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Prequalification Team 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	**Raptim Research Ltd.** A-226, T.T.C., Industrial Area Mahape M.I.D.C Navi Mumbai, 400 710 India The Screening facility was located at Plot no. PAP-A-218/219 & the Archive facility was located at Plot no. A-542 of the abovementioned address.
Name and Address of Bioanalytical Research Site	**Raptim Research Ltd.** A-242, T.T.C., Industrial Area Mahape M.I.D.C Navi Mumbai, 400 710 India
Name and address Statistical Site	**Raptim Research Ltd.** A-242, T.T.C., Industrial Area Mahape M.I.D.C Navi Mumbai, 400 710 India
WHO product numbers covered by the inspection/ Product names/ Study numbers/ Study titles	**WHO application no. HA786** Bioequivalence study of Fixed Dose combination of Dolutegravir 50 mg + Lamivudine 300 mg + Tenofovir Disoproxil Fumarate 300 mg tablets **WHO application no. HA758** Bioequivalence study of Darunavir and Ritonavir Tablets 800 mg/100 mg **WHO application no. HP036** Bioequivalence study of Entecavir Tablets 1 mg

Inspection details	
Dates of inspection	27 -30 May 2024
Type of inspection	Routine
Introduction	
Summary of the activities	The facility was equipped to conduct bioequivalence/bioavailability and in-vitro studies involving both healthy subjects and patients. The CRO recently obtained approval from the Drug Controller General of India (DCGI) for its Phase I facility located at A-542 in Navi Mumbai.
General information about the company and site	Raptim Research Pvt. Ltd. was established in the year 2005. A broad spectrum of services like Pharmacokinetic studies (BA/BE), IVRT, IVAD, Pharmacodynamic studies Phase I, II & III trials, and Dermatology studies were rendered by Raptim to Pharmaceutical industries and/or to CROs. The company has offices in New Jersey, USA, Navi Mumbai, and Gandhinagar, India.
History	The CRO was previously inspected by various National Regulatory Authorities such as the US FDA, MHRA, ANVISA, NPRA, etc. WHO conducted the previous inspection of the CRO in December 2022.
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, dispensing, 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. Coverage of the analytical operations included practices, personnel qualifications, and procedures used during method validations and analytical testing. A review of the clinical study data, analytical method validation, and analytical study data was conducted, along with a comparison of the source data to the study reports.

Scope and limitations	
Out of scope	Since this site was inspected in December 2022, certain aspects that were deemed acceptable during that inspection were not revisited during the current inspection. The previous inspection covered a comprehensive review of the relevant areas, and the findings were satisfactorily addressed, with no significant issues reported. Consequently, to optimize the inspection process and focus on areas requiring further attention, we relied on the prior inspection's outcomes for applicable specific aspects. This approach was intended to ensure a thorough and efficient evaluation.

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
	IVAD	in vitro absorption and distribution
	IVRT	in vitro release testing
	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 provided explaining the activities of the organization.

The CRO was inspected in December 2022. During this inspection, the respective CAPA plan was thoroughly reviewed, and the implementation of the specified actions was verified to ensure compliance with regulatory requirements.

The CRO had an organizational chart depicting key positions and the names of responsible individuals. This organizational chart, dated January 24, 2024, was authorized and maintained to ensure it remained current.

A list of signatures of the authorized personnel performing tasks during each study was available and verified, ensuring traceability and accountability for all activities conducted.

The CRO operates 24/7, utilizing a three-shift system to maintain continuous operations and support around-the-clock activities.

2. Computer systems

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

The computerized systems were assessed to verify the implementation of the most recent CAPA plan.

An updated inventory of all computerized systems on the network was available, clearly identifying those regulated under GxP. All network changes, including the temporary addition or removal of systems, were documented.

There were a sufficient number of computers available to enable personnel to perform necessary data entry, data handling, required calculations, and report compilation. These computers had adequate capacity and memory for their intended use.

