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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	**Clinical Pharmacology Unit** **Sun Pharmaceutical Industries Limited** Hakeem Abdul Hameed Centenary Hospital (2nd Floor) Jamia Hamdard (Hamdard University) Hamdard Nagar New Delhi 110 062 India **(Formerly Majeedia Hospital)**
Name and Address of Bioanalytical & Statistical Research Site	**Clinical Pharmacology & Pharmacokinetics (CPP)** **Sun Pharmaceutical Industries Ltd.** Vill. Sarhaul, Sec-18 Gurugram-122015 Haryana India The study related to WHO application No. HA742 was conducted at the old site, situated at: **Clinical Pharmacology & Pharmacokinetics** **Sun Pharmaceutical Industries Limited** Plot No. GP-5, Sector 18, HSIDC Udyog Vihar Industrial Area Old Delhi –Gurugram Road Gurugram 122 015 Haryana India
Corporate address of the Organization	**Sun Pharmaceutical Industries Limited** SUN HOUSE, CTS No. 201 B/1, Western Express Highway, Goregaon (E), Mumbai - 400063
GPS coordinates	BA facility: 28.486° N, 77.071° E CL facility: 28.515° N, 77.252° E

WHO product numbers covered by the inspection/ Product names/ Study numbers/ Study titles	- **WHO application no. CV015** - **WHO application no. HA742**
Inspection details	
Dates of inspection	25 to 29 September 2023
Type of inspection	Routine
Introduction	
Summary of the activities	The facility performed bioequivalence/bioavailability and in-vitro studies with healthy subjects.
General information about the company and site	Sun Pharmaceutical Industries Limited (SPIL), was founded in 1983 and its headquarters are in Mumbai, India. The company stands as a global and integrated specialty pharmaceutical company. SPIL operates 45 manufacturing sites worldwide, producing various dosage forms. The Clinical Research facility, consisting of CPU & Clinical Laboratory in New Delhi, along with the Clinical Pharmacology and Pharmacokinetics (CPP) department at R&D, Gurugram, was established in 1994. Its primary objective is to conduct clinical pharmacokinetic studies in healthy human volunteers to support the approval of drug candidates for marketing in both domestic and international markets. The formulated drug candidates originate from SPIL's formulation and development unit or any other manufacturer operating under cGMP conditions. The Clinical Research facility aims to evaluate bioavailability and establish bioequivalence between the test drug and a reference listed drug (RLD) from the innovator or an equivalent product from another manufacturer. Additionally, the center conducts bioavailability studies on newly formulated drug candidates to analyze their pharmacokinetic parameters. In June 2021, the BA facility was relocated to a new address. The systems and processes at the new facility were retained in their original form, mirroring those of the previous location at Plot No. GP5.
History	The list of inspections was presented during the opening meeting. The most recent WHO inspection took place in 2019.
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 comparison of the source data to the study reports.
Scope and limitations	
Out of scope	Not applicable

Abbreviations	ADR	adverse drug reaction
	AE	adverse event
	ALCOA	attributable, legible, contemporaneous, original and accurate
	BA	bioanalytical
	BE	bioequivalence
	BDL	below detection limit
	CAPA	corrective actions and preventive actions
	CC	calibration curve
	CPU	clinical pharmacology unit
	CRA	clinical research associate(e)
	CRF	(electronic) case report form
	CRO	contract research organization
	CTM	clinical trial manager
	CoA	certificate of analysis
	CSR	clinical study report
	DQ	design qualification
	ECG	electrocardiogram
	GAMP	good automated manufacturing practice
	GCP	good clinical practice
	GLP	good laboratory practice
	GMP	good manufacturing practice
	HPLC	high-performance liquid chromatograph
	LC-MS/MS	liquid chromatography–mass spectrometry
	IB	investigator's brochure
	ICF	informed consent form

	ICH	International Conference on Harmonization
	(I)EC	(Independent) Ethics Committee
	IMP	investigational medicinal product
	ISF	investigator study file
	ISR	incurred sample reanalysis
	IQ	installation qualification
	LIMS	laboratory information management system
	LLOQ	lowest limit of quantification
	LOD	limit of detection
	MS	mass spectrophotometer
	MVR	monitoring visit report
	NRA	national regulatory agency
	OQ	operational qualification
	PIS	patient information sheet
	PQ	performance qualification
	PQS	pharmaceutical quality system
	QA	quality assurance
	QC	quality control
	QRM	quality risk management
	SAE	serious adverse event
	SAR	serious adverse reaction
	SOP	standard operating procedure
	SUSAR	suspected unexpected serious adverse reaction
	ULOQ	upper limit of quantification
	URS	user requirements specifications

