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WHO Prequalification Unit (PQT) – Team Inspection Services (INS)
WHO PUBLIC INSPECTION REPORT
WHOPIR
Contract Research Organization (CRO)

Part 1	**General information**	
Organization details		
Company information		
Name and Address of Clinical Research Site	Lupin Bioresearch Centre (LBC) Sai Trinity A Wing, Unit 1, 2, 3, & 4, Survey No. 146/2/1B Pashan, Pune, 411021 India	
Name and Address of Bioanalytical Research Site	Lupin Bioresearch Centre Sai Trinity A Wing, Unit 1, 2, 3, & 4, Survey No. 146/2/1B Pashan, Pune, 411021 India	
Name and address Statistical Site	Lupin Bioresearch Centre Sai Trinity A Wing, Unit 1, 2, 3, & 4, Survey No. 146/2/1B Pashan, Pune, 411021 India Spinos Life Science and Research Pvt Ltd, Coimbatore, Tamilnadu, India was responsible for WHO application no. TB403.	
Corporate address of Organization	Lupin Bioresearch Centre Sai Trinity Complex Wing A, Floor 1, 2, 3, 4, 5, 6 and Central Wing, Floor 5 Survey No. 146i2/1B, Pashan, Pune - 411021, India. Ph.: +91-020-66219200	
WHO product numbers covered by the inspection/ Product names/ Study numbers/ Study titles	**WHO application no. TB403**	Bioequivalence Study comparing Pretomanid Tablets 200 mg
	WHO application no. TB402	Bioequivalence Study Comparing Rifapentine Dispersible Tablet 150 mg
	WHO application no. TB411	Bioequivalence Study Comparing Ethambutol Dispersible Tablets 100 mg
	WHO application no. TB410	Bioequivalence Study Comparing Isoniazid Dispersible Tablets 100 mg
	WHO application no. TB409	Bioequivalence Study Comparing Linezolid Dispersible Tablets 150 mg (1 x 4 Tablets)

	WHO application no. TB414	Bioequivalence study comparing fixed dose combination of Rifapentine, Isoniazid, Pyrazinamide, and Moxifloxacin Tablets 300 mg, 75 mg, 375 mg and 100 mg [1 tablet]
	WHO application no. TB415	Bioequivalence study of Rifapentine, Isoniazid, Moxifloxacin tablet 300mg/75mg/100mg
	WHO application no. HA790	Bioequivalence Study Comparing Abacavir, Dolutegravir and Lamivudine Tablets for oral suspension 60mg/5mg/30mg
	WHO application no. TB394	Bioequivalence study comparing Rifapentine and Isoniazid tablet 300 mg/300 mg (1 tablet)
Inspection details		
Dates of inspection	20 – 23 January 2025	
Type of inspection	Routine	
Introduction		
Summary of the activities	LBC is a bioresearch center supporting Lupin's in-vivo and in-vitro BA/BE programs. The CRO consisted of two premises: the Pashan facility for in-vivo studies and the Nande facility for in-vitro studies. Lupin conducts bioanalytical research, focusing on both small molecules and biosimilars. The company specializes in the bioanalysis of drugs and metabolites using highly sensitive assays. In the biosimilars domain, its expertise includes therapeutic proteins and peptides, supporting pharmacokinetic (PK), anti-drug antibody (ADA), neutralizing antibody (nAb), pharmacodynamic (PD), and biomarker assays, utilizing ELISA and MSD-ECL platforms.	
General information about the company and site	LBC was established in 2009 to conduct in-vivo BA/BE studies. In 2012, in-vitro studies commenced, further expanding the research capabilities. In 2016, biosimilar studies were introduced, reinforcing expertise in therapeutic proteins and peptides. In 2024, the clinical facility underwent an expansion. This expansion reflected the company's intention to conduct BE studies necessary for its products using its in-house facilities. Lupin is currently relocating its bioanalytical setup from its Pashan facility to Nande, with key instruments already shifted.	