Access to the software systems containing trial-related information was controlled. The method of access control was specified, and a list of individuals with access to the database was maintained. Secure and unique identifiers and passwords were employed for each user to ensure robust security.

The software programs used to perform key steps were deemed suitable and validated for their intended use. Qualification and/or validation certificates were provided under the user's supervision to ensure that the software was validated for its intended use and developed in a controlled manner in accordance with a Quality Assurance system. The qualification of the selected systems was reviewed.

The performance qualification took into account specific user requirements, regulatory and guideline requirements for BE studies, the operating environment in which the systems were used, and their application within the studies. Quality risk management principles were applied to determine which components required validation, considering all phases of their life cycle.

SOPs for each software program used to perform activities in a BE study were available, ensuring consistent and compliant usage across all processes.

Key software programs were regularly updated as required, following an appropriate risk assessment on the potential impact on current data and qualification or validation status. These updates were carried out in accordance with SOPs.

Software programs used, the frequency of virus testing, data storage, and the procedures for backing up and archiving all relevant electronic data were specified in SOPs, e.g., SOP for Backup of Computer System, including the frequency of backups. The reliability and completeness of these backups were verified through the restoration process.

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

3. Quality management

The CRO maintained appropriate QA and QC systems, supported by written SOPs, to ensure that trials were conducted and data generated, documented, and reported in compliance with the protocol, GCP, GLP, GMP, and applicable regulatory requirements. A software application facilitated these processes of maintaining SOPs.

The forms used in the study activities were issued under the supervision of QA. Upon request by the team, the QA unit issued the forms, and a reconciliation was performed after the study was completed. Any unused forms were kept together in the study binders. This activity was randomly verified to ensure compliance and accuracy.

Both in-process and retrospective QA verifications were performed, including during bioanalysis as samples and standards were being prepared and tested.

The company defined the procedures for audit trail review in the SOP. The audit trail files of the chromatography software were transferred into the respective software application by QA/QC, and the review was e-signed. Additionally, the number of batches in the system was compared with the number of batches transferred into the system. The software audit trail was also available for user review. The audit trail verification of selected computerized systems was checked.

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

4. Archive facilities

The CRO maintained a secure storage facility in a new building located at plot no. A-542 of the same address, specifically in the basement. This facility was used for archiving trial-related documents and was equipped with fireproof measures, humidity control, and pest control. Overall, the CRO ensured the safety and integrity of the documentation through comprehensive security measures.

The archiving activities were managed following the applicable SOP. Access to archive storage areas was controlled and restricted to authorized personnel, with a list of authorized individuals displayed at the entrance of the facility.

Records of document access and return were meticulously maintained. The length of time for which study documentation, including raw data, should be kept in the archive was defined in the SOP and specified in the contract between the sponsor and the CRO.

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

The observation related to the archive facilities was adequately addressed in the respective CAPA plan.

5. Premises

During the inspection, a tour of the facilities, including the new archiving and IMP retention facility located at A-542, was conducted. The new facility featured an archive area, a walk-in cold room (-20°C) for sample retention, and a deep freezer (-70°C). Additionally, the facility included a pharmacy equipped with two stability chambers operating at room temperature and 2-8°C, respectively.

The facilities were kept clean and maintained adequate lighting, ventilation, and environmental controls. Floors, walls, and working bench surfaces were designed to be easily cleaned and decontaminated.

Clinical trials were carried out under conditions that ensured adequate safety for the subjects. The site selected was appropriate for the potential risks involved.

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

Entry to the facility was restricted and controlled through biometric access. Biometric systems were installed to prevent the exit of subjects from clinical facilities, and doors were locked as needed. Emergency evacuation procedures were in place. All entries and exits from the facility were recorded. The emergency exit was amended during the inspection to enable timely exit when needed.

Sites where clinical activities took place included a pharmacy where investigational products were stored under appropriate conditions, with entry and exit restricted by biometric access control. Appropriate entry/exit records of each visit to the pharmacy were maintained.