PART 2	**SUMMARY OF THE FINDINGS AND COMMENTS**

General section

1. Organization and management

A detailed presentation was given to elucidate the organization's activities. The BA facility was relocated to a new address. The clinical and bioanalytical facilities had received approval from CDSCO, Government of India. The clinical and bioanalytical facility's certification was dated 14 Jun 2021, while the BA facility was re-authorized on 25 Feb 2022.

The CRO provided an organizational chart displaying roles and the respective responsible individuals. This chart was electronically signed on 26 Jul 2023.

Each employee had a job description outlining their responsibilities, and it was randomly verified that every job description had been signed and dated by the respective staff member to whom it applied.

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

The principles of Good Laboratory Practices clearly defined the responsibilities of the test facility management. The CRO management acknowledged that, as the investigator was an employee of the CRO, certain responsibilities typically assigned to investigators would also be handled by the CRO management.

The management ensured the implementation and adherence to appropriate and technically valid SOPs, maintaining a well-organized historical file of all SOPs.

The office working hours were Monday to Friday: 8:30 AM - 5:30 PM. The clinical operations were available 24 hours a day, seven days a week.

2. Computer systems

Procedures for Computer System Validation and other relevant SOPs were implemented to ensure that computerized systems fit their intended purposes. These systems were validated, operated, and maintained in compliance with the principles of GCP and GLP, as deemed appropriate. The validation of Excel spreadsheets used for calculating run acceptance was conducted in compliance with the applicable SOPs.

An inventory of all networked computer systems was maintained, clearly identifying those subject to GxP regulations. Any alterations to the network, including temporary additions or removals of systems, were thoroughly documented.

The entire network, including the full client/server architecture and interfaces such as LIMS, was shown to be appropriately designed, qualified, managed, and controlled by the Head of R&D and Quality IT. The flowcharts were made available and reviewed.

A separate team within the organization was responsible for Enterprise Risk Management. This team maintained a Risk registry that included sufficient information about risk descriptions, root causes, mitigation strategies, and action plans. It was observed that the risks stemming from outdated IT software and hardware assets at various locations, such as applications associated with Windows 7, including Empower version 3.0, were appropriately addressed and managed to prevent data loss. The risk assessment was conducted in accordance with the respective SOP.

There were enough computers to enable personnel to perform data entry and data handling required calculations and compilation of reports. Computers had adequate capacity and memory for the intended use.

Access to the software systems containing trial-related information was controlled. The access control method was defined, and a maintained list of individuals with database

access was kept. Secure and unique individual-specific identifiers and passwords were employed. These procedures were comprehensively detailed in the relevant SOP, such as SOP for Computerized System User Access Management.

The software programs utilized for respective tasks were mandated to be appropriate and validated for their intended purposes. Validation approvals were provided under the user's oversight to confirm that the software had been validated for its intended use and developed under controlled conditions in alignment with a quality assurance (QA) system. The review included the verification of the qualification of the randomly selected systems.

The functionality, user access management, security, and alarm logs of the computer station linked to a selected LC-MS/MS associated with the chromatography software system and the digital temperature monitoring system / the associated application were also examined.

Performance qualification considered specific user requirements, regulatory/guideline requirements for bioequivalence studies, the system's operating environment, and its utilization in these studies. Quality risk management guided the selection of components requiring validation, and all phases of their life cycle were taken into consideration. SOPs for software programs used in BE study activities were available.

Regular updates to essential software programs were conducted as needed, following SOP for Computerized Systems Periodic Validation Review.

The SOPs outlined the software programs used, the frequency of virus testing, data storage protocols, and the procedures for backing up and archiving all pertinent electronic data, including the backup frequency.

Self-designed software programs were available.

Data entry procedures, including data validation methods (such as proofreading and double data entry), were designed to mitigate errors. The data entry process for recording, reviewing, and managing raw data was outlined in the SOP.

