20, AVENUE APPIA – CH-1211 GENEVA 27 – SWITZERLAND – TEL CENTRAL +41 22 791 2111 – FAX CENTRAL +41 22 791 3111 – WWW.WHO.INT

Prequalification Team Inspection services
WHO PUBLIC INSPECTION REPORT
WHOPIR
Bio-Equivalence Study

Part 1	**General information**
Organization details	
Company information	
Name and Address of Clinical Research Site	**Veeda Clinical Research Ltd.** - Shivalik site: Shivalik Plaza - A, Near IIM, Ambawadi Ahmedabad, Gujarat 380 015 India - Vedant site: Vedant Complex, 1st, 2nd, 3rd & 4th Floor, Nr. Y.M.C.A. Club S.G.Highway, Vejalpur Ahmedabad Gujarat 380 051 India - Skylar site: Common screening facility of Shivalik unit and Vedant unit: Skylar, 601 to 608, 6th Floor Skylar, Corporate Road, Prahladnagar Ahmedabad - 380015 Gujarat India
Name and Address of Bioanalytical Research Site	**Veeda Clinical Research Ltd** Vedant Complex, 1st, 2nd, 3rd & 4th Floor, Nr. Y.M.C.A. Club S.G.Highway, Vejalpur Ahmedabad Gujarat 380 051 India
Name and address Statistical Site	**Veeda Clinical Research Ltd** Shivalik Plaza , Near IIM, Ambawadi Ahmedabad, Gujarat 380 015 India
Corporate address of the Organization	**Veeda Clinical Research Ltd** Shivalik Plaza, Near IIM, Ambawadi

	Ahmedabad – 380015 Gujarat, India. Phone: +91 79 6777 3000
GPS coordinates	Skylar & Vedant: 23.00539 °N, 72.50445 °E Shivalik: 23.02817 °N, 72.54248 °E
WHO product numbers covered by the inspection	**WHO application no. HA 775** Bioequivalence Study of Sulfamethoxazole and Trimethoprim 800 mg / 160 mg Tablets **WHO application no: HA773** Bioequivalence Study of Co-Trimoxazole 160mg/800mg Tablet
Inspection details	
Dates of inspection	18 – 21 April 2023
Type of inspection	Routine
Introduction	
Summary of the activities	The facility had the necessary equipment to handle contracts related to bioequivalence, bioavailability, and Phase I studies for both healthy subjects and for patients.
General information about the company and site	Veeda is a Contract Research Organization (CRO) established in 2004, with facilities in Shivalik (clinical), Insignia (bioanalytical), Vedant (clinical and bioanalytical), and Skylar (screening facility). Later, the company was expanded to include a clinical and screening facility (Mehsana) in July 2019. The company is also establishing a dedicated bioanalytical facility at a building named Satyamev located in Ahmedabad. This facility will be home to all administrative departments and corporate functions. During the inspection, the Inspection team visited Shivalik, Vedant, and Skylar, the sites responsible for conducting the studies under inspection. Veeda started as ClinSearch Labs Private Limited in Ahmedabad in 2004. In 2005, the company's name was changed to Veeda Clinical Research Private Limited. Since 30 Jun 2021, the company is known as Veeda Clinical Research Limited to provide various contract research services for the pharmaceutical and biotechnology industry. The CRO consists of the following departments: - Biopharmaceutics and Project Management Department - Clinical Research Department

	- Bioanalytical Research Department - Pharmacokinetics and Biostatistics Department - Quality Assurance Department - Clinical Operations Department - Information and Communication Technology Department - Human Resources Department - Administration and Maintenance Department - Finance and Accounts including Purchase and Client Services Department - Business Development Department - Medical Affairs and Pharmacovigilance - Training and Development Department - Data Management Department
History	The following agencies conducted inspections on the CRO: ANVISA, CDSCO, USFDA, AFSSAPS, South Africa (MCC), Malaysia (NPRA), Austria (AGES) and UK MHRA. A list of these inspections with the respective details was provided. The WHO PQT – Inspection Services has inspected this CRO five times. The most recent onsite inspection was conducted in October 2018.
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 between the source data and 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
CDMS	chromatography data management system
CPU	clinical pharmacology unit
CRA	clinical research associate(e)
CRF	(electronic) case report form
CRO	contract research organization
CROMF	contract research organization master file
CTM	clinical trial manager
CoA	certificate of analysis
CSR	clinical study report
DQ	design qualification
ECG	electrocardiogram
GAMP	good automated manufacturing practice
GCP	good clinical practice
GLP	good laboratory practice
GMP	good manufacturing practice
HPLC	high-performance liquid chromatography
LC-MS/MS	liquid chromatography-mass spectrometry
IB	investigator's brochure
ICF	informed consent form
ICH	International Conference on Harmonization
(I)EC	(Independent) Ethics Committee
IMP	investigational medicinal product
ISF	investigator study file
ISR	incurred sample reanalysis
IQ	installation qualification
LIMS	laboratory information management system
LLOQ	lowest limit of quantification

