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

Part 1	**General information**
Organization details	
Company information	
Name and Address of Clinical Research Site	**Cadila Pharmaceuticals Limited** Department of Clinical Pharmacology, Research, and Development Centre 1389, Trasad Road, Dholka–382225 Ahmedabad, Gujarat India
Name and Address of Bioanalytical Research Site	**Cadila Pharmaceuticals Ltd.** Department of Bioanalytical Laboratory Research and Development Centre 1389, Trasad Road, Dholka–382225 Ahmedabad, Gujarat India
Name and address Statistical Site	**Cadila Pharmaceuticals Ltd.** Department of Biostatistics Research and Development Centre 1389, Trasad Road, Dholka–382225 Ahmedabad, Gujarat India
Corporate address of Organization	**Cadila Pharmaceutical Ltd.** Corporate Office Sarkhej-Dholka Road, Bhat-382210 Ahmedabad, Gujarat India, 382210. Fax: +91 2718 225039 Tel +91 2718 351000 +91 2718 251000 +91 2718 225001
GPS coordinates	22.700° N 72.443° E
WHO product numbers covered by the inspection/	**WHO application no. TB406** Bioequivalence study of Ethambutol Hydrochloride Dispersible Tablet 100mg

Product names/ Study numbers/ Study titles	**WHO application no. TB407** Bioequivalence study of Isoniazid Dispersible Tablet 100mg
Inspection details	
Dates of inspection	18 – 22 March 2024
Type of inspection	Routine inspection
Introduction	
Summary of the activities	Cadila CRO provides a range of services, including Bioavailability, Bioequivalence, Phase I studies, Pharmacokinetics, and Biostatistics.
General information about the company and site	Cadila Pharmaceuticals Ltd. was founded in 1951, and its Department of Clinical Pharmacology was established in 2003. In 2002, Cadila CRO originated as the Pharmacology division of Cadila Pharmaceuticals Limited, located within the in-house R&D facility in Dholka, Ahmedabad. By 2005, it transformed into CRO Cadila Pharmaceuticals Ltd. (known as Cadila CRO), aiming to provide contract research services to the pharmaceutical and biotechnology sectors. The in-house R&D facility obtained approvals from the Ministry of Science and Technology in 2003 and the Drug Controller General (India), Directorate General of Health Services in 2006.
History	The CRO has been inspected by regulatory authorities such as DCGI, the Danish Medicines Agency, USFDA, ANVISA, Thai FDA, and NPRA Malaysia. Previously, the CRO underwent inspection by WHO in December 2013.
Brief report of inspection activities undertaken	The following scope and study-related activities were reviewed: The company's history, clinical study performance, informed consent process, ethics committee approvals and correspondence, test article accountability, dispensation and storage, processing and handling of biological (plasma) samples collected during the study, equipment calibration, employee training, computer controls, and a tour of the facility. Regarding the analytical operations, coverage was provided for firm practices, personnel qualifications, and procedures utilized during the method validations and analytical testing.

	A review of the clinical study data, analytical method validation, and analytical study data was conducted, along with the comparison of the source data to the study reports.
Scope and limitations	
Out of scope	N/A

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/CPPU	clinical pharmacology unit
	CRA	clinical research associate(e)
	(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
OVIS	online volunteer information system
PI	principal investigator
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 presentation was provided explaining the activities of the organization in detail.

The CRO presented an organizational chart illustrating key positions and the names of responsible individuals within Cadila CRO. The organogram detailing the members of Cadila CRO Management and CRO staff was dated February 24, 2024. This organogram was also appended to the Quality Manual. An additional organogram for the entire Cadila Pharmaceutical was also available.

The CRO held various certification and approval according to the applicable requirements.

Each employee had a job description outlining their responsibilities. A random verification confirmed that each job description was signed and dated by the respective staff member.

A list of signatures from authorized personnel performing tasks during each study was available.

The principles of Good Laboratory Practices have defined the responsibilities of the test facility management. The CRO management was aware that, as the investigator was an employee of the CRO, certain responsibilities typically assigned to the investigator also rested with the CRO management.

Management ensured the implementation and adherence to appropriate and technically valid SOPs. A well-organized historical file of all SOPs was maintained.

The working hours were from 08:00 to 16:00, Monday through Saturday (apart from the first Saturday of each calendar month).

