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WHO Prequalification Unit (PQT) - Team Inspection Services Team (INS)
WHO PUBLIC INSPECTION REPORT
WHOPIR
Bio-Equivalence Study

Part 1	**General information**
Organization details	
Company information	
Name and Address of Clinical Research Site	N/A
Name and Address of Bioanalytical Research Site	Mylan Clinical Research Centre Saradhi Towers, A4-Rukminipuri, Near Poulomi Hospital AS Rao Nagar, Sainikpuri - ECIL Main Road Secunderabad, 500 062 India
Name and address of Statistical Site	N/A
Corporate address of the Organization	Mylan Laboratories Ltd Plot No 564/A/22, Road No 92, Jubilee Hills Hyderabad - 500 034 Tel: +91-40-3086 6666/6444 / 23550543 Fax: +91-40-30866699
GPS coordinates	Latitude: 17.48217° N Longitude: 78.55313° E
WHO product numbers covered by the inspection/ Product names/ Study numbers/ Study titles	**WHO application no. HA796** Bioequivalence study of Emtricitabine/Tenofovir alafenamide tablets 200mg/25mg **WHO application no. HA801** Bioequivalence Study of Abacavir/Dolutegravir/Lamivudine 600 mg /50 mg /300 mg Tablets **WHO application no. HA804** Bioequivalence study of Emtricitabine, Tenofovir Disoproxil Fumarate, Levonorgestrel and Ethinyl Estradiol Tablets 200 mg/300 mg/0.15 mg/0.03
Inspection details	

Dates of inspection	10 to 13 June 2025
Type of inspection	Routine
Introduction	
Summary of the activities	The primary activities conducted at this facility included bioanalysis (bioequivalence studies), complex molecule analysis, and in vitro studies for Mylan Laboratories Limited.
General information about the company and site	The Clinical Research Center (CRC) in Hyderabad, operated by Mylan Laboratories Ltd. (a Viatris company), was dedicated solely to Viatris projects, with no involvement in third-party activities. Initially established as Matrix Laboratories, the organization transitioned in 2006 from an API manufacturer to a finished dose manufacturer, with a focus on the Generic Drug Development Program for AIDS, addressing challenges related to drug availability and affordability. To support this, in-house capabilities in bioanalysis and clinical research were developed. After Mylan acquired a 100% stake in Matrix in 2007, the company was renamed Mylan Laboratories Ltd. in 2012. Following the 2020 merger of Mylan and Upjohn (a Pfizer division), the global entity became Viatris. However, Mylan Laboratories Ltd. continued to operate under its original name in India, pending further direction.
History	The company had previously been inspected by WHO in March 2022, September 2017, July 2016, March 2015, October 2011, May 2010, August 2009, July 2009, and January 2008. It has also been inspected by various regulatory authorities, and a list of inspections was provided and presented.
Brief report of inspection activities undertaken	Regarding the analytical operations, coverage was provided of the company's practices, personnel qualifications, and procedures utilized during method validations and analytical testing. The company's history, equipment calibration, validation of computerized systems, employee training, and computer controls were reviewed. A tour of the facility was conducted. A review of the 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	The inspection covered only the BA portion of the studies, as Mylan was responsible solely for those activities.

Abbreviations	ADR	adverse drug reaction
	AQ/SS	aqueous / spiking solution
	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
	EXH	highest calibration standard
	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
	IS	internal standard
	ISF	investigator study file
	ISR	incurred sample reanalysis
	IQ	installation qualification
	LIMS	laboratory information management system
	LLOQ	lowest limit of quantification
	LOD	limit of detection
	MS	mass spectrophotometer
	MVR	monitoring visit report

	NRA	national regulatory agency
	OQ	operational qualification
	PIS	patient information sheet
	PQ	performance qualification
	PQS	pharmaceutical quality system
	RS	reference standard
	QA	quality assurance
	QC	quality control
	QMS	quality management system
	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 outlining the activities of the organization.

The Study Centre was registered by CDSCO with a certification valid until 15.09.2026.

Since the 2022 inspection, several SOPs have been updated, including procedures for temperature and humidity monitoring, MSDS handling, freezer qualification, and sample storage. Bioanalytical systems had been upgraded to Windows 10, with corresponding updates to chromatography software systems. Procedures were aligned with ICH M10 and ANVISA requirements. Enhancements were made to data integrity measures, calibration procedures, and water/glassware quality controls. WHO-recommended updates were implemented to address internal standard variation and injector carry-over. Upgrades to the LIMS system and temperature monitoring application were initiated. Annual refresher trainings were conducted, and new tracking measures for checksum errors and sample transfer stability were introduced.