History	Regulatory inspections by agencies including the FDA, ANSM, MHRA, and WHO were conducted. Onsite inspections were conducted regularly from 2010 to 2023, with the FDA conducting multiple assessments. A WHO inspection took place in April 2022. Remote inspections commenced in 2021 and continued through 2024, primarily by the FDA. A summary of these inspections is provided in Annexure III of the CROMF.
Brief report of inspection activities undertaken	The following scope and study-related activities were reviewed: The company's history, clinical study performance, informed consent process, ethics committee approvals and correspondence, test article accountability, dispensation and storage, processing and handling of biological (plasma) samples collected during the study, equipment calibration, employee training, computer controls, and a tour of the facility. Regarding the Analytical operations, coverage was provided to firm practices, qualifications of personnel, and procedures utilized during the method validations and analytical testing. A review of the clinical study data, analytical method validation, and analytical study data was conducted, along with a comparison of the source data to the study reports.
Scope and limitations	
Out of scope	Due to time constraints, the inspection mainly focused on verifying the implementation of corrective actions related to deficiencies identified in the previous inspection, while also covering areas that were not addressed during that inspection.
Abbreviations	**Meaning**
ADR	adverse drug reaction
AE	adverse event
ALCOA	attributable, legible, contemporaneous, original and accurate
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
CoA	certificate of analysis
CS	calibration standard

CSR	clinical study report
CSV	computerized system validation
ECG	electrocardiogram
F/T	Freeze thaw study
GCP	good clinical practice
GLP	good laboratory practice
HPLC	high-performance liquid chromatograph
HQC	high concentration quality control standard
IB	investigator's brochure
ICF	informed consent form
ICH	International Conference on Harmonization
IEC	(independent) ethics committee
IMP	investigational medicinal product
IS	internal standard
ISR	incurred sample reanalysis
ISV	internal standard response variation
JD	job description
LC-MS/MS	liquid chromatography–mass spectrometry
LIMS	laboratory information management system
LLOQ	lowest limit of quantification
LOD	limit of detection
LTS	long term stability
MVR	monitoring visit report
OQ	operational qualification
P&A	precision and accuracy
PIS	patient information sheet
PQ	performance qualification
QA	quality assurance
QCs	quality control samples
QMS	quality management system
RT	retention time
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
WS	working standard

PART 2	SUMMARY OF THE FINDINGS AND COMMENTS

General Section

1. Organization and management

A presentation was provided outlining the organization's activities in detail, including the latest changes since the previous WHO inspection in April 2022. Additionally, it was mentioned that the relocation of the BA facility to the Nande facility was planned, while the clinical facility would remain at its current location.

The CRO had an organizational chart depicting key positions and the names of responsible persons. The chart was dated 19 November 2024, authorized, and maintained up to date.

Job descriptions were defined in Quality Manual Section 22.1, outlining positions, qualifications, roles, and responsibilities for each position. It was randomly verified that each job description was signed and dated by the respective staff member.

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

The CRO was accredited by CDSCO on 7 April 2020, with accreditation valid for five years under the assigned accreditation number.

The standard working hours were from 08:30 to 17:30, with overtime performed as needed.

2. Computer systems

An inventory index and periodic review schedule of GxP computerized software systems on the network were available, with clear identification of GxP-regulated systems. Any changes to the network, including the temporary addition or removal of systems, were documented.

It was communicated that the CRO was in the process of implementing a software (EDC tool) for all clinical activities, with operational readiness expected within a few months from the date of inspection. The system had been customized to align with the CRO’s SOPs and operations.

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

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

The software programs used to perform key steps were required to be suitable and validated for their intended use. Qualification and/or validation certificates were provided under user supervision to confirm that the software was validated for its intended purpose and developed in a controlled manner in accordance with a QA system. The qualification of selected systems was reviewed for verification.

The Performance Qualification considered specific user requirements, regulatory and guideline requirements for BE studies, and the operating environment, including system compatibility, requirements updates, user skill levels, business continuity, and upgrades. The system's usage in studies was also evaluated. SOPs for the usage of each software program supporting BE study activities were available. It was ensured that access rights granted to investigator site staff aligned with delegated responsibilities and respective tasks.

Regular updates to key software programs were performed as needed, following an appropriate risk assessment to evaluate potential impacts on current data. These updates were conducted in accordance with the applicable SOP, which also outlined the management, monitoring, and control of the network. The physical location of the servers was visited. Firewall settings, antivirus authentication requirements, security patching, system monitoring, and penetration testing were considered in accordance with the applicable SOPs.

A flowchart illustrating the network architecture, including the full client/server structure and relevant interfaces, was available. It depicted the overall network layout and outlined client/server connections, highlighting data flow and server functions. Security elements such as firewalls and access control points were also indicated. Additionally, a separate data flowchart showing data exchange processes between systems and interfaces was provided during the inspection and was to be included in the applicable SOP.