2. Computer systems

A list of software and computer systems utilized in the studies was submitted pre-inspection.

An adequate number of computers was available to facilitate personnel in conducting data entry and handling, including necessary calculations and report compilation. The computers possessed sufficient capacity and memory for their intended purposes.

Access to software systems containing trial-related data was regulated. The access control method was delineated, and a roster of individuals with database access was upheld. Secure and unique individual-specific identifiers and passwords were employed.

The qualification documentation of the selected systems was reviewed for verification.

SOPs for using computerized systems, such as SOP for chromatography software program utilized for conducting activities in a BE study and SOP for operating, calibrating, and maintaining the wireless data logging system (digital temperature monitoring system), were accessible.

An SOP specified the software programs used, the frequency of virus testing, the storage of data, and the procedure for backing up all relevant electronic data. The backup was periodically rewritten as part of the process, and the data from previous backups was archived. The reliability and completeness of these backups were regularly and randomly verified.

Observations related to the Computerized systems were adequately 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 the applicable regulatory requirements. Additionally, current and relevant SOPs were provided on a pen drive for the inspectors' reference and use throughout the inspection process.

A Quality manual was provided and reviewed.

QA personnel were not directly involved in trial-related activities. While the Quality Assurance (QA) personnel conducted audits as part of their role, these audits did not substitute for the oversight or supervision that was needed from other teams, e.g., the laboratory's QC team.

The QA unit was responsible for several tasks, including:
- 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 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 adhered to GCP and, if applicable, to GLP: this included auditing of such facilities and following up on any corrective action required.
- Verifying that the trial report accurately and completely reflected the study's data and the methods and procedures followed.
- Promptly reporting the 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.

The QMS included root cause analysis and ensured the implementation of appropriate corrective and preventive actions (CAPA).

Issuance of templates for use within the BA laboratory was conducted under QA supervision. Requests were initiated by the BA lab and recorded in a logbook. The laboratory maintained separate records of the templates requested, while the project manager raised a separate request for the required number of templates for each project.

These requests and records were documented in the logbook for utilization records, which were subject to random verification.

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

4. Archive facilities

The CRO maintained a secure facility for archiving trial-related documents. The facility was equipped with a fireproof door, temperature & humidity monitoring measures, and pest control.

The archiving activities were managed following the applicable SOP.

Access to archive storage areas was controlled and restricted to authorized personnel.

Records of document access and return were maintained, including the defined length of time for which study documentation, including raw data, should be kept in the archive as per the SOP.

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

The observation related to the Archive facility was adequately addressed in the respective CAPA plan.

5. Premises

During the inspection, a tour of the facility was conducted. The facility has a built-up area of approximately 11000 square feet spread over three floors.

The facilities were maintained in a clean condition and had sufficient lighting, ventilation, and environmental control. Floors, walls, and working bench surfaces were designed to be easy to clean and decontaminate.

Clinical trials were conducted under conditions ensuring the safety of the subjects, with the selected site considered appropriate for the potential risks involved. The CRO had adequate space to accommodate personnel and activities required for the studies, with appropriate facilities, including laboratories and equipment.

Access to the facility was restricted and controlled via access control cards. Subjects entering/exiting clinical facilities were monitored through locked doors and CCTV. It was noted that the CCTV footage records were not stored. Emergency evacuation procedures were in place, and all entries to and exits from the facility were recorded.

The site where clinical activities occurred included a pharmacy where investigational products were stored under suitable conditions. The access was controlled, and entry/exit records were maintained for each visit.

The laboratory premises were designed to suit the operations to be conducted within them. Sufficient space was provided to prevent mix-ups, contamination, and cross-contamination. Adequate and appropriate storage space was available for samples, standards, solvents, reagents, and records.

Safety data sheets were provided to staff before testing commenced. Staff working in the laboratory were familiar with and knowledgeable about the material safety data sheets for the chemicals and solvents they handled. However, it was recommended that an index for the binder be provided and organized in a way that enabled staff to find instructions easily. Staff were trained to use firefighting equipment, including fire extinguishers, and instructed to wear laboratory coats or other protective clothing. Highly toxic and/or genotoxic samples were handled in a safety cabinet to avoid the risk of contamination. All containers of chemicals were fully labelled and included prominent warnings (e.g., "flammable") whenever appropriate.