The CRO had an organizational chart depicting key positions and the names of responsible persons. The chart was dated 11 April 2025, approved, and kept up to date.

A job description was available for each employee, outlining their responsibilities. It was randomly verified that each job description had been signed and dated by the respective staff member.

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

It was ensured by the management that appropriate and technically valid SOPs were implemented and followed. The maintenance of a historical file of all SOPs was adequately organized.

Working hours were from 09:00 to 18:30, Monday to Friday.

2. Computer systems

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

Procedures for Computer System Validation—including system development lifecycle, change control of IT systems, configuration management, incident and problem management, backup and archival, data restoration, disaster recovery of critical systems, and periodic review—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. IT security management and administration were governed by global policies. Specific provisions for the business continuity plan for the LIMS system were verified in the appliable SOP.

The Annual Computerized System Validation Master Plan and Report, along with the Master Periodic Review Plan for 2025, were available. These documents included the scheduled verification of backup performance, periodic review of validated spreadsheets, instruments, and user access for computerized systems.

An SOP governing the validation of GxP spreadsheets was in place during the conduct of the study. A master list of validated spreadsheets used for GxP activities was maintained, subject to periodic review every four years, and managed through change control. Most spreadsheets were created in December 2020. Following the last WHO inspection, new spreadsheets were introduced for activities such as the preparation of calibration curve (CC) and quality control (QC) samples with serial dilutions, partial volume analysis, and dilution integrity. On 24 April 2025, a revised version of the spreadsheet for ISTD review was validated and approved in line with WHO recommendations, as documented in the respective documentation. The validation included verification of security features and calculations.

An inventory of all computerized systems connected to the network was available, identifying those subject to GxP regulation, along with corresponding equipment references where applicable. Any network changes, including temporary additions or removals of systems, were appropriately documented.

It was ensured that access rights granted to staff were in accordance with delegations and their respective tasks. User access for systems and equipment was subject to annual review, with evidence of the last periodic review available from May 2025. Furthermore, it was verified that for the chromatography software system, access rights were managed by the Global Team following a request raised by the site IT team through the 'Service Now' application. System users were assigned to the respective operational groups via Active Directory, which was operated by the Local IT team.

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

The chromatography systems were networked. SOP for governing data backup and access restriction of study data folders at the site describes how the network was managed, monitored, and controlled. The physical location of the servers was identified. Firewall settings, antivirus authentication requirements, security patching, system monitoring, and penetration testing were addressed both locally and through the Bangalore site, which served as the international hub for network connectivity. Additionally, a global SOP for the backup and archival of computerized systems was in place.

A detailed flowchart illustrating the network architecture, including the complete client/server structure and all relevant interfaces, was provided and included in the respective SOP during the inspection. Following the implementation, training was conducted for the relevant staff. The flowchart incorporated several key elements: a network overview depicting the overall layout; a client/server architecture section showing client devices (e.g., workstations, terminals) and servers along with their connections and data flow; and security elements such as firewalls and access control points. In addition, a separate data flowchart was provided to illustrate the main data flow for backup and restoration purposes.

The reliability and completeness of these backups were verified. The evidence of data restoration executed on 8 May 2025 was available and reviewed.

3. Quality management

The implementation status of the CAPA plan and the respective effectiveness evaluation for the observations from the last WHO inspection (March 2022) were verified. It was recommended to use controlled forms for attachments related to the CAPA plan implementation.

The Clinical Research Center operated under a comprehensive Quality Management System designed to ensure compliance with Good Laboratory Practice, Good Clinical Practice, and applicable regulatory requirements. The system encompassed defined policies, procedures, and controls across all laboratory operations to maintain data integrity, reliability, and regulatory compliance. Key elements of the QMS included managerial oversight, regular staff training, routine internal and external audits, and established procedures for incident investigation and the implementation of corrective and preventive actions. A dedicated software application was used to store quality system documents, including SOPs, and supported critical QA functions such as version control, approvals, and archival.

A Quality Manual, effective from 13 September 2024, was available. The purpose of the Quality Manual was to describe the Quality Management System established at the Clinical Research Center. The manual provided an overview of the systems, organizational structure, policies, procedures, and practices necessary to meet regulatory requirements for the conduct of comparative bioequivalence studies, complex generics, and in vitro studies at the Clinical Research Center. It also outlined the company's objectives and business areas, serving as a guide to quality management with respect to the processes and systems in the organization. The manual described procedures for operating and maintaining the organization's quality systems, with the aim of improving performance and operational efficiency.