The reliability and completeness of backups were verified. A request was raised within the IT System Management (SM), which was also used to record IT-related incidents. The most recent evidence of data restoration for WHO purposes was available, dated 17 January 2025 as per the applicable form.

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

3. Quality management

The quality management system was designed and planned to ensure the quality of activities, based on ICH-GCP, OECD, and GLP principles, as well as the quality manual and SOPs. It was structured to implement the quality policy by integrating all operational functions, objectives, and activities that contribute to maintaining consistent quality. SOPs were managed manually in paper format. A designated software tool was used as a Learning Management System (LMS) for training on new and revised SOPs.

The CRO was requested to set up a portal for uploading the requested documentation with access for the inspectors. During the inspection, documents, including SOPs and records for various activities, were made available for the inspection team's review and were downloaded for inspection purposes.

A Quality Manual, effective 16 January 2025, was provided. The most recent change to the manual was due to the expansion of the clinical facility by an additional 84 beds. Additionally, the QC function was separated from QA and merged with the respective department. The Quality Manual served as a guide for organizational quality management procedures and was designed to meet data integrity requirements. It outlined the procedures for operating and maintaining the quality management system, ensuring compliance with ICH-GCP and other applicable guidelines. The quality policies and procedures specified in the manual were mandatory for all employees. It was drafted by a team from functional departments and quality teams, reviewed by the Head of Quality Assurance, and approved by the Head of LBC. The manual was reviewed every two years or as needed and was accessible to all employees, who were required to read and understand its contents, objectives, and requirements.

The Quality Assurance Department (QAD) was responsible for ensuring the Quality Management System of LBC operations. The team included the Head of Quality Assurance, Bioanalytical/Clinical Managers, Auditors, an Archival Custodian, a Training Coordinator, and a Documentation Issuance Assistant.

The QAD conducted reviews of at least 20% of the data, coordinated with functional departments to develop quality systems, and performed periodic audits to ensure effective implementation. Its key responsibilities included identifying and preventing quality issues, verifying corrective actions, controlling non-conforming outcomes, and ensuring compliance with regulatory guidelines. The department also managed outsourced CRO qualifications, reviewed retrospective data and study reports, prepared quality-related reports for management, and facilitated audit readiness and regulatory inspections. External agencies could be engaged for third-party audits if required.

Change Control requests were managed through dedicated software, supervised by HQ. This system was used for managing QMS elements, including Change Control (CC), deviations, and CAPA. It had been in use at the site since June 2023.

The company defined in SOP for Quality Assurance Audit at Lupin Bioresearch Center, the audit trail queries and reports to be used for different systems and purposes, specifying the required data for review and the review process. Additionally, a new QA team member with an IT background was hired specifically to review audit trails of the systems.

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

4. Archive facilities

The archive facility was inspected during the previous inspection. A contract was in place with the offsite archiving facility.

The archiving activities were managed following applicable SOPs.

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

5. Premises

The LBC-Pashan facility in Pune spanned approximately 42,000 ft², comprising six floors in Wing A and an extended clinical facility on the fifth floor of the central Wing. The extended clinical facility in the central Wing, on the fifth floor, provided an additional 84 beds to support clinical research operations.

The facilities were maintained in a clean condition with lighting, ventilation, and environmental control. Floors, walls, and workbench surfaces were designed for easy cleaning and decontamination. The CRO had sufficient space to accommodate personnel and study-related activities. The trial site was equipped with appropriate laboratories and equipment. Access to the facility was restricted and controlled through keycards or

biometric systems. Alarm systems were installed to detect subject exits from clinical facilities, and doors were either locked or monitored. Emergency evacuation measures were in place, and all facility entries and exits were recorded.

The sites where clinical activities took place included a pharmacy, where investigational products were stored under appropriate conditions with restricted access. Entry and exit were controlled, and records of each visit were maintained.

As the facility had been thoroughly inspected during the previous inspection and plans were in place to relocate the BA laboratory to a new location, the inspection team did not focus on a facility tour. However, randomly selected LC-MS/MS instruments (with ID no. 2, 9, and 10) were visited and inspected.

An Observation related to the Premises was adequately addressed in the respective CAPA plan.