Electronic data was routinely backed up per the guidelines outlined in a respective Global SOP and an SOP for CPP. The reliability and completeness of these backups were confirmed through a restoration process integrated into a software system, following an annual schedule. The plan for 2023 was available and reviewed. The most recent restoration process, along with its supporting documentation, was documented in the respective system. The history records of each form containing information about requests and reviews were maintained alongside the forms used in study activities, such as sample processing.

The decommissioning of their computerized systems was executed following the guidelines stipulated in the respective SOP. A plan was in place for retiring the decommissioned system, aimed at ensuring the integrity and completeness of the electronic records they contained.

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

3. Quality management

The CRO had well-established QA and QC systems supported by documented SOPs. These systems ensured that trials were carried out and data was produced, recorded, and reported in strict accordance with the protocol, GCP, GLP, and all relevant regulatory requirements.

The issuance of forms involved two distinct processes: General forms were distributed electronically through the Electronic Document Management System in compliance with in-house SOP as per the print privileges. On the other hand, at the bioanalytical lab, study-specific forms were managed using another software system. These forms were initiated upon request by either the analyst or project manager. Subsequently, they were submitted within the system and processed by the Laboratory Quality Control (Lab-QC) team, which held printer access privileges. The Lab-QC team's responsibility was to print the forms in the requested quantity and document this action within the system. It's important to emphasize that although the Lab-QC team had the authority to print additional forms when required, exclusive printing access was limited to the QC team.

Study activities underwent monitoring through the following systems:
- Internal Quality Control: Each unit had its dedicated QC team responsible for internal quality control.
- Independent Quality Assurance.
- Corporate QA Audits.

A Quality Manual with version number 03, effective as of 6 May 2022, was made available. This Quality Manual served as a comprehensive guide for employees, offering insights into the company's Quality Management System. It detailed the procedures for operating and maintaining the organization's quality systems and outlined the process for continual improvement in the performance and efficiency of all operations.

QA personnel were not directly involved in trial-related activities, and an in-process QA personnel audit did not substitute for oversight by another individual when necessary.

The QA unit had the following responsibilities:
- Conducting Study Audits (both In-process and Raw Data/Report audits)
- Providing QA Statements for Final Study Reports
- Conducting Periodic System and Process Audits

- Reviewing SOPs and Study Protocols
- Performing Qualification Audits of Service Providers
- Conducting Periodic Management Reviews

Both in-process and retrospective QA verifications were carried out, particularly in areas such as bioanalysis, during the preparation and testing of samples.

The quality management system consisted of various elements, including root cause analysis, trend tracking, ensuring data integrity, and implementing a suitable CAPA plan. A significant portion of QMS parameters, such as managing deviations, CAPA, and change requests, were facilitated through the respective software system. Additionally, training activities were overseen through the e-Learning Management System.

The company outlined in the SOP that audit trails of software applications used for data generation at CPP India, CPP Romania, MAP, and GTF India needed to undergo regular review.

The change request for relocating CPP (BA-facility), GTF (GLP Test Facility), and QA functions from the SPIL GP-5 location to the 2nd floor of SPIL R&D III in Gurugram was available and reviewed, dated 12 Nov 2020. The reason for this change was to transition from a leased facility to a self-owned facility. All instruments, biosamples, documents, furniture, IPs, and IT assets were moved to the new location by the established protocol. Existing SOPs, processes, and manpower were utilized at the new site. This action was successfully completed on 6 May 2022 and verified on 15 Jun 2022.

4. Archive facilities

The Archiving Facilities overview was provided. It included in-house archive facilities, off-site archives, and a Third-Party archive.

The CRO maintained a secure storage facility at both locations for archiving trial-related documents. These facilities were equipped with fireproof measures, humidity control, and pest control to safeguard the stored documents. Specifically, the archive at the CPU facility was situated on the second floor. In summary, the CRO implemented extensive security measures to ensure the safety and integrity of all archived documentation.

Archiving activities were conducted in accordance with SOP for Archiving of Documents. These activities were facilitated using an electronic system. The Archivist provided a demonstration of this system on Day 3 during the inspection at the CPU facility.

Access to archive storage areas was controlled and limited to authorized personnel. The names of individuals authorized to access the facility were displayed at the entrance. Detailed records of document access and return were diligently maintained in compliance with the timeframes specified in the relevant SOP.

The effectiveness of the trial-related documentation archiving procedures was confirmed through the successful retrieval and traceability of documents during the inspection.

5. Premises

During the inspection, facility tours were conducted on Day 2 (bioanalytical facility) and Day 3 (Clinical facility situated within the hospital premises).

