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Prequalification Team Inspection services
WHO PUBLIC INSPECTION REPORT
Contract Research Organization (CRO)

Part 1 - General information	
Company details	
Name of company	Jeevan Scientific Technology Ltd (JSTL)
Corporate address of company	Plot No. 1&2, Sai Krupa Enclave, Near LANCO Hills, Golconda post, Hyderabad – 500 008, India. Tel: +91-40-6736 4700 Email: info@jeevanscientific.com www.jeevanscientific.com
Inspected site	
Name & address of inspected site	Clinical site: **Jeevan Scientific Technology Limited** No. B-17, TIE, Phase II Balanagar, Hyderabad-500 037. Telangana, India. Tel: +91 40 6736 4700 Fax: +91 40 6736 4707 Email: rajendra.prasad@jeevanscientifii.com GPS co-ordinates: Latitude: 17.4723; Longitude: 78.4446 BA site: **Jeevan Scientific Technology Limited** Plot No. 1 & 2, Sai Krupa Enclave, Near Lanco Hills, Golconda Post, Hyderabad - 500 008, Telangana, India. Tel: +91 40 6736 4700 Fax: +91 40 6736 4707 Email: rajendra.prasad@jeevanscientifii.com GPS co-ordinates: Latitude: 17.4135 & Longitude: 78.3665
Inspection details	
Dates of inspection	**CL site:** 4-5 March 2019 **BA site:** 6-7 March 2019
Type of inspection	Initial

Introduction	
Brief description of activities performed at the site	JSTL Bioanalytical Facility has conducted the Bioequivalence study sample analysis of various therapeutic areas of molecules and various dosage forms like Tablets, Capsules, Extended release preparations, Oral suspensions with collection of biological samples of plasma/serum/Whole blood/urine for solid oral dosage forms and liquid oral dosage form with a therapeutic area of drugs related to Antidepressant, Antacid, Diuretic, Antihypertensive, Antiviral, Oncology, Diabetic, Antiepileptic, Antihypertensive, Antiretroviral, Antibiotic. A detailed list of studies conducted was maintained separately by the Project management.
General information about the company and site	The company was established as Incorporation of Jeevan Softech Pvt. Ltd and became a public limited company in 2001, starting medical writing services in 2011, expanding to full CRO listed in BSE and moved on to the new facility in 2014. The BA facility was approved by DCGI in 2015, followed by approval of clinical facility in 2016.
History of previous 3 years inspections	The Cooperate was inspected by DCGI and USFDA. The CRO was not previously inspected by WHO.
Brief report of inspection activities undertaken – Scope and Limitations	
Areas inspected	The scope of the inspection included a review of the following study-related activities: The company's history, clinical study performance, informed consent process, ethics committee approvals and correspondence, test product accountability, dispensation and storage, processing and handling of plasma samples collected during the study, equipment calibration, employee training, computer controls. Tours of the facilities were also conducted. Regarding the analytical operations, inspection coverage was provided to confirm practices, qualifications of personnel, and procedures used during the method validations and analytical testing. A review of the clinical study data, analytical method validation, and analytical study data including comparison of the source data and the study reports was conducted.
Restrictions	Not applicable
Out of scope	Not applicable

WHO Product number covered by the inspection, Product names, Study number, Study title, Sponsor	**Study number: 18-117** An open label, balanced, randomized, two-treatment, two-sequence, two-period, crossover, single-dose oral bioequivalence study of Efavirenz, Lamivudine and Tenofovir disoproxil fumarate Tablets 600 mg / 300 mg / 300 mg **Study number: 18-119** An open label, balanced, randomized, two-treatment, two-sequence, two-period, cross-over, single-dose oral bioequivalence study of Efavirenz, Lamivudine and Tenofovir disoproxil fumarate Tablets 400 mg/300 mg/300 mg
Abbreviations	**Meaning**
DR	adverse drug reaction
AE	adverse event
ALCOA	attributable, legible, contemporaneous, original and accurate
BE	bioequivalence
BDL	below detection limit
CAPA	corrective actions and preventive actions
CC	calibration curve
CPU	clinical pharmacology unit
CRA	clinical research associate(e)
CRF	(electronic) case report form
CRO	contract research organization
CoA	certificate of analysis
CS	calibration standard
CSR	clinical study report
CSV	computerized system validation
ECG	electrocardiogram
F/T	Freeze thaw study
GCP	good clinical practice
GLP	good laboratory practice
HPLC	high-performance liquid chromatograph
HQC	high concentration quality control standard
IB	investigator's brochure
ICF	informed consent form
ICH	International Conference on Harmonization
IEC	(independent) ethics committee
IMP	investigational medicinal product
IS	internal standard
ISR	incurred sample reanalysis
ISV	internal standard response variation
JD	job description
LC-MS/MS	liquid chromatography–mass spectrometry
LIMS	laboratory information management system
LLOQ	lowest limit of quantification