	LOD	limit of detection
	MS	mass spectrophotometer
	MVR	monitoring visit report
	NRA	national regulatory agency
	OQ	operational qualification
	PI	principal investigator
	PIS	patient information sheet
	PK	pharmacokinetics
	PQ	performance qualification
	PQS	pharmaceutical quality system
	QA	quality assurance
	QC	quality control
	QRM	quality risk management
	SAE	serious adverse event
	SAR	serious adverse reaction
	SOP	standard operating procedure
	SUSAR	suspected unexpected serious adverse reaction
	ULOQ	upper limit of quantification
	URS	user requirements specifications

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

General section

1. Organization and management

A presentation was provided explaining the activities of the organization in detail.

The Veeda Group of Companies comprised three entities: Bioneeds (GLP), Ingenuity (Biosimilars), and Veeda Clinical Research. The organizational chart outlined key positions and responsible persons and was regularly updated and authorized.

There was a job description for each employee, including their responsibilities. Randomly selected job descriptions were checked and confirmed to have been signed and dated by the corresponding staff member. A list of signatures of the authorized personnel performing tasks related to the clinical part of the study was available and verified.

The responsibilities of the test facility management were established by the principles of Good Laboratory Practices. The CRO management understood that, since the investigator was an employee of the CRO, some of the responsibilities that would normally be given to the investigator would also be the responsibility of the CRO management. The management ensured that appropriate and technically valid SOPs were implemented and followed. Maintenance of a historical file of all SOPs was adequately organized. The CROMF contained the complete layout of the facility, including information on the location of each facility as well as designated areas for sample handling and biological waste disposal.

The Drugs Controller General India (DCGI)'s approval was appended to the CROMF, and the local authority granted the necessary permissions as required. The service agreements with sponsors were also available, and the Master Service agreement was reviewed. The contract outlined the duration for retaining records, biological samples, study drugs, and IMP.

The company's working hours were from 9:00 am to 5:30 pm.

2. Computer systems

The computerized systems throughout the company, including Shivalik, Insignia, Skylar and Vedant, were managed by the Information Technology Department.

A list of software and computer systems used in the studies was provided. An inventory of all computerized systems on the network was available, clearly identifying those GxP regulated. Any changes to the network, including the temporary addition or removal of systems from the network, were documented in accordance with the applicable procedures. The process of replacing the Module training system with a new software system was reviewed. This involved decommissioning the old system.

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

There were enough computers available for personnel to enter data and perform calculations required for compiling reports.

To access trial-related information, employees had to fill out a form indicating their required access rights, which then had to be approved by their supervisors and submitted to the IT department. Access to the database was closely monitored, with individuals being assigned unique identification codes and passwords to ensure secure access that can be traced back to each individual staff member.

The qualification and/or validation certificates were provided under the user's supervision to ensure that the software was validated for its intended use and that it was developed in a controlled manner in accordance with a QA system. The qualification of randomly selected systems was reviewed.

To qualify the system's performance, various factors such as the user's specific requirements, regulatory and guideline requirements for BE studies, the environment in which the system was used, and how it was used in the studies were considered. A quality risk management to determine which components needed validation was applicable, considering all phases of their life cycle. SOPs were provided for each software program used in the BE study activities.

Regular updates to key software programs, whenever required, following a risk assessment on the potential impact it could have on current data and qualification or validation status, were carried out per the applicable SOP. The Periodic review plan was described in the document for the periodic review of validated systems. The frequency was determined once every three years after the system's release for intended use. A computer system validation tracker was prepared with information about the software name, version, department, equipment name, location, GAMP category, last validation date, last periodic review, and following periodic review.

Networks, including the full client/server architecture and interfaces such as laboratory information management systems, were designed, qualified, managed, and controlled. Veeda network connectivity illustrated the entire network for the whole company located at different sites.

Data entry procedures, including data validation methodology (proofreading, double data entry, etc.), were designed to prevent errors. The data entry process was specified in the SOP.

The CRO followed the standard operating procedure for backing up electronic data at regular intervals. The reliability and completeness of these backups were verified at predefined intervals. The documentation for data integrity checks on backup data retrieved from tapes belonging to the 2019 backup, dated 16 Jan 2023 was reviewed during the inspection.

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

3. Quality management

The CRO had established quality assurance and quality control systems, complete with written standard operating procedures, to ensure that clinical trials were conducted in accordance with the protocol, as well as with the highest standards of Good Clinical Practice (GCP), Good Laboratory Practice (GLP), Good Manufacturing Practice (GMP), and all relevant regulatory requirements. The systems ensured that all generated data were documented and reported.

