA unit was responsible for:

- verifying all activities undertaken during the study.
- ensuring that the quality management systems were followed, reviewed, and updated.
- determining that the protocol and SOPs were made available to study personnel and were being followed.
- checking all the study data for reliability and traceability.
- planning and performing self-inspections (internal audits) at regular and defined intervals in accordance with an SOP and following up on any corrective action as required to determine if all studies were conducted in accordance with GCP and GLP.
- ensuring that contract facilities adhere to GCP and, if applicable, to GLP. This included auditing such facilities and following up on any corrective action required.
- verifying that the trial report accurately and completely reflected the data from the study and the methods and procedures followed.
- promptly reporting audit findings in writing to management, to the investigator, and to the study director, as applicable.

Both in-process and retrospective QA verifications (e.g., in bioanalysis, as the samples and standards were being prepared and tested) were performed according to the applicable SOP, QAU/004.

The quality management system included root cause analysis, trend tracking, ensuring all aspects of data integrity, and the implementation of appropriate corrective and preventive actions (CAPA).

Observations related to the quality management system were sufficiently addressed in the respective CAPA plan.

4. Archive facilities

The CRO maintained a secure storage facility for archiving trial-related documents. It was equipped with fire extinguishers, humidity and temperature control systems, as well as measures for pest control. Additionally, the archives were safeguarded against flooding with a water disaster management system in place. Overall, the CRO ensured the safety and integrity of the documentation through comprehensive security measures.

The archiving activities were managed following SOP for Request for Retrieval of documents.

Access to the archive storage area was controlled and restricted to authorized personnel, and a list of authorized individuals was displayed at the facility's entrance.

Records of document access and return were diligently maintained in accordance with the defined period outlined in the SOP. This period for retaining study documentation, including raw data, was also stipulated in the contract between the sponsor and the CRO.

During the inspection, the trial-related documentation archiving procedures were verified through successful retrieval and traceability of the documents.

Observations related to the archive facility were sufficiently addressed in the respective CAPA plan.

5. Premises

During the inspection, a tour of the facility was conducted on Day 2 at the Ahmedabad site and Day 3 at the Vadodara site.

The facilities were maintained in a clean condition and provided adequate lighting, ventilation, and environmental control. Surfaces such as floors, walls, and working bench surfaces were designed for easy cleaning and decontamination.

Clinical trials were conducted under conditions ensuring sufficient safety for the subjects, with appropriate site selection based on potential risks.

The CRO had enough space to accommodate personnel and activities necessary for conducting the studies, and the trial site was equipped with adequate facilities, including room for sample processing and equipment.

Access to the facility was restricted and controlled through keycards/biometric access, with provisions for emergency evacuation. Entry and exit were recorded.

Clinical activities were conducted at sites, including a pharmacy where investigational products were stored under suitable conditions. Access to the pharmacy was restricted through a biometric system, ensuring controlled entry and exit. Detailed records of each visit to the pharmacy were meticulously maintained to track entry and exit.

Adequate insulation and spark-proofing measures were implemented for electrical wiring and equipment, including refrigerators.

The premises were equipped with suitable systems for the proper disposal of waste.

An SOP for Handling Power Failure was established to ensure procedures were in place to manage power interruptions. The UPS was tested according to the criteria outlined in this SOP. During the inspection, documentation was provided and reviewed.

The inspection team noted that the hotspot identified during the temperature mapping was indicated by an empty box. The sensor was positioned near the display/controlling sensor. This practice had been previously assessed during the May 2022 inspection and deemed acceptable.

Access and monitoring of the Closed-Circuit Television Cameras (CCTV) were conducted in compliance with the Policy for Access Control, with daily checks performed. Evidence of these activities was available and reviewed. Video records were routinely overwritten based on the system's storage capacity, typically every few days.

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

6. Personnel

A qualified team comprising medical, paramedical, technical, and clerical staff was available to support the trial and respond effectively to foreseeable emergencies. In Ahmedabad, the team consisted of 35 members, while in Vadodara, there were 44 members. Throughout all trial stages, including night-time, trained personnel were present to ensure the subjects' rights, safety, and well-being were protected and to provide care during emergencies. Additionally, contract workers were employed for specific activities to enhance the team's capabilities.

Randomly selected current curricula vitae and training records of personnel involved in trial activities, including both full-time and contract workers, were reviewed and verified.

Clinical section

7. Clinical phase

The clinical phase of the studies was conducted at the CRO premises.