Both facilities maintained a good standard of cleanliness and featured sufficient lighting, ventilation, and environmental control measures. The design of the floors, walls, and working bench surfaces allowed for easy cleaning and decontamination.

Clinical trials were conducted under conditions that prioritized the safety of the subjects. The choice of site was deemed appropriate, considering the potential risks associated with the trials.

The CRO had sufficient space to accommodate the personnel and activities required to perform the studies. The trial site had adequate facilities, including laboratories and equipment.

Access to the facility was carefully controlled and restricted using keycards. Additionally, systems were in place to detect subjects attempting to exit the clinical facilities, and doors were secured when necessary. Emergency evacuation procedures were established. Detailed records were maintained for all entries to and exit from the facility, with constant supervision by security personnel to ensure safety and adherence to protocols.

The sites where clinical activities were conducted included a pharmacy where investigational products were stored under suitable conditions, with controlled and restricted access. Comprehensive entry and exit records for each visit to the pharmacy were consistently maintained. There was a pharmacy located at the BA site specifically designated for the storage and distribution of IMP supplies for the clinical trials.

Laboratory premises were designed to suit the operations to be carried out in them. Sufficient space was provided to avoid mix-ups, contamination, and cross-contamination. Adequate storage space was available for samples, standards, solvents, reagents, and records.

Laboratory premises were designed to provide protection to all employees and authorized external personnel, including inspectors or auditors, by ensuring their safety while handling or working in the presence of chemicals and biological samples.

Safety data sheets were provided. Staff members received comprehensive fire safety training, emphasizing the importance of wearing laboratory coats or other appropriate

protective clothing, including eye protection. To mitigate the risk of contamination, highly toxic samples were exclusively handled within a safety cabinet. Furthermore, chemical containers were meticulously labeled, featuring prominent warnings to ensure safety and proper handling.

Adequate insulation and spark-proofing were provided for electrical wiring and equipment, including refrigerators. Rules on the safe handling of cylinders of compressed gases were observed, Staff was aware of the need to avoid working alone in the laboratory. First-aid materials were provided, and the staff was instructed in first-aid techniques and basic life support.

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

The premises had established suitable systems for waste disposal, fume treatment, and environmental protection in accordance with local and national regulations. These services were carried out by a designated service provider, and a formal service agreement was in place.

Temperature monitoring for various areas, including the Deep Freezer room, refrigerators, and the Balance room, was conducted using the digital temperature monitoring system.

Furthermore, there were four backup generators with adequate capacity at the BA site. The clinical facility also had an ample number of UPS units. A maintenance log was diligently maintained, and daily checks were carried out to ensure their operational readiness.

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

6. Personnel

A qualified team comprising medical, paramedical, technical, and clerical staff was present to support the trial activities and effectively respond to foreseeable emergencies.

In specific activities, contract workers were brought on board to complement the team's capabilities. To ensure the competence of personnel involved in trial activities, random checks were conducted on their current curriculum vitae (CVs) and training records. This review encompassed both full-time and contract workers. CVs and job descriptions (JDs) were signed and approved through the respective software system and were readily accessible upon request.

7. Clinical phase

The clinical phase of the studies took place at the CRO's clinical facility, which was located within Hamdard Hospital and leased by Sun Pharma.

The Clinical Pharmacology Unit was situated on the 2nd floor of HAHC Hospital, Hamdard Nagar, New Delhi. It has been operational since 1994 and spans an area of approximately 24,000 square feet within the hospital premises. The facility was designed to accommodate up to 84 study subjects simultaneously. The CPU had dedicated areas such as a volunteer's reception area, volunteer change rooms, medical screening area, ICF presentation and obtaining areas, a clinical ward, a 3-bed emergency care room, a drug store/pharmacy, a phlebotomy room, a dining area, a sample processing and storage area, physician and nurse restrooms, and archives, among others. In December 2022, a mock drill exercise was conducted to assess the efficiency of transferring subjects to the hospital care unit within a target time frame of 2 minutes.

Facilities for changing and storing clothes, as well as for washing and using the toilet, were readily accessible and suitable for the number of users. Lockable toilets were equipped with alarms, and the design of the doors ensured they could be opened from the outside in case of a medical emergency.