LOD	limit of detection
LTS	long term stability
MVR	monitoring visit report
OQ	operational qualification
P&A	precision and accuracy
PIS	patient information sheet
PQ	performance qualification
QA	quality assurance
QCs	quality control samples
QMS	quality management system
RT	retention time
SAE	serious adverse event
SAR	serious adverse reaction
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
ULOQ	upper limit of quantification
URS	user requirements specifications
WS	working standard

Part 2	**Summary of the findings and comments (where applicable)**

General section

1. Organization and management

The Protocol and bioavailability/bioequivalence study reports of New Drugs from Bioanalytical Laboratories at M/s. Jeevan Scientific Technology Limited, Plot No.: 1 & 2, Sai Krupa Enclave Manikonda Jagir, Near Lanco Hills, Golconda (Post), Hyderabad -500008, Telangana, India were accepted by the Office of Drug Controller General issued on 9 Oct 2017.

The principles of GCP and GLP were adequately ensured and around 200 qualified full-time personnel were available to support the conduct of BE study operations at this Site. Job descriptions for selected staff, including a description of their responsibilities were verified.

A delegation list with details about activities was available for each study.

The Organizational charts depicting key positions and the names of responsible persons dated February 2019 were available.

The Master service agreement with Laurus Labs Limited was reviewed. The Retention times for both study-related documentation and bio-samples were specified in the agreement. Project agreements for both studies 18/117 and 18/119 were also available, respectively dated 9 Jul 2018 and 20 Sept 2018,

The general working hours were from 9am to 5:30pm unless more shifts were required depending on on-going studies.

2. Computer systems

A list of software systems was provided. As indicated in the list of software systems, programs necessary for data management were available. Data in the computer system were protected against data loss, corruption and unauthorized access. Procedures were in place for restriction of unauthorized access to ensure data confidentiality and data security, on computer systems at JSTL.

An SOP for data backup was also available with sufficient description of procedures for backups and restoration. Backup was performed on a continuous basis as incremental and full back ups on Tapes through Veritas software using an inbuilt automated function. An Incremental Backup was done every day from the file server located at the site in addition to a full backup which was done every Friday.

There was an SOP in place for usage of Analyst software used to perform BE study activities. Data generated through Analyst® software system was stored on D: drive where it was twice daily transferred to the file server located at the BA-site. There was an automated inbuilt system which provided data back up on a tape drive using the server-based Veritas back up software system. Another back up was also provided on CDs which were archived in the archive facility.

Each site at JSTL acted as backup for the other site continuing the operations. In case of disaster, the crisis management team would handle such incident and plan for disaster recovery as in accordance with the policy.

Access to each component of the system by the different users of Analyst® software was appropriately defined and documented. The granted access was recorded in a logbook with information about the assigned role for each employee, which was also used upon termination of employment in accordance with the applicable SOP. The URS for audit trail used for Analyst® software and SOP for User levels and privileges for analytical software system, as well justifications for rights granted to Manager role were reviewed.

Working instruction for handling of validated Excel worksheet/spreadsheet was reviewed. A folder for storing of all validated Excel worksheets was designated.

The selected LC-MS/MS and the pertaining Analyst software were visited at the bioanalytical laboratory. Access rights to the software and last calibration of the instrument on 12 Oct 2018 were verified. All LC-MS/MS were internally networked, but not connected to external websites.

The observation made with relation to the computerized systems was adequately addressed in the CAPA provided by the CRO.

3. Quality management

The CRO's Quality management was reviewed to determine whether appropriate and technically valid SOPs were established and followed in a proper manner.

An adequate CRO Master File was provided.

A Quality Assurance programme was available with designated personnel, performing audit and quality control activities in accordance with the applicable requirements, independent of the work they were assuring, including study specific audits.

The Quality Assurance department was responsible for establishing and maintaining the Quality Assurance systems.