In Ahmedabad, there were 94 beds distributed between Wing A (60 beds) and Wing B (34 beds). In Vadodara, there were 140 beds spread across Wing A (60 beds), Wing B (36 beds), and Wing D (44 beds). Each wing was equipped with emergency alarms, sample collection/dosing areas, sample separation areas, washrooms with emergency alarms, recreational areas, physical examination rooms, dining areas, and change rooms with lockers. Additionally, there were ICU beds shared between the wings. Screening activities, including consent, registration, ECG, physical examinations, and sample collection, took place in designated areas. The pharmacy had separate acceptance and dispensing areas with storage at room temperature and 2-8°C. Cold storage facilities included deep freezers at -20°C and -70°C. The in-house archive facility was available, and an ambulance was on-site and equipped for emergencies.

Systems were in place in the accommodation facilities to enable subjects to alert CRO staff in case of need.

The CRO had made agreements with external service providers for X-ray execution when applicable. In Vadodara, for the study related to WHO application no. HA787, two facilities were utilized. The date and registration number of the volunteer were recorded on the X-ray image. The most recent agreement with one of the facilities was available and reviewed. The facility provided X-ray, pathological laboratory, and ambulance services. Agreements with the hospital were renewed every two years.

The facilities for changing and storing clothes, as well as for washing and toilet purposes, were clean, easily accessible, and suitable for the number of users. Lockable toilets were equipped with alarms, and doors were designed to allow opening from the outside in case of a medical emergency.

Provisions were in place for the urgent transportation of subjects to the hospitals in Ahmedabad and Vadodara, if needed.

Access to the password-secured randomization list, transmitted via email was restricted to the pharmacist responsible for the study.

The equipment was regularly calibrated at predefined intervals. The proper function and performance of equipment available for emergency use, such as defibrillators, were verified at suitable intervals.

The IQ & OQ documentation for the centrifuge machine, conducted in November 2015, was provided and reviewed. Additionally, the last calibration certificate dated February 23, 2024, was reviewed.

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

8. Clinical laboratory

External clinical laboratories, all of which were accredited, were employed to analyse samples.

For the study related to WHO application no. HA715, the screening process commenced on April 1, 2023. Blood and urine samples collected for screening on April 1, 3, and 4, 2023, were initially sent to the existing Pathology Laboratory. However, it was identified that the Laboratory did not comply with the terms and conditions outlined in the agreement. This non-compliance resulted in the use of an external laboratory for some parameters without informing Accutest, leading to delays in receipt of the results. On April 5, 2023, another Laboratory was contracted, starting from April 6, 2023, blood and samples were sent to the new Laboratory, following protocol amendment version 02. Subjects screened on April 1, 3, and 4, 2023, were not considered for the study. The respective submission to the Institutional Ethics Committee (IEC) was sent on April 13, 2023, and the documentation related to this submission was available and reviewed.

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

A software system was employed to ensure the reliability of sample labelling, receipt, storage, and chain of custody. Samples were transported to the laboratory in boxes with ice packs by designated laboratory personnel.

In Vadodara, the CRO utilized the Laboratory system to generate labels for the samples, producing only the necessary quantity corresponding to the collected samples.

The CRO received information about the laboratory's analytical methods, a dated list of laboratory normal ranges, and the laboratory's accreditation certificate.

The laboratory created individual reports for each subject, which were included in the CRFs.

9. Ethics

The trials were approved by independent ethics committees (IECs) before any study was conducted. The respective approvals were randomly checked. Verification of their respective member lists confirmed these committees' independence from the sponsor, investigator, and CRO. Approval letters, along with the review of documentation, recommendations, and decisions from the IEC meetings, were thoroughly examined.

The IECs were given ample time to review protocols, informed consent forms (ICFs), and related documentation. Any necessary additional information was promptly provided to the IECs as needed.

Informed consent form

Information for study participants was provided in vernacular languages, i.e., Hindi and Gujarati, both orally and in writing, at a level of complexity suitable for their understanding.

Prior to commencing any trial-related activities, informed consent was obtained from the subjects and documented in writing. The information conveyed was clear, emphasizing the voluntary nature of participation and the right of the subject to withdraw from the study at any time without providing a reason. Reasons for withdrawal were recorded in the study records.

Information regarding insurance coverage and procedures for compensation or treatment in the event of injury or disability resulting from participation in the trial was available. The insurance policy was with a specific policy number.

Volunteers or subjects were encouraged to discuss any concerns about potential side effects or reactions from using the investigational products with a physician before participating in the trial.