Access to the randomization list was limited solely to the pharmacist responsible for overseeing the study. The request for access was transmitted to the statistician via email. The randomization list was securely stored in a shared folder within the NuGenesis SDMS application system, and the process of its distribution was diligently documented.

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

8. Clinical laboratory

The Clinical Laboratory was situated on the 2nd floor of HAHC Hospital in Hamdard Nagar, New Delhi. It played a role in supporting the CPU by assisting in the screening of volunteers and handling end-of-study safety samples. This laboratory held accreditation from NABL (National Accreditation Board for Testing and Calibration Laboratories) and CAP (College of American Pathologists). The laboratory was equipped with instrumentation, which was integrated with CLIS.

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

Sample labeling, receipt, storage, and chain of custody ensured full traceability and sample integrity.

The CRO was provided with pertinent information regarding the laboratory's analytical methods, a current list of laboratory normal ranges, and the laboratory's accreditation certificate. The range of normal values had been established by the clinical laboratory and was documented in the quality control plan. Additionally, acceptable limits for laboratory parameters for inclusion in study were defined and included as an annex to the protocol.

The current and signed curriculum vitae of the Head of the Clinical Laboratory was reviewed.

The laboratory created individual reports for each subject and included them in the CRFs. Source or raw data for all tests performed were archived by the laboratory in electronic or paper formats, depending on their source and the laboratory's storage capacity.

Data integrity requirements for all study-related tests were maintained by employing validated systems for sample analysis integrated with the respective software application.

9. Ethics

The trials underwent approval from the independent ethics committee (IEC) prior to the commencement of any study. The independence of this committee from the sponsor, investigator, and CRO was confirmed by reviewing the respective member list. Comprehensive minutes of the IEC meetings were maintained, documenting discussions, recommendations, and decisions. The IEC was provided with ample time to thoroughly review protocols, informed consent forms (ICFs), and associated documentation.

Informed consent form

Information for study participants was given to them in vernacular language, i.e., Hindi and English, and at a level of complexity appropriate to their understanding, both orally and in writing.

Informed consent was given by the subject and documented in writing before starting any trial-related activities. The information was clear: participation was voluntary, and the subjects had the right to withdraw from the study on their initiative at any time without giving a reason. The reasons for withdrawal from the study were included in the study records.

Information regarding insurance and procedures for compensation or treatment in the event of injury or disability resulting from participation in the trial was accessible through the insurance policy. The insurance policy covering the study duration related to application CV015 was available and reviewed. This insurance policy was renewed every year.

Volunteers or subjects had the opportunity to consult with a physician to address any concerns they might have regarding potential side effects or reactions from using investigational products before participating in the trial.

Furthermore, the certificate of translation and back translation of the informed consent documents were reviewed.

10. Monitoring

The study was monitored by monitors employed by CRO/sponsor (Sun Pharma). The monitor was appropriately qualified to ensure that the study was conducted in accordance with the protocol, GCP, GLP, and applicable ethical and regulatory requirements. This included verifying the use of correct procedures for completing CRFs and verifying the accuracy of data obtained.

Pre- and post-study visits and monitoring visits were conducted as per the monitoring plan. The monitor generated written reports after each visit and communicated any issues to facilitate swift corrective actions. These communications and corrective actions were duly documented. Evidence of the monitor's presence during the study related to application CV015 was accessible via the HR's system application.

11. Investigators

The Principal Investigator oversaw the clinical study, covering study design, product administration, interactions with local authorities and ethics committee, and protocol and final study report sign-off.

GCP and protocol training for co-investigators were available and reviewed.

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

Details regarding the receipt, storage, handling, and accountability of investigational products at all trial stages were diligently documented. This included verifying information related to the shipment, delivery, receipt, description, storage (including conditions), dispensing, administration, reconciliation, return, and/or destruction of any remaining pharmaceutical products. The recorded information also encompassed specifics of the pharmaceutical products used, such as dosage form, strength, lot number, and expiry date.

Pharmaceutical products were stored under the conditions stipulated in the official product information provided by the sponsor. These conditions were rigorously monitored using the digital temperature monitoring system.

Randomization procedures were carried out in adherence to the relevant SOP, and records were maintained. Controlled access was implemented for the respective e-management systems, containing the randomization list and seed.

The IPs were accurately labelled, with a thorough check conducted to ensure compliance with the randomization list after printing and prior to labelling the containers. Labels were securely affixed to the containers to prevent information loss when the lid was removed.