Veeda Clinical Research Limited had a Quality Manual (QM). This manual served as a guide for identifying and describing the company's quality policies, objectives, and procedures. It included information about the Quality Management System (QMS) and various operations and services offered by the company. Additionally, the QM clearly defined the CRO's Quality Policy. On the first day of inspection, the CRO provided the inspection team with the current SOPs related to Bioanalytical, Clinical, IT, QA, and Statistics activities.

At each Shivalik, Insignia and Vedant units, there was an independent Quality Assurance Department (QAD). QA personnel were not directly involved in trial-related activities, and an in-process QA personnel audit did not replace another person's oversight when required. The QA Unit responsibilities were defined in the respective SOPs.

QA verification during the preparation and testing of samples and standards in bioanalysis was documented in reports signed by the QA. These verifications included both in-process and retrospective checks.

The quality management system included among others:

- Root cause analysis.
- Tracking for trends.
- Ensuring all aspects of data integrity.
- The implementation of appropriate corrective and preventive action (CAPA) through the respective software application.

The QA team utilized the system to export Excel sheets for creating trend reports that were presented during the Management Review. The software was also used to handle change requests. Their procedure for change control was discussed.

The issuance of logbooks and templates was performed in accordance with the SOP for the Controlling and Distribution of documents. The request for the distribution of templates and logbooks was recorded in the respective logbook before their generation. The reconciliation of study documents/data and templates was performed after the completion of the study, with information about the issuance of used and unused templates. Any unused templates were kept in the study file.

The process for auditing bioavailability/bioequivalence studies was outlined in the respective SOP. Verification of audit trails for live systems or software on the QA desktop was conducted as needed.

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

4. Archive facilities

Each facility had its own in-house archive, with additional archive facilities for long-term archiving.

The CRO had enough secure storage space to archive trial-related documentation. The storage space was fireproof, pest-controlled, and maintained the right level of humidity. The certificate for the fire-resistant door (4hrs) was available. The archiving activities were in line with the SOP for Management of archiving.

Access to archive storage areas was controlled and restricted to authorized personnel. A list of authorized personnel was displayed at the entrance of the facility.

Records of document access and return were maintained. The study documentation retention time, including raw data, was defined in the SOP and specified in the contract between the sponsor and the CRO. The contract also included provisions for financing the archiving.

During an inspection, the CRO was able to successfully retrieve and trace the trial-related documents, to enable the inspection team to verify the archiving procedures.

The observation related to the Archive facility was addressed in the CRO's CAPA plan.

5. Premises

During the inspection, the Inspection team conducted a tour of the facilities in Vedant, Skylar, and Shivalik:

- Screening facility (Skylar) consisting of the registration area, counselling area, clinical examination, ECG, phlebotomy, urine collection, Electric and UPS Room, Staff seating areas, volunteer dining area, and document store areas
- Shivalik facility (Clinical facility), offering the Clinical phase of BE studies with a total of 182 beds + 7 Special care (ICU) beds. The facility also included Quality Assurance and PK/Statistical phase of BA / BE studies, as well as Information, and Communication Technology departments.
- Vedant Facility offered services for the clinical phase of BE studies with a total of 244 beds (including 18 Phase1 beds) + 8 Special care (ICU) beds, and the bioanalytical phase of studies.

Members of the Administrative and Maintenance department were present at all Veeda facilities. This department was responsible for a variety of activities, including defining procedures and systems for general cleaning and pest control, managing entry and exit for staff and visitors, ensuring fire safety through extinguishers and alarms, procuring materials, and managing the operation of air conditioners, generators, and non-biological waste.

The facilities were well-maintained with sufficient lighting, ventilation, and environmental control. The floors, walls, and working bench surfaces were easy to clean and decontaminate. Clinical trials were conducted under safe conditions, ensuring the subjects' safety. The trial site was chosen appropriately, considering the potential risks involved. The CRO had ample 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 limited to the staff with keycards. Alarm systems and camera surveillance to detect the exit of subjects from clinical facilities were installed, and the doors were locked. Any entry to and exit from the facility was generally recorded.

The Emergency evacuation was ensured, and a Mock drill for transporting volunteers to the hospital was performed. Another Mock run was carried out for the evacuation of the employees. The most recent Mock drill (hospital transportation) documentation dated 12 Jan 2023 for both the peak and the off-peak hours was reviewed.

Clinical activities were conducted at various units, including a pharmacy that stored investigational products under controlled conditions. Access to the pharmacy was restricted by access control, and entry and exit records were kept for each visit.