Laboratory premises were designed to suit the operations carried out in them, providing sufficient space to avoid mix-ups, contamination, and cross-contamination.

Safety data sheets were available to staff before testing commenced. Laboratory staff were familiar with the material safety data sheets for the chemicals and solvents they handled. Staff were instructed to wear laboratory coats or other protective clothing, including eye protection.

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

The premises had suitable systems in place for waste disposal, fume treatment, and environmental protection in conformance with local or national regulations.

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

6. Personnel

A sufficient and qualified team of medical, paramedical, technical, and clerical staff was available to support the trial and effectively respond to foreseeable emergencies. At all stages of the trial, including night-time, qualified and trained personnel were present to ensure the subjects' rights, safety, and well-being were safeguarded and to provide care in emergencies. Contract workers were employed for specific activities to complement the team's capabilities.

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

Clinical section

7. Clinical phase

The clinical phase of the studies was performed on the premises of the CRO.

The following changes were implemented in the clinical facility since the last inspection:

- Phase I studies in NCE (New Chemical Entity) were planned to be initiated in the new building located at plot no. A-542.
- Two walk-in chambers (maintained at +20ºC and 2-8ºC) for the storage of IPs were installed at A-542. In addition to the formulation storage cabinets at A-226, these walk-in chambers were used for the storage of retention IPs.
- Retention IMPs previously stored in the pharmacy's refrigerator at A-226 were shifted to the walk-in chamber at A-542. Consequently, one refrigerator at A-226 was sufficient to store the IMPs for the ongoing studies.

Provisions were made for the urgent transportation of subjects to the hospital, including an ambulance facility equipped in accordance with the corresponding SOP.

Access to the randomization list was restricted to the pharmacist in charge of the study. These documents were password-protected to ensure confidentiality.

The equipment used was appropriately calibrated at predefined intervals. The proper function and performance of emergency-use equipment, such as defibrillators, were verified at appropriate intervals.

8. Clinical laboratory

An in-house clinical laboratory was used for analyzing samples, and the laboratory was accredited.

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 maintained information about the laboratory's analytical methods and a dated list of laboratory normal ranges.

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 format or paper format (for screening and post-study testing).

Data integrity requirements were ensured for all tests related to the study through adequately validated systems used for sample analysis.

9. Ethics

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

Informed consent form

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

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

Information about insurance and procedures for compensation or treatment in case of injury or disability resulting from trial participation was available through the Insurance policy.

Volunteers or subjects were allowed to discuss potential side effects or reactions to the investigational products with a physician before participating in the trial.

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

10. Monitoring

The study related to WHO application HA786 was monitored by a monitor employed by the sponsor. 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 correct procedures for completing CRFs and ensuring the accuracy of the obtained data.

A monitoring visit was performed during the first period of the trial. The monitor shared the monitoring outcome in an email, including a few observations.

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

11. Investigators

The principal investigator (PI) was responsible for the clinical conduct of the study, including the clinical aspects of study design, administration of the investigational products, communication with local authorities and the ethics committee, and signing the protocol and the final study report.

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

Information regarding the receipt, storage, handling, and accountability of investigational products at every stage of the trial was recorded. This included details about the shipment, delivery, receipt, description, storage conditions, dispensing, administration, reconciliation, return, and/or destruction of any remaining pharmaceutical products. Details of the pharmaceutical product used, such as dosage form and strength, lot number, and expiry date, were also verified.

Pharmaceutical products were stored under appropriate conditions as specified in the official product information provided by the sponsor, and these conditions were monitored through a digital temperature and humidity control system.

Randomization was performed in accordance with SOP for Generation of Randomization Schedule for Clinical Trial. Records, including the randomization list and seed number, were maintained. The randomization list was accessible only to the person who generated it, the dispensing pharmacist, and the statistician.