6. Personnel

A sufficient and qualified team of medical, paramedical, technical, and clerical staff, totaling 150 employees, was available to support the trial and respond effectively to foreseeable emergencies. Qualified and trained personnel were present at all trial stages, including nighttime, to safeguard subjects' rights, safety, and well-being and to provide emergency care. Contract workers were employed for specific activities to complement the team's capabilities.

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

The personnel training system was demonstrated on Day 1. The system functioned as a repository for SOPs, where new or revised SOPs were uploaded and assigned to applicable staff. Staff members were required to study the SOPs and complete a quiz or test within the system. Training compliance was monitored by QA through the generation of reports indicating completed and pending training. Notifications were sent to the respective personnel, requesting the completion of outstanding training.

The CRO was undergoing significant organizational and system changes, including the digitalization of activities. Therefore, it was strongly recommended that comprehensive training be provided on the computerized systems used for various activities to ensure their effective implementation.

Clinical section

7. Clinical phase

The clinical phase of the studies was conducted on the CRO's premises. The clinical department was expanded with the addition of two new clinics in the central Wing of the adjacent building on the fifth floor. This area was visited during the inspection to verify the cross-participation verification operation during the first dosing.

Provisions were made for the urgent transportation of subjects to the hospital. An agreement was available and reviewed.

Access to the randomization list was restricted to the pharmacist in charge of the study. The pharmacist requested the randomization list, and the biostatistician provided it as a password-protected PDF. The password was sent exclusively to the pharmacist responsible for dispensing. After dispensing, the investigational product was securely stored until the completion of the CSR.

The equipment used was appropriately calibrated at predefined intervals. The adequate function and performance of emergency-use equipment were verified at defined intervals.

8. Clinical laboratory

A clinical laboratory was used for sample analysis. Although the laboratory was not accredited, it was noted to be in the process of obtaining CAP accreditation.

Hematological tests, urine analysis, and other required tests were conducted as specified in the study protocol. The CRO received a dated list of laboratory normal ranges. Clinically accepted result ranges were appended to the respective study protocol.

The laboratory generated individual reports for each subject included in the CRFs.

Data integrity requirements for all study-related tests were ensured through validated systems used for sample analysis. The laboratory was visited during the inspection, and data integrity measures were discussed and reviewed.

9. Ethics

Trials were approved by the Independent Ethics Committee (IEC) before any study was conducted. The committee’s independence from the sponsor, investigator, and CRO was verified through its member list. Detailed minutes of meetings documented discussions, recommendations, and decisions. The IEC was given sufficient time to review protocols, informed consent forms (ICFs), and related documentation.

The Ethics Committees associated with the facility were appropriately composed to safeguard the interests and welfare of the community. Their membership included representatives from diverse age groups, genders, and communities. The committee consisted of a medical scientist, a clinician, a legal expert, a social scientist or representative of an NGO, a philosopher, an ethicist, or theologian, and a layperson.

Informed consent form

Information for study participants was provided in vernacular languages (English, Marathi and Hindi) at a complexity level appropriate to their understanding, both orally and in writing.

Informed consent was obtained from each subject and documented in writing before initiating any trial-related activities. The information provided clearly stated that participation was voluntary and that subjects had the right to withdraw from the study at any time without providing a reason. The reasons for withdrawal were documented in the study records.

Information regarding insurance coverage and procedures for compensation or treatment in the event of injury or disability due to trial participation was available through the insurance.

Subjects were given the opportunity to discuss potential side effects or reactions related to the investigational products with a physician before participation.

The certificate of translation and back translation of the informed consent form was reviewed.

10. Monitoring

The study was monitored by a representative of the sponsor. The monitor was appropriately qualified to ensure that the study was conducted in compliance with the protocol, GCP, GLP, and applicable ethical and regulatory requirements. This included verifying the correct procedures for completing CRFs and ensuring the accuracy of the collected data.

A monitoring visit was conducted during the trial for dosing. The monitor prepared a written report for both periods, with no observations noted for the selected study; therefore, no CAPA was required.

11. Investigators

This section had been inspected during the previous inspection without any deficiencies noted.

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

The receipt, storage, handling, and accountability of investigational products at all stages of the trial were documented. Information regarding shipment, delivery, receipt, description, storage conditions, dispensing, administration, reconciliation, return, and destruction of any remaining pharmaceutical products was verified. The details of the pharmaceutical products used, including dosage form, strength, lot number, and expiry date, were also reviewed.