The issuance of templates was conducted in accordance with SOP for Document Control Management, effective 16 November 2023. The issuance was recorded using an Excel sheet, which was then uploaded into the respective application during the first week of each month to protect it from editing. The list could be accessed in PDF format, containing details such as the issuer's name, date of issue, and form ID number. This practice commenced in November 2023. Templates were printed with the date of printing and the initials of the QA issuer.

The respective Change control requests made since the last WHO inspection were presented during the opening meeting.

The SOP for Data Integrity Risk Assessment, effective 29 March 2024, was established to define the process for conducting Data Integrity Risk Assessments (DIRA) to ensure the reliability and accuracy of analytical data, and to provide a structured approach for

identifying, evaluating, and mitigating data integrity risks in compliance with regulatory requirements and organizational standards. This SOP applies to all personnel involved in the generation, collection, processing, storage, and retrieval of analytical data within Mylan Laboratories Limited (a Viatris company), CRC, Hyderabad. It covered all analytical GxP systems, processes, and activities impacting data integrity. Data integrity audits were required to be conducted as per the system audit schedule. A list of identified critical data systems was available. These systems were regularly audited using a defined system audit checklist.

The audit report of Aizant CRO, responsible for the clinical portion of study HA804, was available and reviewed. The initial audit was conducted in May 2022, followed by a subsequent audit in July 2022 in response to WHO findings. It was determined that the CRO should be audited for each new specific study. Accordingly, a remote site selection assessment was performed on 17 March 2023, and an additional assessment was conducted on 9 January 2024 due to a change in the Principal Investigator.

Both in-process and retrospective QA verifications were performed, including during bioanalysis, as samples and standards were being prepared and tested. SOP for Change Control categorized documents into three classes, with Category 1 documents managed through the document management software using a Change Request Notice (CRN) and tracked via a dedicated register. Closure timelines were defined within a 90-day window, with the possibility of up to three extensions.

SOP for governing QA responsibilities and audit management was reviewed. The 2024 audit plan was verified and found to be satisfactory, covering bioanalytical, clinical, and QA areas.

Internal audits were executed as planned, with findings appropriately categorized and no critical observations reported. CAPAs were implemented for major and minor findings. The company defined, in the respective SOP, the audit trail queries or reports to be used for different systems and specific purposes

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

4. Archive facilities

This section had been covered during the previous inspection. The archiving procedures for trial-related documentation were verified through effective retrieval and traceability of documents during the inspection.

5. Premises

During the inspection, a tour of the facility, including the laboratory areas, was conducted on Day 3. The facilities were well-maintained, with adequate cleanliness, lighting, ventilation, and environmental control. Floors, walls, and workbench surfaces were designed to allow easy cleaning and decontamination. The company had sufficient space to accommodate the personnel and activities necessary for the conduct of the studies. Access to the facility was restricted and controlled through biometric fingerprint authentication.

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

Safety data sheets were made available to staff prior to testing activities. Laboratory personnel were familiar with and knowledgeable about the material safety data sheets for the chemicals and solvents they were handling. A mock drill schedule was in place, and the 2024 schedule was reviewed. The report for the planned mock drill conducted on 20 December 2024, simulating a spent solvent fire, was available and included actions related to emergency communication, firefighting, evacuation, headcount, and call-off procedures. Another report was provided for the mock drill conducted on 7 May 2024, simulating an acid spill. 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. Rules for the safe handling of compressed gas cylinders were observed. Staff were aware of the requirement to avoid working alone in the laboratory. The training attendance record for First Aid training, dated 23 August 2024, was available and reviewed.

The premises had suitable systems in place for the disposal of waste.

The Diesel Generators, UPS, and server room were visited. All were well maintained and under adequate supervision, with restricted access. SOP for the operation and maintenance of the UPS (Version 5) and the corresponding maintenance logbook were available. Similarly, SOP for the operation and maintenance of the diesel generator set (Version 5) and its respective logbooks were also available.

6. Personnel

This section had been adequately inspected during the previous inspection.