Adequate insulation and spark-proofing were implemented for electrical wiring and equipment, including refrigerators. Staff were aware of the importance of avoiding working alone in the laboratory. First-aid materials were readily available, and the staff received first-aid awareness training provided by the Indian Red Cross Society. Evidence of training, including an attendee list dated March 9, 2024, was available, with 30 attendees recorded.

Containers containing volatile organic solvents, such as mobile phases or liquid/liquid extraction solvents, were sealed appropriately. Handling of volatile organic chemicals occurred under fume hoods, and safety and eye showers were accessible in the laboratory.

The premises had appropriate systems in place for waste disposal and protect the environment in accordance with local and national regulations.

A generator and UPS systems provided support for the premises to address electricity interruptions. An external service provider maintained these systems.

6. Personnel

A sufficient and qualified team comprising medical, paramedical, technical, and clerical staff was available to support the trial and promptly address anticipated emergencies. Throughout all trial phases, including night shifts, competent and trained personnel were present to uphold the rights, safety, and well-being of subjects and to provide emergency care when needed.

Randomly selected current curricula vitae and training records of both full-time and contract workers involved in trial activities were reviewed for verification purposes.

The observation related to the personnel was sufficiently addressed in their respective CAPA plan.

Clinical section

7. Clinical phase

The clinical phase of the studies was conducted within the premises of the CRO. The volunteer screening area is situated on the ground floor of the R&D-I facility, serving as the venue for volunteer registration and screening. This area included sections for counseling, audiovisual recording, clinical examination, ECG, phlebotomy, urine collection, and document storage. The Clinical Department was located on the ground and first floors.

The Clinical Department was further subdivided into two clinical housing and investigational areas: Clinic-I, with 36 beds, and Clinic-II, with 30 beds, located on the ground floor and first floor, respectively. Each clinic also had an Intensive Care Unit. These areas were self-contained and equipped to accommodate mixed-gender studies. It included facilities for changing into ward uniforms, subject housing (clinical ward), phlebotomy, sample processing and storage, dining, recreational activities, documentation, and monitoring, as well as separate toilets and showers.

The ICUs were equipped with a multi-parameter monitor, defibrillator, suction machine, ECG machine, oxygen cylinder, and Ambu bag. Emergency medicines and ambulance support were available.

Systems were established within the accommodation facilities to enable subjects to promptly alert CRO staff in case of any requirements or emergencies.

The facilities for changing and storing clothes, as well as for washing and toilet purposes, were maintained in a clean, well-organized, and easily accessible manner, suitable for the number of users. Additionally, lockable toilets were equipped with alarms to ensure added security and safety.

Provisions were also arranged for the immediate transportation of subjects to the nearby hospital in case of urgent medical care needs.

Access to the randomization list was limited to the pharmacist in charge of the IMP handling of the study. The document was securely stored in a designated electronic folder. A biostatistician generated the randomization list using SAS. Quality Assurance (QA) oversaw the control and release of the list. The pharmacist was tasked with generating the corresponding labels.

The equipment used was appropriately calibrated at predefined intervals. At appropriate intervals, the adequate function and performance of emergency-use equipment (e.g., defibrillators) were verified.

Observations related to the Clinical Phase were adequately addressed in their respective CAPA plan.

8. Clinical laboratory

An external clinical laboratory was contracted for sample analysis during the clinical trial. The laboratory held accreditation valid until 8 November 2024, in accordance with ISO 15189 standards.

Hematological tests, urine analysis, and other specified tests outlined in the study protocol were conducted at this laboratory.

Sample labeling, receipt, storage, and chain of custody procedures were implemented to ensure complete traceability and maintain sample integrity throughout the trial.

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

The current and signed curricula vitae of the Head of the Clinical Laboratory were thoroughly reviewed.

The laboratory generated individual reports for each subject, along with the corresponding data, which were included in the Case Report Forms (CRFs).

The Laboratory underwent its most recent audit by the CRO on 25 May 2022.

9. Ethics

Before any study activities commenced, the trials received approval from the Independent Ethics Committee (IEC). The respective member list was reviewed to confirm the committee's independence from the sponsor, investigator, and CRO. Detailed minutes of the IEC meetings were meticulously maintained, and discussions, recommendations, and decisions were documented.

The IEC was allotted sufficient time to review protocols, ICFs, and related documentation thoroughly.