Pharmaceutical products were stored under appropriate conditions as specified in the official product information provided by the sponsor. Storage conditions were monitored using digital temperature and humidity monitoring system. Additionally, a pharmacy walk-in stability chamber was available for controlled storage.

Randomization was performed in accordance with SOP for the generation of randomization schedules for bioavailability and bioequivalence studies. Records, including the randomization list and seed, were maintained. Access to the randomization list was restricted to the person who generated it, the dispensing pharmacist, and the statistician.

The investigational products were properly labeled. Compliance of all labels with the randomization list was verified after printing and before labeling the containers. Labels were affixed securely to the containers to ensure that the information remained intact even after the lid was removed.

Adequate routines for labeling and documenting the administration of the investigational product were established to ensure that each subject received the correct dispensed product. Labels with a tear-off portion were used, with one label affixed to the container and the second attached to the CRF at the time of dosing.

Empty containers were labeled separately for test and reference investigational products. They were securely stored in a segregated, locked area to prevent any potential mix-ups until the dispensing stage.

Dispensing and packaging procedures were conducted in accordance with the specified requirements. Dosing was performed as per the applicable SOP.

The surface used for product handling was cleaned before introducing product bottles into the area. Any product containers (full or empty), loose dosage formulations, labeling materials, contaminants, dirt, and debris were removed. A second person verified that the area was clear and clean before product containers were introduced and opened. IMPs were handled using appropriate utensils. Tablets were dispensed into each container according to the randomization list for the test or comparator product. Test and reference products, including labeled containers, were handled at separate times. All steps were recorded sequentially in detail.

Investigational product accountability and dispensing records were consistently maintained. Each activity was documented in real-time, including records of doses administered, returned, or destroyed. Verification by a second person was recorded for each step.

Investigational product reconciliation after dosing was verified by a second responsible person. Samples of the product in its original container were retained for potential confirmatory testing for a specified period as per regulatory requirements at the clinical site. Sample retention procedures were defined in the applicable SOP. Dispensed products that were not administered were also retained. The Certificate of Analysis (CoA) for the IMP (Ethambutol) was requested and reviewed, along with the respective expiry dates.

13. Case report forms

Randomly selected CRFs from the study were reviewed. The data collected for each volunteer was specified in the trial protocol. Copies of clinical laboratory reports and all ECGs were included in the CRFs for each subject. Information related to screening and study activities was documented in the CRFs.

14. Volunteers, recruitment methods

Procedures for recruiting volunteers were specified in the respective SOP. A database was maintained solely for volunteer registration, while information on screening and study participation was recorded on a paper-based Volunteer Status Record. Access to the database was password-controlled to ensure the confidentiality of volunteer and subject information.

Volunteer and subject identification was ensured through a biometric system using fingerprints. A picture of the volunteer's Aadhaar card was uploaded into the system. An audit report was printed from OVIS (cross-participation database) to confirm that study volunteers were blocked in the system.

It was noted that OVIS audit records were retained for only one month. The OVIS system was visited and discussed with the respective management. Volunteers and study subjects were blocked in the system on the same day of dosing in the first period, and eligibility could be verified either by full name or fingerprint. Names were recorded as spelled on their Aadhaar records. The OVIS system allowed modifications, which were recorded in the audit trail and retained for one month. Report printouts were provided as evidence.

The screening facility used the ECG machine, operated in accordance with the respective SOP. Administrator and technician privileges were assigned accordingly. Stored records on the SD card were transferred to the file server once 80% of the memory was full, with a ticket raised in an IT system. The system's time synchronization was verified, and memory cleaning was documented in the respective logbook when performed.

Alcohol and drug urine tests were conducted. However, details of the kit used for pregnancy testing were not available, although the results were documented in the respective CRF, which was reviewed.

15. Food and fluids

Meals were standardized, adequately controlled, and scheduled during study days. The CRO arranged standardized meals, snacks, and drinks for study subjects as specified in the clinical trial protocol and in accordance with the agreement with the catering service. The invoice related to the Ethambutol study was provided and reviewed, detailing the number of meals required for each period.

The timing, duration, and quantity of food and fluids consumed were recorded. A qualified and trained dietitian designed the standardized meals, which were also approved by the IRB.