The investigational products were properly labeled. Once they were printed and before labeling the containers, compliance of all labels with the randomization list was verified.

Labels were affixed to the containers in a way that ensured the information remained intact even if the lid was removed.

Adequate routines for labeling and documenting the administration of the IMP were established to verify that each subject received the correct product. This was achieved by using labels with a tear-off portion designed to have two identical parts: one affixed to the container and the other one to be pasted onto the CRF at the time of dosing.

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

Dispensing and packaging procedures were performed in accordance with the specifications, and the requirements specified in SOP for the Dispensing of Investigational Products.

The surface on which the product was handled was thoroughly cleaned before bringing bottles of the product into the area. Any product containers (full or empty), other dosage formulations, labeling materials, contaminants, dirt, and debris were removed. A second person verified that the surface area/line was clear and clean before bringing in and opening containers of the product. The IMPs were handled with appropriate accessories. Tablets were distributed into each container in accordance with the randomization list for the comparator/reference or the test product as appropriate. The two products, Test and Reference, were handled at different times. This also applied to the labeled containers. Every step was recorded sequentially in detail. The surface upon which the product was handled, and its surroundings were cleared and cleaned immediately before and after initiating the dispensing of the following product, also in the same study.

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

Dosing was carried out following SOP for Dosing the subject and monitoring restrictions in clinical studies, under the supervision of the investigator and a qualified staff member explicitly delegated this task in writing. The label was checked before dosing, and the exact time of dosing was documented on the CRF's designated page or in the respective module of the software system. For solid oral dosage forms, a mouth check was performed using a tongue depressor or spatula and a penlight to look under the tongue, under the lips, in the corners of the mouth, and between the gums and cheeks to ensure

the subject had swallowed the IP. Dosing was directly documented either in the CRFs or in the software application's dedicated module, depending on the agreement with the respective sponsor.

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

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

13. Case report forms

Randomly selected CRFs related to the studies related to WHO application HA786 and HP036 underwent a thorough review. This process entailed a detailed examination of the documents to ensure data accuracy and consistency. The data required to be collected on each volunteer was specified in the trial protocol.

The CRFs for each subject included copies of the clinical laboratory reports and all ECGs. Additionally, information about clinical activities, including both inclusion and exclusion criteria, was recorded in the CRFs.

The CRO had the option to use either paper CRFs or eCRFs, with the latter being facilitated by the software application, depending on the agreement with the sponsor. For the studies within the scope of this inspection, the sponsors had requested the paper version. However, during the site tour, a study utilizing eCRFs for dosing and sample collection was observed.

14. Volunteers, recruitment methods

The recruitment of volunteers followed the same procedure as per the last inspection in December 2022, and this was verified during the current inspection.

The volunteer database was checked to confirm the existence of the volunteers and to verify source data, including demographic information, weight, and height.

Screening activities, including ECG recording, sample collection, and physical examinations, were also verified during the facility tour and through the review of the respective documentation.

15. Food and fluids

Meals were standardized, adequately controlled, and scheduled during the study days. The CRO successfully arranged standardized meals, snacks, and drinks for the study subjects as outlined in the clinical trial protocol and in accordance with the agreement with the catering service.

The timing, duration, and amount of food and fluids consumed were recorded. Before obtaining samples from ambulatory subjects, they were queried about their food and drink consumption. A dietitian with the appropriate qualifications, training, and experience designed the standardized meals.

16. Safety, adverse events, adverse event reporting

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

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

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

Bioanalytical section

The inspection focused on the study related to WHO application HA786 (specifically Dolutegravir in the presence of Lamivudine and Tenofovir in K_3EDTA-based human plasma samples), including the associated validation projects. Spot checks were also performed for the other analytes and the two other studies in the scope of the inspection. Specifically, the following records and activities were investigated:

- Source documentation and raw data for validation of the bioanalytical methods
- Analysis of subject plasma samples, along with 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 these 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 reasons for study sample repeat analyses and instrument failures were reviewed. The provisions and documentation of the ISRs were confirmed to be in accordance with the applicable SOP. The documentation and justification for the reinjection of the analytical runs were verified and compared to the provisions.