The laboratory premises were specifically designed to accommodate the operations that took place within it. To prevent mix-ups, contamination, and cross-contamination, the area had ample space. There was also adequate storage space for samples, standards, solvents, reagents, and records.

Laboratory premises were designed to provide adequate 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.

Before conducting any tests, the laboratory staff had access to safety data sheets. They were familiar with the material safety data sheets for the chemicals and solvents they were handling. The staff had received training on how to use firefighting equipment, such as fire extinguishers. They were also instructed to wear protective clothing, including laboratory coats and eye protection. All containers of chemicals were properly labelled with clear warnings, such as "flammable”.

The electrical wiring and equipment, including refrigerators, were insulated and spark-proofed for safety. The staff was informed to avoid working alone in the laboratory. First-aid materials were available, and the staff was trained in first-aid techniques, emergency care, and antidotes.

In the laboratory, containers holding volatile organic solvents, including mobile phases and liquid/liquid extraction solvents, were securely closed using an appropriate seal. Safety measures, including eye showers, were also available. Additionally, the premises had effective waste disposal systems, fume treatment, and environmental protection measures in compliance with local and national regulations.

The observation related to the Premises was adequately addressed.

6. Personnel

During the trial, there were enough qualified medical, paramedical, technical, and clerical staff to respond to any foreseeable emergencies. Qualified and trained personnel were present at all stages of the trial, including at night, to ensure the safety and well-being of the subjects and to care for them in emergencies. Contract workers were also employed to perform certain activities within the clinical activities. To verify the qualifications of personnel involved in the trial, current curricula vitae and training records for both full-time and contract workers were randomly reviewed.

Clinical section

7. Clinical phase

The clinical trials were conducted at Shivalik & Vedant's CRO location. The screening process occurred at the Skylar facility, which was visited on the first day.

Before being admitted for testing, the volunteers underwent a security frisking procedure. They were then checked for drug and alcohol consumption using urine sample kits and a colour chart to confirm detection. Accommodation facilities were equipped with systems for volunteers to alert CRO staff in case of any emergencies.

The changing and storage areas, as well as the bathing and toilet facilities, were clean, well-organized, and easily accessible. They were also appropriate for the number of people using them. The toilets were equipped with locks and alarms, and the doors could be opened from the outside in case of a medical emergency.

The clinical site consisted of

- subjects' registration and screening; obtaining informed consent of individual subjects without compromising privacy
- CPU
- subjects' recreation
- pharmacy
- room for the administration of the investigational products and sample collection
- sample processing (e.g., plasma separation) and storage (freezer)
- archive facility
- a dining hall
- ICU

An agreement with a Clinic was signed to handle the X-ray procedures. The clinic was located near the Skylar screening facility.

The statistician uploaded the randomization list to a folder that only the pharmacist in charge could access. Provisions were made for the urgent transportation of subjects to the hospital and the notification was acknowledged by the hospital through email.

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.

The observation related to the Clinical phase was adequately addressed in the CAPA plan.

8. Clinical laboratory

An external clinical laboratory was utilized for sample analysis. This laboratory was accredited by NABL (valid until 8 Nov 2024) and CAP (valid until 14 Sep 2025). The relevant accreditation for the study period was reviewed and provided. The laboratory underwent audits as per the audit planner and the most recent audit report was issued in 2023.

As part of the clinical trial, the study protocol required various tests, such as haematological, biochemistry and urine analysis to be conducted. Additionally, adequate measures were taken for sample labelling, receipt, storage, and chain of custody to ensure the traceability and integrity of the samples.

In the SOP for Clinical Evaluation of Laboratory Parameters, the analytical methods used in the laboratory, a list of laboratory normal ranges, and an acceptable range for admission safety and post-study were defined. The applicable and signed curricula vitae of the Head of the Clinical Laboratory was reviewed.

To streamline the screening process, the laboratory was granted access to the respective application to upload lab results directly. Individual reports presenting the results of post-study safety samples were provided in paper format for each subject and incorporated into the CRFs.

9. Ethics

Before conducting any study, the independent ethics committee (IEC) approved the trials. To ensure the committee's independence from the sponsor, investigator, and CRO, the respective member list was verified. The IEC kept detailed meeting minutes, including discussions, recommendations, and decisions. Sufficient time was given to the IEC to review protocols, informed consent forms (ICFs), and related documentation.

Informed consent form

Participants in the study were provided information in the Gujarati and Hindi languages, both verbally and in writing, at a level that was appropriate for their comprehension.

Before any trial-related activities began, subjects gave informed consent in writing and through recorded video. The information provided explained that participation was voluntary, and subjects had the right to withdraw from the study at any time without explanation. Withdrawal reasons were documented. Information about insurance and compensation procedures in case of injury or disability was available through the insurance company.