16. Safety, adverse events, adverse event reporting

The study was planned, organized, conducted, and monitored to ensure an acceptable safety profile, including for volunteers. A medical doctor was responsible for medical decisions in case of adverse events and for notifying the relevant health authorities, the sponsor, and, when applicable, the ethics committee, particularly in the event 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 administered to a subject was documented in the CRF and supported by ICU records.

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

Bioanalytical section

The inspection focused on studies related to WHO application no. TB410 and WHO application no. TB411, including the associated method validation projects. Spot checks were also conducted for the rest of the studies in the scope of inspection during and prior to the inspection. Specifically, the following records and activities were selectively reviewed:

- Source documentation and raw data for the validation of bioanalytical methods were reviewed.
- The analysis of subject plasma samples and the respective electronic data was examined.
- Audit trails for electronic data capture and handling related to the BE studies were assessed.
- Results of calibration standards, quality control samples (QCs), and subject plasma samples in analytical runs, along with the chromatograms generated from the analytical runs, were evaluated.
- The preparation of analyte stock solutions, calibration standards, QCs, internal standards, and reagents was verified.

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 reasons for the study sample repeat analyses and all instrument failures were reviewed. The provisions and 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 the review of the study documentation, adequate support was received from well-informed and transparent personnel. Access to the study data and the respective audit trail on the respective chromatography software system was provided to the inspection team.

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

The method development process was adequately described and documented, and the use of the Internal Standard was justified based on relevant literature. A copy of the literature was available. After method development, a Draft Analytical Procedure was provided as a basis for method validation. A stable isotope-labeled internal standard was used in the MS methods where applicable, and an anticoagulant, such as K_2EDTA, was applied.

During method validation an analytical run batch determination was performed to establish a batch size with an adequate number of QC and CC samples. This batch size was designed to be comparable in length to those expected for study sample analysis, based on the method used in the respective study.

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

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

The review of the entire method validation included assessments of precision and accuracy (P&A), sensitivity, selectivity, matrix effect, haemolysis, lipemic effect, calibration curve, autosampler carry-over, dilution integrity, stability (including freeze-thaw stability and stock solution stability), haemolytic effect, recovery, and reinjection reproducibility. Partial validation was performed following the requirements.

The matrix used for analytical method validation was the same as that of the study samples, including anticoagulants. The purchase documentation for plasma from a supplier in Ahmedabad, India—including records of receipt, storage, retrieval, preparation, and consumption of pooled plasma—along with the respective logbook for receipt, storage, and retrieval of the biological matrix and related templates, was reviewed and discussed. An audit was conducted by the CRO on 4 Jun 2019, followed by a remote audit. Subsequently, another supplier was audited for interim use. However, the supplier in Ahmedabad was used for the studies within the scope of the inspection. The preparation of stock solutions, spike solutions, and calibration curve (CC) standards, as well as QC samples in the biological matrix, was documented. The storage of biological samples was recorded in the respective deep freezer logbooks, which were available and reviewed.

Excel sheets used for the calculation of acceptance criteria were validated in accordance with the respective SOP.

The calibration range had been determined during the method development phase, validated during method validation, and consistently used throughout the sample analysis.

The CRO used a software system for printing chromatographic data. Upon completing the acquisition run, the generated data was printed into the system using the "Print" option in the Chromatography software. The results were stored and made available in the database. For the calculation of batch acceptance criteria, another option was used, where the data was printed into a Note file or Word document and then pasted into a validated Excel sheet. After the calculation, the results were printed into the database.

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 within the same run. The acceptance criteria for the analytical runs were confirmed through a review of the analytes' retention time, the accuracy of calibration standards and quality control samples, peak integration, and IS peak areas, in accordance with the applicable SOPs. A system performance check using six LLOQ samples and a system suitability test using six ULOQ samples were conducted before the start of runs each day or after any interruption, following SOP for System Suitability, System Performance, and Auto Sampler Carryover. System performance was assessed after the system suitability experiment met the acceptance criteria by injecting six replicate injections of LLOQ samples.

The acceptance criteria were clearly defined in SOP for ISR. Furthermore, the overall batch acceptance evaluation was conducted based on SOP for Study Sample Analysis and Analytical Run Acceptance Criteria.

The system audit trail review was conducted at the time of the studies within the scope of the inspection for 20% of the runs, and adequate training was provided to the responsible personnel through documented records. However, the CRO informed that this practice had been amended, and a 100% verification was now being performed.