Further, it was noted that a web-based training management system application was used to ensure compliance with training requirements under the QA system, covering SOPs, policies, and relevant technical guidelines. A sufficient and qualified team of approximately 80 personnel was in place. Randomly selected current curricula vitae and training records of personnel involved in trial activities, including both full-time and contract workers, were reviewed for verification. Employee confidentiality and secrecy agreements were also randomly checked.

The company operated under a confidentiality and secrecy agreement, which was required to be signed by all employees. It was recommended that the company ensure the agreement is updated after each revision if the revised content is intended to apply retrospectively.

7. Investigational medicinal products and comparator products

The GCPh (Global Clinical Pharmacology) department oversaw all activities related to investigational and comparator products, including receipt, storage, handling, sampling, dispensing, and disposal, in accordance with defined SOPs. Upon receipt, the Clinical Study Operations Lead recorded product details in the Investigational Products Log and verified the availability of Certificates of Analysis.

Test products related to the WHO application HA804 were received by the CRC directly from the manufacturer on 23 March 2024 and shipped to the clinical facility under controlled temperature conditions using data loggers. Reference products were shipped directly from distributors. Shipment documentation, temperature records, and data logger calibration certificates were reviewed. While shipment records lacked specific product details and quantities, this information could be reconstructed from the Investigational Drug Products Log.

Products were stored in a restricted-access walk-in chamber, monitored for temperature and humidity using the Thermolab software. Alarm logs for the storage period relevant to study related to the WHO application HA804 were requested. The chamber was equipped with an alarm system capable of sending text message alerts in case of excursions, and security staff responded during out-of-office hours. The room was clean, well-maintained, and equipped with an additional application for daily manual temperature checks.

Bioanalytical section

The inspection focused on study related to WHO application HA804, including the associated validation projects. Spot checks were also conducted for studies related to WHO application no. HA796 & HA801. The runs related to the LC-MS/MS system suitability for the latter study were specifically checked. The following records and activities were investigated:

- Source documentation and raw data for validation of the bioanalytical methods.
- Analysis of subject plasma samples as well as the respective electronic data.
- Audit trails for electronic data capture and handling related to the BE studies.
- Results of calibration standards, 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.
- Concentration of predose samples for Levonorgestrel and ethinylestradiol was checked.

Furthermore, chromatograms and their integration, the absence of signals in blank samples, and the absence of any unexplained interruptions in the injection sequences were verified. The reasons for the study sample repeat analyses and all instrument failures were reviewed. The provisions and documentation of the incurred sample reanalysis were confirmed. The documentation and justification for the reinjection of analytical runs were verified and assessed for compliance with the established provisions.

During the review of the study documentation, the inspection team received adequate support from well-informed and transparent personnel. Study data were made available on dedicated PCs in the inspection room with full access, and the LIMS was provided on a laptop. The data were reviewed in collaboration with the analyst. Relevant SOPs were also made available for review.

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

The method development process was adequately described and documented, and the use of internal standards (IS) was justified based on relevant literature or previous methods, in accordance with SOP for the Development of Bioanalytical Method and Project Initiation. A copy of the supporting literature was available. Following method development, an Analytical Method Plan (AMP) was provided as the basis for method validation. Stable isotope-labelled internal standards were consistently used in MS methods. K_2EDTA or K_3EDTA was applied/tested as anticoagulants, with K_2EDTA specifically used for the study samples in the study related to the WHO application no HA804.

For emtricitabine and tenofovir (HA804), a method was developed to assess their analysis in the presence of ethinylestradiol and levonorgestrel, considering potential interferences and interactions, based on earlier methods. After confirming that the method remained applicable for emtricitabine and tenofovir in the presence of ethinylestradiol and levonorgestrel, a so-called partial validation was performed on the respective LC-MS/MS instrument, documented as Supplement 9. Nevertheless, a full validation was conducted in accordance with Report Number VR-168 Supplement-09 — Partial validation of determination of emtricitabine and tenofovir in the presence of ethinylestradiol and levonorgestrel in human plasma using liquid chromatography-mass spectrometry (LCMS) — and SOP for method validation, despite the title referring to it as a "partial validation." An investigation was also carried out to assess the potential interferences related to the use of anticoagulants K_2EDTA and K_3EDTA, which showed no significant differences.

During method validation, in accordance with the applicable SOP, a run was performed to determine a batch containing adequate numbers of QCs and CCs, referred to as a simulated run. This run was designed to be comparable in length to those expected during actual sample analysis. For study HA804, version 5.0 of the method validation SOP, effective 13 May 2022, was applicable.