Before participating in the trial, the volunteers or subjects were allowed to discuss any concerns they had about potential side effects or reactions from using the investigational products with a physician. The certificate of translation for the informed consent was reviewed. For BA/BE studies, a sample back translation of the ICD of any ongoing projects was done at least once every six months or on a change in the translator agency, whichever occurred earlier. This back translation was then approved by the EC in accordance with SOP for Preparation and review of protocol and ICD.

10. Monitoring

The studies were monitored by the Clinical Quality monitor employed by CRO. 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 COVID-19-related compliance, related activities, and equipment functionality, including ICU readiness, phlebotomy room, sample separation room, in-process activities, such as sample collection, pre-dosing sample collection, dosing administration, vital examination, biological sample segregation, etc. Observations were communicated to the responsible group in a timely manner. The monitoring covered both periods and was carried out in accordance with the SOP for Roles and Responsibilities of the Clinical Quality monitor, on a form/checklist for monitoring clinical study activities. A study-specific form was arranged for each study. After each site visit, the monitor prepared a written report and communicated any issues to CRO.

The monitor prepared a written report after each site visit and communicated any issues to the CRO in a timely manner, even while the study was being conducted, to enable prompt corrective action. The respective communications and corrective actions were documented. The monitor's job description was randomly selected and reviewed. The monitor's presence was also verified for study related to WHO application HA773 by verifying their HR attendance summary report.

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

11. Investigators

The PI had multiple responsibilities, such as overseeing the clinical aspects of the study's design, administering the investigational products, liaising with local authorities and the ethics committee, and signing the protocol and final study report.

12. Receiving, storage and handling of investigational drug products

The information concerning the receipt, storage, handling, and accountability of investigational products at every stage of the trial was recorded. The information about the shipment, delivery, receipt, description, storage (including storage conditions), dispensing, administration, reconciliation, return, and retention of any remaining pharmaceutical products were also verified. Details of the pharmaceutical product used included dosage form and strength, lot number, and expiry date.

The pharmaceutical products were stored according to the official product information provided by the sponsor, and their conditions were monitored through a digital temperature monitoring system. The Inspection team reviewed the system.

The randomization process followed the guidelines outlined in SOP for creating a randomization schedule. Detailed records were maintained, including the randomization list and seed number. The list was only available to the authorized personnel.

The IMPs were labelled, and their compliance with the randomization list was verified before they were applied to the containers. However, due to time constraints, the activity of checking the label application was not confirmed during the inspection. Labels were affixed to the containers to ensure the information was kept when the lid was removed.

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

The empty containers for the test and reference IMPs were labelled separately and kept in a secure area under lock and key until they were dispensed. This ensured that there was no risk of any mix-ups occurring.

Dispensing and packaging procedures were performed in accordance with the applicable requirements. Dosing was performed in accordance with SOP for the Administration of IMPs.

Before introducing packages of the product into the area, the surface was thoroughly cleaned. Any debris, contaminants, dirt, empty or full product containers, labelling materials, and dosage formulations were removed from the area. The pharmacy manager and a QA representative checked and confirmed that the surface area/line was clear and clean before opening the product containers. IMPs were handled using appropriate utensils, and tablets were distributed into each container according to the randomization list for the appropriate test product or comparator. Test and reference products were handled separately, and every step was carefully documented. The surface and its surroundings were cleaned before and after dispensing each product in the same study.

IMP 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. The records of verification by a second person for each step were available.

During the inspection, the administration of the medication was carried out in adherence to the SOP with oversight from the investigator and qualified staff member. This task was assigned in writing, including QC, QA, and sponsor monitor. The SOP required checking the label before dosing and recording the exact time of dosing on the CRF's designated page. A mouth check was conducted using a spatula and penlight to ensure the subject had swallowed the medication, for solid oral dosage forms. The dosing was directly documented in the CRFs and verified by QC.

A second responsible person confirmed the reconciliation of the investigational product after dosing. The original container of the product was kept for at least one year after the expiry date of the newest product in case confirmatory testing was needed. This retention time was outlined in the SOP for Handling IMP and specified in the contract between the sponsor and the CRO. Additionally, any dispensed products that were not administered were also retained.

The observation related to the Handling of IMP was adequately addressed.

13. Case report forms

Randomly selected CRFs from study related to WHO application HA773 were reviewed.

The trial protocol specified the data collected on each volunteer. The CRF consisted of both eCRF using a designated application for screening activities and paper CRF for admission and period visits. This allowed for direct documentation of ECG, lab reports for screening, and demographic data in the system. The clinical laboratory had access to the software system and could submit lab reports directly into the system. The study investigator verified the lab parameters in the system. After the study was completed, copies of the clinical laboratory post-study reports were included in the paper CRFs for each subject, when applicable.