A clinical information form/bioanalysis form was available to document details of the samples received by the laboratory. If subjects were dropped and replaced by reserve subjects, this was indicated by the clinical department using (R), e.g., sub 1(R) in the Isoniazid study.

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

The specifications 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 required to be conducted per the applicable SOPs.

Actual sampling times and deviations from the prespecified sampling times were recorded, and these deviations were considered when calculating the pharmacokinetic parameters. The number of deviations could increase at the 48- and 72-hour time points of the respective studies when subjects had already left the site and were required to return for these time points. The site was expected to identify alternative measures to minimize time deviations at any time point beyond the clinical team's control.

The labeling of collected samples was clear to ensure correct identification and traceability. All storage conditions, including freezer temperature, were controlled, monitored, and recorded throughout the storage period and during transportation. Records of sample storage and retrieval were maintained. Samples were duplicated in aliquots, shipped, and stored separately.

As per SOP for Study Sample Management in the Bioanalytical Research Department, study samples, QC samples, and pooled matrices were required to be discarded. A reconciliation was only provided upon the sponsor's request for sample disposal. However, during the inspection, a spot check was performed to verify the consumption of QC, CC, and plasma within the studies.

19. Data processing and documentation

The smoothing factor was kept low enough to avoid masking 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 analytical runs contained complete information on the original first evaluation of runs, including all calibration samples, when an analysis was repeated. Repeat analysis was performed in accordance with the applicable. The calibration range was adequately truncated. Internal standard variations were trended and considered as part of the verification of result validity.

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

All original analytical raw data, including calculations, chromatograms, and their associated audit trails, were documented in a manner ensuring traceability concerning the sample number, equipment used, date and time of analysis, and the name(s) of the technician(s). The quality assessment of chromatograms was conducted in accordance with the respective SOP, including the acceptability of retention times. All audit trail files were retained, such as the results table audit trail, project audit trail, and instrument audit trail.

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

Data entry procedures, including data validation methodologies such as proofreading and double data entry, were designed to prevent errors. The data entry process was specified in accordance with the applicable SOP.

20. Good laboratory practices

A tour of the facility was conducted on Day 2 to verify its suitability in terms of arrangement.

The general principles of Good Laboratory Practice were followed during the bioanalytical phase of the BE studies, and an established and appropriate QA system was established.

Deep freezers used for sample storage were adequately qualified, calibrated, and maintained. An alarm system was associated with the digital temperature and humidity monitoring system. Daily monitoring and all alarm checks were documented.

For qualification verification, the temperature mapping of a Deep Freezer was reviewed to verify the hotspot and the location of the respective sensor. The temperature mapping process had been properly conducted at the time of the inspection.

The room temperature of facilities, such as the LC-MS/MS room, was monitored using another digital temperature monitoring system. An SOP for the system's usage was in place.

Balances, measuring devices, equipment, and instruments used during the conduct of the trial were periodically calibrated and verified before use to ensure fitness 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 through a random review of the following equipment used in study-related activities. The equipment and its components were labeled with the respective ID number, date of calibration, and date of the next calibration. Equipment usage was documented in the analytical sheets and respective logbooks for instrument usage. The use of columns was recorded in the logbook for column usage.

- Balance
- LC-MS/MS

An observation related to Good Laboratory Practices was sufficiently addressed in the respective CAPA plan.

Pharmacokinetic, statistical calculations, and reporting section

21. Pharmacokinetic, statistical calculations

A database of trial records was maintained and locked in accordance with the applicable SOP. In July 2023, a provision for a Data Review Meeting with the sponsor and the requirement for sponsor approval prior to database lock were incorporated into sections 6.1.1.7 and 6.1.1.9, respectively. This SOP applied to all clinical studies, whether paper-based or conducted using an EDC system, intended for submission to regulatory authorities across various geographical regions, including the USFDA, WHO, EMA, MHRA, Health Canada, and TGA. These studies were managed at or by the Lupin Bioresearch Center.

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 during the inspection.

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 responsible staff and management also approved the bioanalytical reports. Monitoring and audit reports were available before the release of the final study report.

Miscellaneous	
Samples taken	Not applicable
Assessment of the CRO master file	The CRO Master File (CROMF), effective 30 May 2024, version 01 was 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 ***Lupin Bioresearch Centre***, located at ***Sai Trinity A Wing, Unit 1, 2, 3, & 4, Survey No. 146/2/1B, Pashan, Pune, 411021; 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