Sample processing was documented using the respective forms. When applicable, a report was provided to record any unexpected activities during sample processing.

The investigation regarding a potential interaction between the internal standard for tenofovir and a concomitant medication, Ondansetron, which had been administered to three subjects in one of the studies, was reviewed and discussed.

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

The review of the complete method validation included assessments of precision and accuracy (P&A), sensitivity, selectivity, matrix effect (evaluated during method development), calibration curve performance, injector carry-over, dilution integrity, and various stability parameters. These included freeze-thaw stability, stock solution stability (short-term and long-term), haemolytic effect, recovery, reinjection reproducibility, and whole blood stability. A full overview of the method validation runs, including the partial validation, was provided and discussed during the inspection.

Partial validation was performed following the applicable requirements. The matrix used for analytical method validation matched that of the study samples, including the use of the same anticoagulants. The purchase documentation for plasma sourced from the plasma

providers was reviewed. This included records of receipt, associated dataloggers, as well as documentation related to the storage, retrieval, preparation, and consumption of the pooled plasma. The documentation for the emtricitabine and tenofovir (E&T) study under WHO application HA804 was reviewed and randomly verified.

A reconciliation template for tracking the templates issued, used, and unused for each study was available.

According to version 5.0 of the method validation SOP applicable at the time of the study related to the WHO application no. HA804, the injector carry-over test was reviewed and discussed to ensure that the practice has been updated in alignment with ICH M10 guidelines.

It was verified that the CRO, in its current practice, lipemic plasma with proper documentation and verification of triglyceride content was used. The acceptable level was defined as greater than 300 mg/dL.

Each analytical run included calibration curve standards, quality control samples interspersed throughout the run, and subject samples, all processed simultaneously. The exact processing sequence was predefined and documented. All samples collected from a given subject during all trial periods were analysed within the same run. The acceptance criteria for analytical runs were confirmed through a review of analyte retention times, the accuracy of calibration standards and QC samples, peak integration, and internal standard peak areas, as per the applicable SOPs.

A system suitability and stabilization/system equilibrium test was conducted prior to the start of analytical runs in accordance with the respective SOP, and results were recorded on the applicable form. This form could be reused for two system suitability tests if the initial test failed or if the repeat was performed on the same day following a system interruption. The system suitability test was performed in scenarios defined by the SOP, for example, once daily prior to the start of an analytical run during method validation, partial validation, or study sample analysis. A system suitability test was not required if batch analysis was conducted continuously without interruption.

System suitability and stabilization tests for the study related to the WHO application HA801 were spot-checked, and it was verified that, following each run interruption, the required tests were performed accordingly.

Incurred Sample Reanalysis, sample selection, and the respective acceptance criteria were defined in SOP for the Reanalysis of Incurred Bioanalytical Samples.

All graphs illustrating the Internal Standard Variation trends were included in the respective bioanalytical report. The ISV plots for two studies were randomly reviewed and discussed during the inspection.

The system audit trail review for the studies within the scope of the inspection was conducted in accordance with Job Aid for the Data Integrity (CS) audit checklist and Job Aid ID for the Biostudy Raw Data and Time-Concentration Profile audit checklist. The completed checklists for a selected audit trail, dated 24 May, 27 May, and 31 May 2024, were available and discussed. It was noted that certain controls were implemented at the Windows level, some offline, and others through the application itself.

The preparation of haemolysed plasma QC samples for a selected method validation was verified.

9. Sample storage and handling of biological material

The labelling of collected samples was clear, ensuring proper identification and traceability of each sample. Storage conditions, such as freezer temperature, were controlled, monitored, and recorded throughout the shipment from the clinical site, along with the respective accountability and datalogger records, and during the storage period. Records of sample storage and retrieval were maintained. Requests for sample transfer for analysis were made through Watson LIMS. A report was generated by the analyst detailing the retrieval and subsequent restorage of the subject samples.

The number of aliquots used in the study related to the WHO application no. HA804, was discussed.

Disaster management and recovery procedures for deep freezers were in place.

The management of study samples, QC samples, and pooled matrix after study completion was investigated. The reconciliation of QC and CC samples, as well as the pooled matrix related to the Emtricitabine and Tenofovir study, was verified during the inspection.

10. Data processing and documentation

Integration settings were science-based and justifiable. The smoothing factor was kept sufficiently low to avoid masking potential interferences or alterations in peak geometry.