Information about inclusion/exclusion criteria, meal records, protocol procedures, dosing administration, blood sample collection, vital signs, and physical exams were recorded in the CRFs.

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

14. Volunteers, recruitment methods

To ensure proper recruitment of volunteers, the CRO followed an SOP that outlined various methods for recruitment. A database was used to keep track of volunteers and prevent cross-participation between studies. The SOP specified a minimum time between a volunteer's participation in one study and the next. Access to this confidential database was password-controlled, and identification was verified through a biometric system that used a fingerprint reader. The biometric system's performance was regularly verified and documented in a logbook.

Before being allowed to participate in the study, potential subjects were given information about the screening procedures required to determine their eligibility, as well as information about the research portion of the study itself. The study's protocol outlined the criteria for selecting subjects (both inclusion and exclusion criteria) and the screening procedures that would be used. To ensure that no subjects had previously participated in a different trial, a software system called OVIS was utilized, with participation data being uploaded to a central repository. Password control was implemented to restrict database access.

Since July 2022, it has been permissible to recruit illiterate volunteers; however, the SOP was revised after a recent inspection by the US FDA to restrict such recruitment. It was made clear that recruitment of illiterate volunteers in India can only be conducted in accordance with the New Drugs and Clinical Trials Rules.

15. Food and fluids

During the study days, meals were carefully regulated and standardized. Standardized meals were designed by a qualified and experienced dietitian. The CRO arranged for standard meals, snacks, and drinks for study participants as outlined in the clinical trial protocol and agreed upon with a catering service provider. An invoice for the meals prepared for study related to WHO application HA773 in September was provided.

The amount, timing, and duration of food and fluids consumed were recorded, and participants were asked about their consumption before ambulatory samples were taken.

16. Safety, adverse events, adverse event reporting

The study was planned, organized, and executed to ensure the safety of the participants. A medical doctor oversaw medical decisions in the event of any negative effects and promptly informed the relevant authorities, sponsors, and ethics committee in the case of a serious adverse event.

The study site was equipped with first-aid supplies and rescue medication, readily available in case of an emergency. All treatments administered to participants were recorded in the CRF and supporting documentation in the ICU.

The CRO included adverse event registration and reporting forms in the CRF.

Bioanalytical section

During the inspection, the bioanalytical part was reviewed with a focus on the studies related to WHO application HA775 and HA773. The inspection team investigated various records and activities related to these studies, specifically:

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

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

The personnel involved in the study provided the inspection team with helpful and transparent support to review the documentation. The inspectors were given access to the raw electronic data and metadata from the chromatography software system, as well as the electronic raw data generated by LIMS application during the calculation of analyte concentrations and run acceptance criteria evaluation.

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

The process of developing the method was well-documented and explained, and the use of Internal Standard was backed up by relevant literature. There was also a copy of the literature available. Once the method was developed, an analytical plan was provided as a foundation for validating the method. In the MS methods, a stable isotope-labelled internal standard was consistently used, and K_2EDTA was utilized as an anticoagulant. As part of the method validation process outlined in SOP for Bioanalytical Method Validation, an analytical run with an adequate number of quality control and calibration curve samples was performed. This run, known as the "Batch Size Experiment," was designed to imitate the batch size anticipated for the actual analysis.

The processing of the samples was documented on the appropriate forms. Additionally, an incident form was provided to record any unexpected activity that occurred during the sample processing, when necessary.

Before the studies began, there were data available to confirm that the samples would remain stable under the specified conditions and storage duration. However, long-term stability testing was conducted before the study reports were issued.

The method validation review covered a range of tests to ensure accuracy and precision, including Precision & Accuracy (P&A), sensitivity, selectivity, matrix effect, calibration curve, autosampler carry-over, dilution integrity, stability, haemolytic effect, recovery, and reinjection reproducibility. The analytical method validation was performed using the same matrix as the study samples, including anticoagulants and additives. The purchase documentation of the plasma from a qualified vendor, including receipt, storage, retrieval, preparation, and consumption, was thoroughly reviewed, and discussed. Partial validation was also conducted as required.

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 analysed in the same run. The acceptance criteria for the analytical runs were confirmed by a review of the analytes' retention time, the accuracy of calibration standard and quality control samples, peak integration, and IS peak areas, as per the applicable SOPs. A system suitability and a stabilization test were done before the start of runs on each day.

Out of the initial 1000 samples, 10% were used for Incurred Sample Reanalysis (ISR), while 5% of the following samples were used for the same purpose. The samples were chosen based on their concentration near C_{max} and during the elimination phase. The acceptance criteria were explicitly outlined in the applicable SOP.

During the inspection, a review of the system audit trail was conducted, and it was found that the personnel were sufficiently qualified for the task at hand.