The certificate of translation and back-translation of the informed consent were available. For the study related to WHO application no. HA715, a translation office was utilized, and the documentation was thoroughly reviewed.

10. Monitoring

It was verified that a randomly selected study was monitored by monitors employed by the sponsor. These monitors were adequately qualified to ensure adherence to the protocol, applicable GxP, and ethical and regulatory requirements. Their responsibilities included verifying the use of the correct procedures for completing CRFs and ensuring the accuracy of the data obtained.

Pre- and post-study visits, as well as monitoring visits during the trial, were conducted as required by the sponsor. Following each site visit, the monitor prepared a written report and promptly communicated any issues to both the CRO and the sponsor to facilitate swift corrective action, if possible, even while the study was ongoing. Communications and subsequent corrective actions were documented.

The study related to WHO application no. HA715 did not undergo monitoring by the sponsor. For the study related to WHO application no. HA787, the presence of monitors was confirmed through verification against the respective visitor logbook.

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.

11. Receiving, storage, and handling of investigational drug products

Information regarding the receipt, storage, handling, and accountability of investigational products throughout the trial was documented. Additionally, details concerning the shipment, delivery, receipt, description, storage conditions, dispensing, administration, reconciliation, return, and/or destruction of any remaining pharmaceutical products were verified. Key details of the IMP, such as dosage form, strength, lot number, and expiry date, were also recorded.

Pharmaceutical products were stored under suitable conditions as per the official product information supplied by the sponsor. Monitoring of these conditions was facilitated through the digital monitoring system. Additionally, a dehumidifier was made available in the pharmacy storage area and utilized selectively during more humid seasons. At Vadodara, the documentation of IMP for the study related to the WHO application no. HA787 was thoroughly verified. An excursion of temperature during the shipment (32.7°C for 1 hour and 40 minutes) was appropriately investigated and documented. Importantly, it was confirmed that this temperature variation had no impact on the stability of the IMP, providing the respective evidence.

Randomization was conducted following the respective SOP, and the records were documented, encompassing the randomization list and the respective seed number. Access to the randomization list was restricted solely to the dispensing pharmacist and statistical personnel.

The IPs were properly labelled in accordance with SOP for Labelling. Compliance of all labels with the randomization list was verified once they were printed and before labelling the containers. Labels for WHO products were printed using Microsoft Word, while the CRO used another software application for other products. That application could not be used for WHO products, as the system lacked the features needed to complete WHO product labels according to the respective requirements. Labels were affixed to the containers to ensure the information was retained even when the lid was removed. Adequate routines for labelling and documenting the administration of the IP were established to verify that each subject received the correct product dispensed to them. This was achieved by using labels with a tear-off portion. These labels were designed to have two identical parts: one to be affixed to the container and the other to be attached to 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 a secure area under lock and key to avoid the risk of any potential mix-ups until the dispensing stage. Dispensing and packaging procedures were carried out in accordance with the applicable requirements as outlined in the respective SOPs.

The surface on which the product was handled was cleaned before introducing the bottles into the area. All product containers (full or empty), individual dosage formulations, labelling materials, contaminants, dirt, and debris were removed from the area. A second person verified that the surface and surrounding area were clear and clean before opening and handling the product containers. The investigational medicinal products were managed with appropriate utensils. Tablets were allocated to each container in accordance with the randomization list for either the comparator or the test product as required. The Test and Reference products were handled at different times to avoid cross-contamination. Every step was recorded sequentially and in detail. The surface and its

surroundings were cleared and cleaned immediately before and after dispensing each subsequent product within the same study.

Investigational product accountability and dispensing records were always maintained. Each activity was documented at the time it was performed, including records of doses administered and returned or destroyed and records of verification by a second person/QA.

Dosing was performed in accordance with the applicable SOP, under the supervision of the investigator and a qualified staff member who was explicitly delegated this task in writing. For solid oral dosage forms, a mouth check was conducted using a tongue spatula and a penlight to ensure the subject had swallowed the investigational product. Dosing was directly documented in the CRFs.

Investigational product reconciliation after dosing was verified by a second responsible person. Samples of the product in the original container were retained for potential confirmatory testing in accordance with regulatory requirements. Sample retention was defined and described in an SOP and specified in the contract between the sponsor and the CRO. Dispensed products that were not administered were also retained.

The observation related to the IMP handling was adequately addressed in the respective CAPA plan.

12. Case report forms

Randomly selected CRFs, using studies related to WHO application numbers HA715, HA787, and CV026 were reviewed. The data collected on each volunteer was specified in the trial protocol.