Adequate routines for labelling and documenting the administration of the IP were implemented to ensure that each subject received the correct product. This was achieved using labels featuring a tear-off portion. These labels were designed with two identical sections: one portion was affixed to the container, and the second label was attached to the CRF at the time of dosing.

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

Dispensing and packaging procedures were carried out in accordance with the requirements outlined in the respective SOP, while dosing procedures were conducted in compliance with the applicable SOP.

The product-handling surface was cleaned before introducing product bottles. Any containers, dosage forms, labelling materials, contaminants, or debris were promptly removed. A second person verified cleanliness before opening product containers. IMPs were handled with suitable utensils. Tablet distribution followed the randomization list for test or reference products. Test and reference products, along with labelled containers, were handled separately, and each step was recorded in sequence.

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

Dosing followed SOP guidelines, supervised by the investigator and a qualified staff member with a written delegation. Prior to dosing, the label was verified, and the exact dosing time was recorded on the CRF. A mouth check, including under the tongue, lips, corners of the mouth, and between gums and cheeks, was performed using appropriate tools (tongue depressor or spatula) and a penlight for solid oral dosage forms to confirm swallowing. Dosing details were promptly documented in the CRFs.

Investigational product reconciliation post-dosing was confirmed by a second responsible person. Samples from the original container were preserved for potential confirmatory testing 5 years beyond the expiry date, following the guidelines outlined in SOP for Handling investigational products. Additionally, any dispensed products that were not administered were also retained.

13. Case report forms

Randomly selected CRFs from the study underwent review. The trial protocol outlined the specific data to be collected for each volunteer.

CRFs for each subject included copies of clinical laboratory reports and ECGs. These CRFs contained information related to inclusion/exclusion criteria, study-specific restrictions, drug administration records, details of biological sample collection, meal and water consumption, admission criteria (including alcohol and drug tests), and clinical examinations.

For studies within the scope of this inspection, paper CRFs were provided. However, the organization has implemented electronic systems for recording most screening and study activities.

Screening activities followed a CPU SOP, where volunteers were assessed to determine their compliance with screening criteria. Once accepted, a form detailing inclusion and exclusion criteria was completed during check-in to verify the subjects' eligibility for the studies.

14. Volunteers, recruitment methods

Recruitment procedures for volunteers were detailed in the SOP, including potential methods employed by the CRO, primarily relying on word-of-mouth referrals. To prevent cross-participation and specify a minimum interval between a volunteer's participation in studies, a database was maintained using a software application. Access to this database was password-controlled to safeguard the confidentiality of information pertaining to volunteers or subjects.

Volunteer and subject identification was secured through a biometric system utilizing left and right thumbs. This biometric system was subject to periodic validation.

Potential subjects provided initial informed consent for first-time enrollment and any required screening procedures to determine study eligibility, along with consent for participation in the research segment of the study. The clinical trial protocol outlined subject selection criteria (inclusion and exclusion criteria) and screening procedures.
A software system, OVIS,was used to check for prior trial participation among subjects. Participation data was uploaded to this central repository to prevent over-volunteering.

15. Food and fluids

Meals were standardized, controlled, and scheduled during study days. The CRO arranged standardized meals, snacks, and drinks as outlined in the clinical trial protocol/meal schedule and per the agreement with the catering service, supported by available respective invoices.

Prespecified menus provided by the nutritionist were chosen by the CRO. The meal schedule was prepared and approved by the nutritionist.

The timing, duration, and quantity of food and fluids consumed were documented. Ambulatory subjects were questioned about their food and drink intake before sample collection. The nutritionist possessed appropriate qualifications, training, and experience for designing 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 necessary rescue medication were readily available in the Emergency Care room at the study site, with all treatments administered documented in both the CRF and supporting Emergency records in the respective logbooks. Additionally, the CRO maintained an agreement with Hakeem Abdul Hameed Centenary Hospital for emergency transfers to the intensive care unit. A Mock Drill exercise was conducted, ensuring a response within 2 minutes. Risk assessments and mitigation strategies were established for each protocol involving IP-related risks, with the option of appointing a medical expert or external clinical co-investigator to assist with any post-dose SAEs.

Furthermore, the CRO maintained adverse event registration and reporting forms.