During the review of the study documentation, the inspection team received adequate support from well-informed and transparent personnel. The inspector was granted administrative rights for the chromatography software system during the inspection to review the raw data on the system.

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

The method development process was described and documented in accordance with the SOP for Method Development, and the usage of the Internal Standard was justified based on the literature. References to the literature used in the method development were noted in the respective notebook. After method development, a Standard Test Procedure (STP) was provided as a basis for method validation. A stable isotope-labeled internal standard, when applicable, and an anticoagulant were used in the MS methods. K_3EDTA was applied as an anticoagulant for the study related to WHO application HA786.

During the method validation, as per SOP for Bioanalytical Method Validation Master Copy, an analytical run was performed to determine the batch with sufficient samples of QCs and CCs (referred to as Analytical Run Batch Determination). This run was comparable in length to those expected to be used for the analysis.

The sample processing was documented in the respective forms. Additionally, a note was provided to record any unexpected activities during sample processing when applicable.

Data supporting the stability of the samples under the stated conditions and period of storage was available before the start of the studies.

The review of the entire method validation included precision and accuracy testing (P&A), sensitivity, selectivity, matrix effect, calibration curve, autosampler carry-over, dilution integrity, stability (including freeze-thaw stability, stock solution stability, and reference standard storage stability), haemolytic effect, recovery, and reinjection reproducibility. Partial validation was performed according to the requirements. The matrix used for the analytical method validation was the same as that of the study samples, including anticoagulants and additives. The documentation of the plasma from

the supplier for the study related to WHO application HA786 in 2023, including receipt, storage, retrieval, preparation, and consumption of the pooled plasma, was reviewed and discussed. The vendor was audited in accordance with the applicable SOP, dated 1 Jul 2022. The audit report was provided and reviewed.

The usage of the reference standard for method validation and study analysis for both Dolutegravir and the respective Internal Standard was available and reviewed. The records were documented on a controlled template.

Each analytical run included calibration curve (CC) standards, QC samples interspersed throughout the run, and subject samples, all processed simultaneously. The exact sequence of processing was defined and documented. All samples collected from a given subject during all trial periods were analyzed in the same run.

The acceptance criteria for the analytical runs were confirmed by a review of the analytes' retention time, the accuracy of calibration standards and quality control samples, peak integration, and IS peak areas, as per the applicable SOPs. A system suitability, stabilization, and solution check test were performed according to the respective SOP.

Incurred Sample Reanalysis (ISR) was performed according to the applicable SOP. The samples were selected with concentrations around C_{max} and in the elimination phase. The acceptance criteria were clearly defined in the SOP.

The system audit trail review was conducted during the studies within the scope of the inspection, as per the applicable SOP. The records were provided and reviewed.

The observation related to the sample analysis was adequately addressed in the respective CAPA plan.

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

The specification of samples (blood plasma), sampling method, volume, and number of samples were stated in the clinical trial protocol and provided to the volunteers. The collection, preparation, transport, shipping, and storage of samples were conducted in accordance with SOP for Procedure for Receipt, Handling, Storage, and Disposal of Biological Matrix and Biological Samples, effective 18 Mar 24. This version was not applicable at the time of studies within the scope of the inspection. Since the last inspection in December 2022, the new version implemented the following amendments: periodic revision, updated SOP format as per revised standards, inclusion of Amendment 01 and Amendment 02 into the SOP, and minor modifications in forms for better documentation clarity.

In their current practice, a software system was used for sample management, and the software has an option to verify each individual sample. However, if the software system was not used for the sample management of a study, the sample management was recorded on paper forms, and the sample accountability was documented along with the number of missing or haemolyzed samples. The transfer record of the study samples related to the WHO application HA786 were reviewed and discussed. The aforementioned software system was not used for the sample management of this study; instead, the collection and transfer of the samples were recorded on paper forms, and the records were subsequently uploaded into the system, per their agreement with the respective sponsor. The aliquots were transferred from the clinical unit separately and verified subject-wise upon receipt.