The clinical laboratory reports provided by the laboratory and all ECGs were included in the CRFs for each subject. Information recorded in the CRFs included screening records, details of ICF, preliminary evaluations, demographic profiles, medical histories, physical examinations, X-ray results from external facilities (when applicable), volunteer participation details, inclusion and exclusion criteria acceptance, dosing administration, sample collections, and drug abuse urine sample collections.

Evidence of drug abuse testing (e.g. for the study related to WHO application no. HA715) was separately provided using a kit for 6 narcotics prior to check-in for Period I and Period II.

Observations regarding the clinical phase were adequately addressed in the respective CAPA plan.

13. Volunteers, recruitment methods

Procedures for recruiting volunteers were specified in the SOP for Screening and Enrolment of Volunteers, which included a description of the potential methods the CRO used for this purpose. A database was maintained on volunteers to avoid cross-participation and to specify the 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 their names and a biometric system using fingerprints (two thumbs and two index fingers).

Informed consent was obtained from potential subjects for any screening procedures required to determine eligibility for the study. The informed consent for participation in the research portion was study-specific. The clinical trial protocol described criteria for subject selection, including inclusion and exclusion criteria and screening procedures. A software system, OVIS version 4.0, was used to determine whether any of the subjects had participated in a previous trial conducted by other CROs registered in the system. Participation data was uploaded to this central repository to prevent over-volunteering.

Screening procedures, including the informed consent process, interviews, inclusion and exclusion criteria checks, physical exams, ECG, alcohol tests, blood sampling, and urine sampling, were reviewed and checked. The ECG machine had no saving option.

The evidence of bank transactions for the participants in the study related to WHO application no. HA715 was verified.

14. Food and fluids

Meals were standardized, adequately controlled, and scheduled during the study days. The CRO arranged standardized meals, snacks, and drinks for the study subjects as described in the clinical trial protocol and according to agreements with Catering Services.

The 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 the standardized meals.

The meal invoice for the study related to WHO application no. HA715 was provided and reviewed.

The observation regarding the meals and fluids was sufficiently addressed in the respective CAPA plan.

15. Safety, adverse events, adverse event reporting

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

First-aid equipment and appropriate rescue medication were available in the ICU and ready for emergency use at the study site. Any treatment given to a subject was documented and included in the CRF and the supporting documentation in the ICU.

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

16. 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, shipping, and storage of samples were conducted in accordance with the respective SOPs, i.e., for Blood Sample Collection, Processing, and Storage, for Segregation, Transfer, Retention, and Disposal of Biological Samples, for Transport of Biological Samples Outside the Study Centre and for Missing Samples.

Actual sampling times and deviations from the prespecified sampling times were recorded.

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 after the completion of each period, shipped, and stored separately. For the study related to WHO application no. HA715, aliquot I was shipped to the BA lab, and aliquot II was stored in the facility and later discarded in March 2024. The remaining aliquots were normally discarded six months after the completion of the study. The CRO was recommended to store the aliquots separately from the beginning.

The mapping report of one of the freezers was reviewed and verified at the time of inspection.

17. Data processing and documentation

Audit trails were activated on the software systems.

Each data point was traceable to a specific sample, including the sample number, time of collection, time of centrifugation, time when the sample was placed in the freezer, and time of sample analysis. This traceability ensured that any aberrant results could be investigated for potential sample mishandling.

Reporting section

18. Study report

The study reports were provided in accordance with the SOP for Clinical Study Reports. Each site had its own report-writing group. The report writing group in Vadodara was visited and interviewed to explain the process. The documentation was saved in a secure folder with restricted access. The source documents were archived within 30 days after the completion of the Clinical Study Report in accordance with the applicable SOP.

Miscellaneous	
Samples taken	Not applicable
Assessment of the CRO master file	CROMF/001/02, effective 12 May 2023, was provided prior to the inspection and reviewed.
Annexes attached	Not applicable

Part 3	**Conclusion – inspection outcome**

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:

Satellite site
4th Floor, The Grand Monarch
Near Seema Hall, Anand Nagar Road
Satellite, Ahmedabad, 380015
India

Vadodara site
1st & 2nd Floor, Synergy Square Complex
Krishna Industrial Estate
BIDC, Gorwa
Vadodara, 390016
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, before 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.

Part 4	**List of guidelines referenced in the inspection report**

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***

2. Bioanalytical Method Validation and Study Sample Analysis M10, ICH Harmonised Guideline, Final version, Adopted on 24 May 2022
   Short name: ICH M10

3. 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

4. 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

5. 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

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***

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