The criteria for the acceptance and exclusion of calibration curve standards and quality control samples, as well as batch acceptance, were defined in the applicable SOPs. The source data for analytical runs included all information from the original first evaluation (containing all calibration samples) in cases where the analysis was repeated. The calibration range was appropriately truncated. Internal standard variations were monitored and trended as part of the verification of result validity, in accordance with

SOP for Reassay and Reinjection of Clinical Samples and Reporting of Final Concentration.

All original analytical raw data—such as calculations performed using LIMS software system, chromatograms, and their associated audit trails—were documented in a manner that ensured full traceability, including sample numbers, equipment used, date and time of analysis, and the names of the technicians involved. All 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 sample collection, time of centrifugation, time of placement in the freezer, and time of sample analysis, allowing for the identification of any aberrant results potentially caused by sample mishandling.

Data entry procedures, including data validation methodologies such as proofreading and double data entry, were designed to prevent errors.

11. Good laboratory practices

A tour of the facility was conducted to verify its suitability in terms of layout and safety.

The general principles of Good Laboratory Practice were followed during the bioanalytical portion of the bioequivalence studies, supported by an established and appropriate QA system.

Deep freezers used for sample storage and refrigerators used for storing reference standards were adequately qualified, calibrated, and maintained. An alarm system was integrated with the digital thermometer. There were three deep freezer rooms located in the basement. The DF room in the basement was visited to inspect the remaining CC and QC samples for the Emtricitabine and Tenofovir study (HA804).

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

The operation, use, calibration, checks, and preventive maintenance of equipment were described in the respective SOPs, and records were maintained in accordance with applicable requirements. These activities were verified through a random review of equipment used in study-related activities. Equipment and its components were labelled with the corresponding ID number, date of calibration, and date of next calibration. Equipment usage was adequately documented in the analytical sheets and the respective instrument usage logbooks. The use of chromatographic columns was recorded in a dedicated logbook for column usage.

The Change Control Request for the configuration of the UHPLC system with the API-4000 was reviewed. This instrument was used for the study related to application HA804, and a partial validation was performed on it, as reported in Supplement 11 of MV 168. Documentation of the instrument's requalification was available and reviewed, conducted in accordance with the applicable SOP using the respective form.

The reference standard storage facilities were also visited. The storage was considered well-maintained. The presence of Emtricitabin RS used for the study was verified.

Pharmacokinetic, statistical calculations and reporting section

12. Pharmacokinetic, statistical calculations

Not applicable.

13. Study report

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

Miscellaneous	
Samples taken	N/A
Assessment of the CRO master file	The site Master File version 4.0, effective from 14 April 2025, was submitted and reviewed.
Annexes attached	N/A

Part 3	**Conclusion – inspection**

Based on the areas inspected, the people met, and the documents reviewed and considering the findings of the inspection, including the observations listed in the Inspection Report, as well as the corrective actions taken and planned, the studies were considered to have been conducted at an acceptable level of compliance with WHO GCP/GLP/BE guidelines at, ***Mylan Clinical Research Centre***, located at ***Saradhi Towers, A4-Rukminipuri, Near Poulomi Hospital, AS Rao Nagar, Sainikpuri - ECIL Main Road, Secunderabad, 500 062; India***.

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

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

Part 4	List of guidelines referenced in the inspection report

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

2. Good clinical laboratory practice (GCLP), WHO, on behalf of the Special Programme for Research and Training in Tropical Diseases. Geneva, 2009
   Short name: WHO GCLP

3. Guidelines for good clinical practice for trials on pharmaceutical products. WHO Technical Report Series, No. 850, 1995 (pp. 97–137).
   Short name: WHO GCP

4. Handbook – Good Laboratory Practice (GLP): quality practices for regulated non-clinical research and development – Annex I: The OECD Principles on GLP, 2nd ed., 2009. ***Short name: OECD GLP***

5. Standards and operational guidance for ethics review of health-related research with human participants. Guidance Document. Geneva, World Health Organization, 2011.
   Short name: WHO Ethics Committee Guidance

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

7. Model guidance for the storage and transport of time-and temperature-sensitive pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth Report. Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 9.
   Short name: WHO storage and transport guidance or ***TRS 961 Annex 9***

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

9. Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability. Republication of multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability. WHO Technical Report Series No. 992, Annex 7 with a new appendix 2. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-first Report Geneva, World Health Organization, 2017 (WHO Technical Report Series, No. 1003), Annex 6.
Short name: TRS 1003 Annex 6

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

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

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