SOP for Quality review meetings was available. An agenda, including CAPA and trend analysis was required to be provided prior to the management review meeting.

A List of changes since the last inspection (USFDA Jan 2018) was provided with five items, including the setup of a new X-ray facility and implementation of BEeDC software system for the management of volunteer registration and screening. The SOP for change control was reviewed. The SOP for change control process at JSTL applied to all modifications, including approved SOP/protocol, facility, software systems, IT infra-structure or any other changes which would affect the QMS.

The Quality Management system includes a quality policy, quality manual, CRO site master file, documented procedures and any other records necessary to ensure the effective planning, operation and control of processes.

The Quality system comprised of the following levels of documents,

- Quality Manual
- CRO Site Master File
- Policies
- Protocol
- SOP/Work Instructions
- Records (Forms, Templates and Logs)

JSTL had a Quality Assurance (QA) function which was independent from rest of the operations. QA function as a separate department and Head QA reported directly to the management. The management had entrusted the QA department with the responsibility to implement, maintain, oversee and continually revise the quality standards and procedures.

The Management of SOPs was inspected to determine whether the reviewed activities were performed in accordance with the organization's SOPs and written protocols. A change control request would be raised upon revision of SOPs in accordance with the SOP for Change control request.

The QA-department was responsible for planning and executing the study specific in-process as well as retrospective audit activities in accordance with the SOP for Internal audit. An In-process audit included audit of ICD presentation, admission, dispensing, dosing, sample collection, processing and storage. A retrospective audit of all raw data was carried out after the completion of the study.

The QA-department was also responsible for issuance of forms and templates based on the request from the respective department in accordance with SOP for Document control and distribution.

SOP for Internal Audit was reviewed. System audit plans for 2018 and 2019 were provided but had not been implemented.

Deviation management required an identification number to be assigned to each deviation in the "Deviation number issue and tracking log". Logbooks were properly bound. However, there were incidents of blank spaces. It is recommended that unused blank spaces be struck through.

SOP for External audits and service providers audit plans for 2017, 2018 and 2019 were provided.

The observation made with relation to the QMS was adequately addressed in the CAPA provided by the CRO.

4. Archive facilities

There was an interim archive room accessed by only QA-personnel at the clinical site, used for storage of study binders to be prepared to be transferred to the main archive facility at the BA site after completion of the study activities and pertaining reconciliation of forms and templates used in the respective study.

The Inhouse archive facility was located at the BA site, as an appropriately secure storage space temperature, humidity and pest controlled. A fire extinguisher was available. The access to the archive storage area was restricted to only authorized archivists. Pest-control service was carried out every 15 days.

Folders were correctly arranged based on the type of documentation. The retrieval of documentation after the inspection request was reviewed. The archive processes were tested by the successful recall of study documentation and supporting records during the conduct of the inspection.

The observation made with relation to the archive facility was adequately addressed in the CAPA provided by the CRO.

5. Premises

The premises were clean, had adequate lighting and ventilation and humidity control where necessary and floors, walls and working bench surfaces were easy to clean and to decontaminate.

The premises were equipped with smoke detectors, fire extinguishers and emergency exit with appropriate setup to ensure adequate safety for subjects and personnel. Adequate safety measures were also taken.

The premises consisted of various facilities, all restricted by key card access to only authorized personnel. Entry to and exit from restricted facilities were recorded in respective logbooks.

The facility was powered by a continuous commercial electricity supply. There was a Diesel Generator (DG) set for power generation with the respective SOP and maintenance logbook available. Additionally, a UPS for use at the site in case of power failure incidents was available. A Diesel generator service was carried out monthly on a checklist. The service was provided by Sterling Company.

Suitable systems were in place to dispose the waste by sorting the waste according to their predefined category in accordance with applicable procedures.

GPS coordinated clocks were used throughout the facilities for correct and harmonized record of time of events.

Clinical site

The X-ray images from the inhouse facility were sent to the qualified (CV verified) radiologist for evaluation purposes together with a radiology report template to document the assessment.

A dedicated Phlebotomy and Sample separation area was in the respective CPU where biological samples were collected, processed and stored in the respective deep freezers. Biological waste and general waste were collected in color coded bins in line with BioMedical Waste Management Rules. Separated bio-waste was moved to dedicated area located on ground floor backside of the building for pickup by biomedical waste management agency for disposal.

Pharmacy:

Pharmacy temperature and humidity condition were monitored by a designated record software system.