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

Bioanalytical section

The inspection focused on the study related to application CV015, including the associated validation projects. Spot checks were also performed for the study related to application HA742. 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, other verifications were conducted on several aspects, including the integration of chromatograms, the absence of signals in the blank samples, the absence of any unexplained interruptions in the injected sequences, the review of randomly selected study sample repeat analyses and instrument failures, the confirmation of the provisions and documentation of the ISRs, and the verification and comparison of the documentation and justification for the reinjection of the analytical runs to the provisions.

The inspection team received sufficient support from knowledgeable and transparent personnel for the review of the study documentation. The SOPs used applicable for the time of the studies within the scope of the inspection, and the chromatograms' raw data, along with their respective audit trails, were provided to the inspection team, during the inspection.

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

The method development process was described and documented, and the utilization of the Internal Standard (IS) was substantiated through relevant literature. A copy of this literature was readily accessible. Following the method development, an Analytical Test Procedure (ATP) was provided as the foundation for method validation. Mass Spectrometry (MS) methods incorporated a stable isotope-labelled internal standard, and K_3EDTA was employed as an anticoagulant.

The management of RS utilization was overseen through the software. While primarily employed for biological sample management, the software also recorded the usage of RS and working standards. The system maintained the record of the procurement, consumption, and disposal of N-Hydroxy cytidine and compared it to the relevant documentation for the preparation of QC and CCs for the stock solution utilized in the respective method validation. For this study, the IS used was 13C 15N2 – EIDD-1931 (N4 – Hydroxycytidine 13C, 15N2).

Sample management, including storage of subject samples, pooled plasma, QCs, and CCs employed for method validation and sample analysis, was exclusively handled via the same software system. A freezer logbook was solely utilized in the event of system downtime. This system facilitated the verification of sample storage and retrieval times.

During the method validation following the applicable SOP, an extended PA (Precission_Accuracy) run, involving 180 samples of QCs and CCs was carried out. This run, known as Extended precision and accuracy run, was of a comparable length to what was anticipated for the study sample analyses.

The Pre-study validation run for the project related to application CV015, which replaced a partial validation, was carried out in accordance with SOP for Preparation of CC and QC samples, the organization of analytical runs, and the establishment of acceptance criteria.

The documentation of sample processing was completed in the respective forms. Additionally, a note to file was provided to record any unexpected activity during sample processing, as applicable.

Data supporting the stability of the samples under the stated conditions and storage period were available prior to the commencement of the studies. The long-term stability study, however, was conducted before the issuance of the study report.

The comprehensive method validation review covered P&A, sensitivity, selectivity, matrix effect, calibration curve, autosampler carry-over, dilution integrity, stability (including freeze-thaw, stock solution, reference standard, and whole blood stability), haemolytic effect, recovery, and reinjection reproducibility. Partial validation was conducted as required. The matrix used for validation matched the study sample matrix. The inspector also reviewed the purchase, receipt, storage, retrieval, preparation, and consumption of pooled plasma for one of the studies in the scope of inspection.

Each analytical run involved the simultaneous processing of calibration standards (CC), QC samples evenly distributed throughout the run. A specific and documented processing sequence was followed. All samples from the same subject across trial periods were analyzed within the same run. The acceptance criteria for the analytical runs were validated by reviewing analytes' retention times, calibration standard and quality control sample accuracy, peak integration, and IS peak areas, following relevant SOPs. System suitability and IC (Instrument conditioning) were performed before each day's runs unless they were consecutively scheduled. A software application was employed to upload and document calculations for batch acceptance using validated Excel spreadsheets and other applicable tools.

For clinical studies, the procedure for selecting the minimum number of samples for conducting Incurred Sample Reanalysis (ISR) was as follows: For studies with a total number of subject samples equal to or less than 1000, at least 10% of the total subject samples collected were used for ISR. For studies with a total number of subject samples exceeding 1000, the minimum number for ISR was calculated as follows: 10% of the first 1000 samples, and additionally, at least 5% of the remaining subject samples were selected for ISR. The selection and acceptance criteria were explicitly defined in the SOP for Incurred Sample Reanalysis.

The review of the system audit trail was conducted during the studies within the scope of the inspection. Adequate training for responsible personnel was provided through documentation uploaded in the respective software system.

On 1 Feb 2019, the withdrawn subjects of study HA742 underwent the applicable sample analysis. It was noted that their concentrations were not included in the statistical analysis. Additionally, it was confirmed that one of the subjects had been withdrawn before dosing.