Furthermore, study subjects were insured through an Insurance Company, ensuring coverage for unforeseen circumstances during the trial period.

Informed consent form

Information for study participants was provided in English and Gujarati, ensuring accessibility and comprehension across diverse language preferences. The content was tailored to suit the participants' understanding, both verbally and in written form.

Subjects provided informed consent, which was documented in writing, prior to engaging in any trial-related activities. The information conveyed the voluntary nature of participation, granting subjects the right to withdraw from the study at any time without explanation. Reasons for withdrawal were duly recorded in the study records.

Details regarding insurance coverage and procedures for compensation or treatment in case of injury or disability resulting from participation in the trial were made available through the insurance policy.

Participants were allowed to discuss any concerns regarding potential side effects or reactions to the investigational products with a physician before consenting to participate in the trial.

Certificates of translation and back-translation of the informed consent documents were available.

The observation related to the Ethics committee and informed consent forms was adequately addressed in the respective CAPA plan.

10. Monitoring

The studies were monitored by the monitor contracted by the sponsor. The monitor possessed appropriate qualifications to ensure adherence to the protocol, GCP, GLP, and relevant ethical and regulatory standards. This included confirming the proper completion of CRFs and validating data accuracy.

Throughout the trial, both close-out and monitoring visits were conducted. Following each site visit, the monitor produced a written report and promptly conveyed any issues to the CRO and sponsor, facilitating corrective measures even during the study period whenever feasible. All communications and subsequent corrective actions were duly documented.

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.

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

Information regarding the receipt, storage, handling, and tracking of investigational products throughout the trial was meticulously documented. This encompassed details such as shipment, delivery, receipt, description, storage conditions, dispensing, administration, reconciliation, return to the pharmacy, and/or destruction of any remaining pharmaceutical products. Specifics of the pharmaceutical products utilized, including dosage form, strength, lot number, and expiry date, were also verified.

Pharmaceutical products were stored according to the specifications outlined in the official product information supplied by the sponsor. These conditions were monitored via the temperature and humidity monitoring system.

Randomization was carried out following SOP for the generation of the randomization schedule, ensuring adherence to protocol guidelines. The respective records, including the randomization list and seed, were kept.

The IPs were properly labelled. Once they were printed and prior to labelling the containers, compliance of all labels with the randomization list was verified. Labels were pasted onto the container to ensure that the information was not lost once the lid was removed.

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 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 performed according to the requirements. Dosing was performed according to the applicable SOP. The handling of investigational products was specified in the respective SOP.

Before bringing the IMP containers into the area, the cleanliness of the handling surface was ensured. Any irrelevant item was removed. Prior to bringing in and opening product containers, a second individual confirmed the clearance and cleanliness of the surface area. IMPs were managed using appropriate utensils. Tablet distribution into each container adhered to the randomization list for the respective comparator or test product. Handling of the two products, Test & Reference, occurred at separate times, extending to the labelled containers as well. Each step was meticulously documented in chronological order.

The investigation product accountability and dispensing were adequately documented. Every activity was recorded at the moment of execution, including details of doses administered, returned, or destroyed. Additionally, verification by a second individual for each step was recorded.

Dosing procedures were conducted under the supervision of both the investigator and designated QA staff, as explicitly delegated in writing. Prior to dosing, the label was checked, and the precise time of dosing was recorded on the designated page of the CRF. For solid oral dosage forms, a mouth check, by inspecting under the tongue using a tongue depressor or spatula along with a penlight, was performed to confirm the subject's ingestion. Documentation of dosing activities was directly entered into the CRFs.

A second responsible person verified investigational product reconciliation after dosing. Samples of the product in the original container were retained for possible confirmatory testing for at least one year after the expiry date of the newest product. 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.

13. Case report forms

Randomly selected CRFs from the studies were reviewed.

The trial protocol outlined the specific data to be collected for each volunteer.

Each subject's CRF included copies of clinical laboratory reports and all electrocardiograms (ECGs). Details regarding dosing administration, sample collection,

food intake, physical examinations, and screening activities were documented in the CRF.

14. Volunteers, recruitment methods

Procedures for recruiting volunteers were outlined in SOP for Screening of volunteers, for Registration of volunteers, and for handling and checking in OVIS, including a description of the potential methods utilized by the CRO for this purpose. An Excel application was utilized to manage volunteers, preventing cross-participation and establishing a minimum interval between their participation in studies. Access to this application was password-protected to ensure the confidentiality of volunteer information. Although a new volunteer database was in the process of implementation, it was not operational at the time of inspection. Volunteers were identified by matching their photo in the Excel application with their official ID card.