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

The collected samples were clearly labeled to ensure 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, transferred, and stored separately.

The temperature records from the digital thermometer for the period of the study related to WHO application HA786 were provided and reviewed for randomly selected deep freezers. The temperature records were checked daily for excursions, and system-generated messages were reviewed and addressed. Specifically, the message indicating, "*The maximum pending emails have been reached, HI-HI Alarm Email will not be processed. For more information, please contact your supplier*," was managed by IT, and adequate corrective action was implemented to direct the emails to the correct mail server.

The study samples, QC samples, and pooled matrix were discarded in accordance with the respective SOP. The pooled plasma remaining from the study related to WHO application HA786, stored in the designated DF, was still available.

The observation related to sample collection was adequately addressed in the respective CAPA plan.

19. Data processing and documentation

Integration settings were science-based and entirely justifiable. The smoothing factor was kept low enough to avoid masking possible interferences and changes in peak geometry.

The criteria for acceptance and exclusion of CC standards and QC samples, as well as batch acceptance, were clearly defined in the applicable SOP. The source data for all analytical runs contained comprehensive information about the original first evaluation of runs (including all calibration samples) when the analysis was repeated. The calibration range was adequately truncated. Internal standard variations (ISV) were trended and used as part of the verification of result validity. ISV trends for the study related to WHO application HA786 were reviewed and discussed.

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

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). Audit trail files were retained, including results table audit trails, project audit trails, and instrument audit trails.

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

20. Good laboratory practices

A tour of the facility was conducted to inspect the instruments used in method validation and analytical runs of the study related to WHO application HA786, as well as the storage of samples and reference standards. The instruments and the respective chromatography software application were checked. The workstations were verified to be networked.

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

The laboratory was visited during the last inspection, and any corrective actions suggested in the CAPA plan were reviewed during this inspection to verify the implementation of the actions.

The observation related to Good Laboratory Practices was adequately addressed in the respective CAPA plan.

Pharmacokinetic, statistical calculations and reporting section

21. Pharmacokinetic, statistical calculations

The pharmacokinetic (PK) parameters were calculated using Phoenix® WinNonlin® Software. The statistical analysis was performed using SAS®.

This part of the process was already inspected during the previous inspection and was not reviewed in the current inspection.

22. Study report

No discrepancies were identified between the results stated in the report and the original (raw) data during the inspection.

The study report included a detailed account of the bioanalytical part of the trial, describing the bioanalytical method used and a report on the validation of this method. Monitoring and audit reports were available before the release of the final study report.

Miscellaneous	
Samples taken	N/A
Assessment of the CRO master file	The CRO Master File, with document no. RRL/CROMF/001 version 00, dated 26 Apr 2024, was submitted prior to the inspection.
Annexes attached	N/A

Part 3	Conclusion

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 ***Raptim Research Pvt. Ltd***., located at ***A-226/242/218/219/542, T.T.C., Industrial Area, Mahape M.I.D.C, Navi Mumbai, 400 710; India***.

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

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

Part 4	List of guidelines referenced in the inspection report

1. Guidance for organizations performing in vivo bioequivalence studies. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fiftieth Report Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 9.
   Short name: WHO BE guidance or ***TRS996 Annex 9***

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

3. Good chromatography practice. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fourth Report. Geneva, World Health Organization, 2020 (WHO Technical Report Series, No. 1025), Annex 4.
   Short name: WHO TRS No. 1025, Annex 4

4. Guideline on data integrity. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fifth Report. Geneva, World Health Organization, 2021 (WHO Technical Report Series, No. 1033), Annex 4.
   Short name: WHO TRS 1033, Annex 4

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