18. Sample collection, storage and handling of biological material

The clinical trial protocol and information given to volunteers outlined the details of blood plasma sample specification, sampling method, volume, and number of samples. The collection, preparation, transport, shipping, and storage of samples followed the SOP for Subject Sample Management. Additionally, the SOP for transferring samples from the clinical site to BA was reviewed and discussed.

Actual sampling times and deviations from the prespecified sampling times were recorded. These deviations were considered when calculating the pharmacokinetic measurements.

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

According to SOP for Managing study samples, the study samples, QC samples, and pooled matrix were disposed of. Once the project sample analysis was complete and the final study report was signed, the deep freezer custodian should consult with the Head - BRD or designee to inform the sponsor of the options for further storage, transfer, or disposal of the subject samples as per the SOP for Handling and disposal of biowaste. It was required to obtain written confirmation from the sponsor for these decisions. The discard of study samples related to WHO application HA773 was reviewed and discussed.

The observation related to the Handling of biological samples was sufficiently addressed.

19. Data processing and documentation

Integration settings were science-based and entirely justifiable. The smoothing factor was set at a low enough level to avoid covering up any potential interferences or changes in peak geometry.

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

Before, during, and after the method validation and studies of interest, all analytical instruments had full audit trails activated.

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

To ensure accurate results, each data point was linked to a particular sample, with details such as the sample number, collection time, centrifugation time, freezing time, and analysis time recorded. This enabled the identification of any potential sample mishandling that could have caused any abnormal outcomes.

20. Good laboratory practices

On Day 2 and Day 3, a facility tour was conducted to ensure it was arranged appropriately and safe for use.

The general principles of Good Laboratory Practice were followed during the bioanalytical part of BE studies, with an established QA system.

Specific procedures for temperature mapping and maintenance of deep freezers for samples and refrigerators for reference standards were followed to ensure proper storage. The digital temperature monitoring system included an alarm that alerted security personnel who then notified the appropriate custodians for maintenance. The automatic alarm system was checked during the inspection to ensure it was functioning correctly. All daily monitoring and alarm checks were documented for record-keeping purposes.

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

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 standard operating procedures (SOPs) provided detailed instructions on how to operate, calibrate, check, and maintain the equipment. To ensure compliance, the laboratory kept records of these activities according to relevant regulations. The inspectors randomly reviewed the equipment used during study-related activities. Each piece of equipment and its components were labelled with an ID number, calibration date, and next calibration date. The usage of equipment and columns was documented in analytical sheets and logbooks.

The calibration records of analytical balance, pH meter, micropipette, and selected chromatography instruments were verified.

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

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

Pharmacokinetic, statistical calculations and reporting section

21. Pharmacokinetic, statistical calculations

The Pharmacokinetics and Biostatistics Department was located on the 3rd floor of the Shivalik – B wing.

The protocol established the number of subjects needed and the reasoning for the sample size. A randomization schedule was then created to determine the sequence in which each subject would receive the test and reference formulations during each study period. Requests for randomization were submitted via email by the Pharmacist, Medical Writer, Principal Investigator, or Project Manager, who provided information on the study design and number of subjects. The Biostatistician then received the approved protocol and relevant documents from the respective department through an electronic shared folder. Using SAS application and a unique seed number, generated a randomization schedule upon receipt of a requested document from the respective department. The biostatistician then signed and reviewed the password-protected schedule before sending it to QC.

The statistical model underlying the primary BE analysis was stated in the protocol and/or a statistical analysis plan. The plan included how the area under the curve from time zero to infinity (AUCinf) was derived (i.e., how the points used for extrapolation were selected). Data analysis conformed to these requirements.

The estimation of pharmacokinetic parameters was done using Phoenix WinNonlin application.

The statistician's qualifications were confirmed by reviewing the respective CV. Additionally, a presentation was given to explain the workflow of the Pharmacokinetics and Biostatistics Department.

22. Study report

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

The study report contained information about the bioanalytical aspect of the trial, including details about the method used and confirmation of its validity. The Principal Investigator reviewed and approved the clinical study reports before sending the data to the statistical department. The bioanalytical reports were also approved by the relevant staff and management. Additionally, monitoring and audit reports were obtained and reviewed before the final study report was released.