The informed consent process ensured that potential subjects provided consent for any screening procedures necessary to determine their eligibility for the study, as well as consent for participation in the research aspect of the study. The clinical trial protocol outlined criteria for subject selection, including both inclusion and exclusion criteria, as well as the screening procedures to be followed. A software system called OVIS was utilized to verify whether subjects had participated in previous trials, with participation data being uploaded to this central repository to prevent over-volunteering. Access to the database was secured using fingerprint identification. The inclusion of subjects in OVIS was documented after the administration of the first dose during Period I.

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. The CRO prepared the food in the facility's 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 contracted dietitian with appropriate qualifications, training, and experience designed standardized meals.

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 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.

Bioanalytical Section

The inspection focused on studies TB407, including the associated validation projects. Spot-checks were also performed for study TB406. More specifically, the following records & activities were investigated:

- Source documentation and raw data for validation of the bioanalytical methods.
- Analysis of subject plasma samples as well as the respective electronic data.
- Audit trails for electronic data capture and handling related to the BE studies.
- Results of calibration standards, quality control samples (QCs), and subject plasma samples in analytical runs, along with the chromatograms generated from the analytical runs.
- Preparation of analyte stock solutions, calibration standards, QCs, internal standards, and reagents.

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 verified. The reason for the study sample repeat analyses and all instrument failures was reviewed when applicable. The provisions and the documentation of the ISRs were confirmed. The documentation and justification for the reinjection of the analytical runs were reviewed and compared to the provisions.

During the review of study documentation, the inspection team received sufficient assistance from knowledgeable and transparent personnel. Access to the Chromatography software application and the source data / metadata of the projects within the scope of the inspection was readily provided.

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

The method development process was adequately described and documented, and the usage of any Internal Standard (IS) was justified based on the relevant literature. A copy of the literature was available. After method development, an analytical plan, known as Method STP, was prepared to be the basis for method validation. The mass spectrometry (MS) methods applied a stable isotope-labeled internal standard, and K_2EDTA was employed as an anticoagulant. The utilization of reference standards was documented in the relevant controlled templates, including disposal procedures. Cadila Pharmaceutical supplied the working standards used in the studies, such as Isoniazid WS, and the corresponding documentation was available.

During the method validation, following SOP for Bioanalytical Method Validation, a run was conducted to establish the batch containing sufficient samples (e.g., 138 for Isoniazid study) of quality controls (QCs) and calibration curves (CCs), termed as "Analytical run batch determination," comparable in length to those expected to be used for study sample analysis.

The sample processing was documented in the respective forms. An investigation report 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) – including reproducibility, sensitivity, selectivity, matrix effect, calibration curve, autosampler carry-over, dilution integrity, stability (including freeze-thaw stability, stock solution stability, and reference standard storage stability), hemolytic 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. The plasma was provided in-house, and documentation regarding the collection of lots, identification, hand delivery, and usage was accessible and reviewed for study related to application TB407.

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, such as SOP for Study sample analysis and batch acceptance criteria. A system suitability and a stabilization test were performed prior to the start of runs on each day or after each interruption.

The number of samples selected for Incurred Sample Reanalysis (ISR) should meet the following criteria: at least 10% of the first 1000 samples and 5% of the remaining samples (after the first 1000 samples), or two samples from each period of all study subjects, preferably one sample at Cmax time point and one sample at elimination phase (approximately ≥ 3 times of LLOQ Concentration). The acceptance criteria were explicitly outlined in SOP for Incurred Sample Reanalysis.

The observation related to the Sample Analysis was adequately addressed in their respective CAPA plan.

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

The specification of blood plasma samples, including sampling method, volume, and quantity, was outlined in both the clinical trial protocol and the information provided to the volunteers. The collection, preparation, transportation, and storage of samples were conducted in accordance with the SOP for Subject Sample Management.

The retrieval and storage of biological samples were documented in Annexure II of the respective SOP and in the respective Deep Freezer logbook, as well as on the batch processing form.