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

The clinical trial protocol and information given to volunteers clearly outlined the specifications for blood plasma samples, including the sampling method, volume, and quantity. The collection, preparation, transportation, shipping, and storage of these samples adhered to SOP for Transfer and Receipt of biological samples, as well as another applicable SOP. The Bio-Sample Management System, as detailed in the SOP, played an essential role. The complete sample management process was efficiently managed using the software application, which was reviewed during the inspection.

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

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

The study samples, QC samples, and the pooled matrix would be disposed of in accordance with an SOP, which described the Receipt, Log-in, Log-out, Transfer, Bulk Movement, and Disposal of Samples from the Freezer room.

19. Data processing and documentation

The integration settings were rooted in scientific principles and were justifiable. The smoothing factor was maintained at a low level to ensure it did not obscure potential interferences or alterations in peak geometry.

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

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

Original analytical raw data, including calculations and chromatograms with audit trails, were documented for traceability, noting sample numbers, equipment, analysis date and time, and technician names. All audit trail files, such as results table audit trail, project audit trail, and instrument audit trail, were retained. A software served as a printer/storage facility for raw data generated in the chromatography software system, including the storage of calculations.

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. A sample management application system was used for the sample management, including plasma, pooled plasma, QC, and CCs.

20. Good laboratory practices

On Day 2, a facility tour was conducted to assess its suitability in terms of arrangement and safety.

The bioanalytical phase of BE studies adhered to the principles of Good Laboratory Practice, supported by a well-established QA system.

The deep freezers used for sample storage and refrigerators for storing reference standards underwent thorough qualification, calibration, and regular maintenance. An alarm system linked to digital thermometers was in place to trigger email and call notifications to the facility's custodians responsible for maintenance. During the inspection, the automatic alarm system was tested to ensure its proper operation. Comprehensive documentation of daily monitoring and alarm checks was maintained.

To verify the qualification of the Deep Freezer, the inspectors reviewed the temperature mapping conducted on 7 Jun 2021, for a randomly selected Deep Freezer. The focus was on confirming the hotspot and the sensor's placement, aligning with the Protocol for temperature mapping of Deep Freezers. The temperature mapping was executed correctly. The thermometer sensor was properly stored in a container with ethanol and accurately positioned in the deep freezer at the designated spot.

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

The operation, use, calibration, inspections, and preventive maintenance of equipment were detailed in their respective SOPs, with records kept in compliance with relevant regulations. Random reviews of equipment used in study-related tasks validated these procedures. Equipment and its components were clearly labelled with their respective ID numbers, calibration date, and the next calibration date. Equipment usage was comprehensively documented in analytical sheets and the corresponding instrument

logbooks. The utilization of columns was recorded in the Pharmacy Management System module dedicated to column usage.

Chemicals, reference substances, reagents, solvents, and solutions were labeled to specify identity, purity, concentration when applicable, expiry date, and any specific storage instructions. Information regarding source, preparation date, and stability was included either on the label or in the Certificate of Analysis (CoA). The management of chemicals, solvents, and chromatography columns was handled through the self-developed software application, i.e., the Pharmacy Management system.

Pharmacokinetic, statistical calculations and reporting section

21. Pharmacokinetic, statistical calculations

During the inspection on Day 5, a presentation detailing the respective procedures was provided.

Randomization was accomplished using SAS software, and the generated list was printed into the respective application, where it was e-signed as prepared.

The PK Team and Statistical Team, comprising eight staff members, were involved in this process. The statistical model, specifically identifying its type for the primary BE analysis, was clearly outlined in the protocol.

Data lock was initiated once the concentration results were finalized in the application software, following SOP for Handling Project Data and its workflow.

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.

Miscellaneous	
Samples taken	N/A
Assessment of the CRO master file	CRO master file, version 10 effective 14 Feb 2022 was submitted and reviewed.
Annexes attached	N/A

Part 3	**Initial 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:

Clinical Pharmacology Unit
Hakeem Abdul Hameed Centenary Hospital (2nd Floor)
Jamia Hamdard (Hamdard University)
Hamdard Nagar
New Delhi 110 062
India

Clinical Pharmacology & Pharmacokinetics (CPP)
Vill. Sarhaul, Sec-18
Gurugram-122015
Haryana
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. Fifties 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, Frothiest report, World Health Organization, 2006 (Technical Report Series, No. 937), Annex 4.
Short name: WHO No. 937, Annex 4