Miscellaneous	
Samples taken	N/A
Assessment of the CRO master file	Veeda Master File (Ahmedabad) was provided and reviewed.
Annexes attached	N/A

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 ***Veeda Clinical Research Ltd***, located at the following addresses:

- **Shivalik site:**
  Shivalik Plaza A, Near IIM, Ambawadi
  Ahmedabad, Gujarat 380 015, India
- **Vedant site:**
  Vedant Complex, 1st, 2nd, 3rd & 4th Floor, Nr. Y.M.C.A. Club
  S.G.Highway, Vejalpur
  Ahmedabad
  Gujarat 380 051, India
- **Skylar site:**
  Skylar, 601 to 608, 6th Floor
  Skylar, Corporate Road, Prahladnagar
  Ahmedabad - 380015
  Gujarat, India

All the non-compliances observed during the inspection that were listed in the complete report as well as those reflected in the WHOPIR, were addressed by the CRO, to a satisfactory level, prior to the publication of the WHOPIR.

This WHOPIR will remain valid for three years, provided that the outcome of any inspection conducted during this period is positive.

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***
   https://apps.who.int/iris/bitstream/handle/10665/255338/9789241209960-eng.pdf?sequence=1&isAllowed=y

2. Good clinical laboratory practice (GCLP), WHO on behalf of the Special Programme for Research and Training in Tropical Diseases. Geneva, 2009
   Short name: WHO GCLP
   https://apps.who.int/iris/handle/10665/44092

3. Guidelines for good clinical practice for trials on pharmaceutical products. WHO Technical Report Series, No. 850, 1995 (pp. 97–137).
   Short name: WHO GCP
   https://www.who.int/publications/i/item/9241208503

4. Handbook – Good Laboratory Practice (GLP): quality practices for regulated non-clinical research and development – Annex I: The OECD Principles on GLP, 2nd ed., 2009. ***Short name: OECD GLP***
   http://www.who.int/tdr/publications/documents/glp-handbook.pdf

5. Standards and operational guidance for ethics review of health-related research with human participants. Guidance Document. Geneva, World Health Organization, 2011.
   Short name: WHO Ethics Committee Guidance
   https://www.who.int/publications/i/item/9789241502948

6. Guidelines for the preparation of a contract research organization master file, WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957), Annex 7.
   Short name: WHO CROMF Guidelines or ***TRS No. 957, Annex 7***
   https://www.who.int/publications/i/item/WHO_TRS_957

7. Model guidance for the storage and transport of time-and temperature-sensitive pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth Report. Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 9.
Short name: WHO storage and transport guidance or ***TRS 961 Annex 9***
https://apps.who.int/iris/bitstream/handle/10665/44079/WHO_TRS_961_eng.pdf?sequence=1&isAllowed=y

8. Glove use information leaflet, Patient Safety, Save lives clean your hands. Geneva, World Health Organization, 2009 (revised).
Short name: Glove use information leaflet
https://www.who.int/publications/m/item/glove-use-information-leaflet-(revised-august-2009)

9. Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability. Republication of multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability. WHO Technical Report Series No. 992, Annex 7 with a new appendix 2. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-first Report Geneva, World Health Organization, 2017 (WHO Technical Report Series, No. 1003), Annex 6.
Short name: TRS 1003 Annex 6
chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://www.who.int/docs/default-source/medicines/norms-and-standards/guidelines/regulatory-standards/trs1003-annex6-who-multisource-pharmaceutical-products-interchangeability.pdf

10. Good chromatography practice. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fourth Report. Geneva, World Health Organization, 2020 (WHO Technical Report Series, No. 1025), Annex 4.
Short name: WHO TRS No. 1025, Annex 4
https://apps.who.int/iris/handle/10665/331814

11. Guideline on data integrity. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fifth Report. Geneva, World Health Organization, 2021 (WHO Technical Report Series, No. 1033), Annex 4.
Short name: WHO TRS 1033, Annex 4
https://apps.who.int/iris/handle/10665/340323

12. Declaration of Helsinki, World Medical Association Declaration of Helsinki, Ethical principles for medical research involving human subjects, Bulletin of the World Health Organization, 2001 (79(4)).
Short name: Declaration of Helsinki
https://apps.who.int/iris/handle/10665/268312

13. Bioanalytical Method Validation and Study Sample Analysis M10, ICH Harmonised Guideline, Final version, Adopted on 24 May 2022
Short name: ICH M10
https://database.ich.org/sites/default/files/M10_Guideline_Step4_2022_0524.pdf

14. Good Manufacturing Practices: Guidelines on validation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-Third Report Geneva, World Health Organization, 2019 (WHO Technical Report Series, No. 1019), Annex 3.
Short name: WHO TRS No. 1019, Annex 3
https://www.who.int/publications/m/item/trs-1019---annex-3-good-manufacturing-practices-guidelines-on-validation

15. Supplementary guidelines on good manufacturing practices: validation, WHO Expert Committee on Specifications for Pharmaceutical Preparations, Fortieth report, World Health Organization, 2006 (Technical Report Series, No. 937), Annex 4.
Short name: WHO No. 937, Annex 4
https://apps.who.int/iris/handle/10665/43443