Actual sampling times and deviations from the predetermined sampling schedule were documented, and these 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 into aliquots and then transferred to the Bioanalytical Laboratory's Deep Freezer room under the supervision of the custodian. These aliquots were transferred and stored separately within the Deep Freezer room at the Bioanalytical (BA) facility. All pertinent details were documented in the form for the Transfer of Biological Samples from the Clinical Facility to the Bioanalytical Laboratory.

In accordance with the SOP for Handling and Discarding of Biological Study Samples, the study samples, quality control (QC) samples, and pooled matrix were discarded upon the study's completion. The discard process for QC, calibration curve (CC), and pooled matrix for study related to the application TB407 was reviewed and verified, including the form for Reconciliation of CC & QC samples.

Additionally, following the procedure for Solution Preparation, the analyst was instructed to discard all spiking and stock solutions after completing the project or method validation (if not required for further activities).

Observations related to the biological sample storage were adequately addressed in the respective CAPA plan.

19. Data processing and documentation

Integration settings were science-based and fully justified. The smoothing factor was maintained at a low level to ensure that potential interferences and alterations in peak geometry were not obscured.

The relevant SOPs described the criteria for accepting and excluding calibration curve (CC) standards and quality control (QC) samples, as well as batch acceptance. The source data for all analytical runs encompassed comprehensive information regarding the initial evaluation of runs, which included all calibration samples, even when the analysis was repeated. Adequate truncation of the calibration range was ensured. Internal standard variations were calculated and incorporated into the verification process to validate the results.

Full audit trails were always activated on all analytical instruments before, during, and after the method validation and the studies of interest. The service provider provided training for audit trail review during system upgrades.

All original analytical raw data (e.g., calculations, chromatograms, and their associated audit trails) were documented in a manner that ensured traceability concerning the sample number, equipment used, date and time of analysis, and the name(s) of the technician(s). 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.

The observation related to Data processing was adequately addressed in the respective CAPA plan.

20. Good laboratory practices

On Day 3, a facility tour was conducted to assess its suitability in terms of arrangement and safety.

Throughout the bioanalytical segment of Bioequivalence (BE) studies, adherence to the general principles of Good Laboratory Practice was observed, complemented by an appropriate Quality Assurance (QA) system.

The facility housed a total of five LC-MS/MS instruments.

Deep freezers used for sample storage and refrigerators used for reference standards were qualified, calibrated, and maintained. An alarm system integrated with digital thermometers was in place to trigger email notifications to custodians overseeing facility maintenance. During the inspection, the automatic alarm system linked to the Deep Freezer in the sample processing room associated with CPPU I was tested to verify its functionality. Daily monitoring and alarm checks were meticulously documented within the system.

For the purposes of qualification verification, the temperature mapping of the deep freezer was reviewed to verify the hot spot and the location of the respective sensor. The temperature mapping process was properly carried out at the time of inspection. As there was no documentation available regarding the defrosting of freezers, the inspectors were unable to verify the appropriateness of the transfer of samples to equivalent storage units during maintenance and repair procedures.

Balances, equipment, and instruments used during the trial were periodically calibrated and verified before being used to fit 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 usage of columns was documented in controlled forms designed to record the column usage.

The performance verification/calibration of the randomly selected equipment was reviewed.

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.

Observations related to the Good Laboratory Practices were adequately addressed in their respective CAPA plan.

Pharmacokinetic, statistical calculations and reporting section

21. Pharmacokinetic, statistical calculations

On Day 5, the biostatistician delivered a presentation encompassing various parts of the study results calculation and reporting section. The presentation covered pharmacokinetic and statistical analyses and addressed aspects such as the transfer and storage of study data. This approach ensured an understanding of the study's statistical methodologies and data management practices.

22. Study report

The process of writing the study report was verified during the inspection. Procedures were established to ensure the quality and integrity of the study report.

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 before data transfer to the statistical department. The staff and management responsible also approved the bioanalytical reports. Monitoring and audit reports were available before the release of the final study report.

The observation related to the Study report was sufficiently addressed.

Part 3	**Conclusion – inspection**

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 ***Cadila Pharmaceuticals Limited***, located at ***1389, Trasad Road, Dholka–382225, Ahmedabad, Gujarat; 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. 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

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

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***

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

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***

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***

8. Glove use information leaflet, Patient Safety, Save lives clean your hands. Geneva, World Health Organization, 2009 (revised).
   Short name: Glove use information leaflet

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

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

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

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

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

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

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