The pharmacy was visited during the inspection and compliant handling of medicinal products, including reconciliation of retained samples from the studies in the scope of inspection was verified.

Security was available round the clock at the facility. All the areas where subject mobility was possible was under CCTV Surveillance and access-controlled doors. All staff were required to access the areas in the facility with their access card and required to login the computer system with their credentials to maintain data confidentiality, data security on computer system at JSTL.

The observation made with relation to the Premises was adequately addressed in the CAPA provided by the CRO.

6. Personnel

All newly hired employees were trained on SOPs and given on-the-job training with respect to their job description and assignments as scheduled in the training plan. Each employee (permanent and contract employees) at JSTL underwent training on policies and/or procedures as planned in the training modules. Staff SOP training was assessed through an evaluation test. Retraining/Refresher training was conducted every alternate year or as and when required.

Study personnel were delegated study activities based on their job description after completion of specific protocol training. Delegation lists signed by PI and Project in charge (PIC) for both clinical and bioanalytical activities were verified. On-call staff were delegated study specific studies by PI on the applicable from per SOP for Protocol training and study delegation. Both the Clinical investigator, CRP and PIC were authorized to provide protocol training to nurses and on-call staff as soon as they were trained by PI.

JSTL arranged a training on GCP/GLP training and Fire Safety every year, provided by Fire Safety System company, last performed on 3 Dec 2018. Concerned personnel were identified and sent for participation in external trainings/ lectures/workshops/seminars related to specialized subjects, methodologies, procedures, instrumentation technique and management related areas as necessary.

The Line manager/HOD was responsible for identifying staff competency requirements and ensured that the staff were trained and competent before the respective task was assigned.

Each employee was required to document his/her training details in the individual training record. A training file that contained CV, JD, training plan, training record, training evaluation sheets and professional certifications was available for each employee. The training documentation of randomly selected on-call and permanent staff was reviewed.

A Training Matrix for on-call and permanent staff was available.

The observation made with relation to the personnel was adequately addressed in the CAPA provided by the CRO.

Clinical section

7. Clinical phase

There was sufficient space to accommodate the study subjects with adequate equipment and alarms next to the bed to alert staff assigned to monitor the CPU activities.

The study site had rooms and areas appropriate for all activities referenced in Annex 9, 9.6.

An Agreement for the urgent transportation of subjects to hospital BBR Super Speciality Hospital for their emergency care when required was in place. The adequate function and performance of emergency-use equipment in the ICU and in the ambulance was verified to be appropriately calibrated. A list of equipment in ICU was available. A portable defibrillator was available to be carried to the ambulance in cases of emergency.

Dosing administration was observed during the inspection. Volunteers were identified with ID badges with photo. The ID was checked properly prior to administration of doses, followed by mouth check with spatula and torch which was monitored by a second person, and properly documented. The second part of IMP label was affixed to the CRF.

The observation made with relation to the Clinical phase was adequately addressed in the CAPA provided by the CRO.

8. Clinical laboratory

JSTL outsourced Pathology Laboratory services to Medcis Pathlabs India for analysis of the volunteer screening samples and subjects' safety samples. JSTL sent a request for sample analysis to Pathology Laboratory along with the sample shipment for analysis.

All the samples (screening and study samples) were collected in respective vacutainers for laboratory investigations by designated phlebotomists as per the request and transferred the samples to outsourced pathology laboratory in a sample transfer box with coolants in order to maintain the sample integrity. The Sample transfer box temperature conditions were recorded with data logger and monitored that the sample integrity was maintained during sample transfer. Visits of the clinical pathology laboratory representative were verified for the period of the studies in the scope of inspection. The vacutainer used to collect the samples at the time of screening was marked with only the subject registration number and not prelabelled.

On receipt of samples at pathology laboratory, samples were verified against test request form and the samples processed for analysis as per the laboratory procedures.

9. Ethics

Studies, including protocols, informed consent and other required documentation were approved by independent ethics committees before the studies were conducted. Minutes were kept of the decisions of the IEC meeting. The list of IEC members was also available.

The ICF was available in both English and the applicable local language.

10. Monitoring

The two monitoring visits *(for each of the studies*) occurred on the two dosing days. The visits were verified by review of the visitor logbooks.

The correctness of the report and validity of the statements that the monitoring was carried out in accordance with the protocol, SOP's, applicable regulatory requirements and monitoring checklist were verified.

11. Investigators

Investigators qualification and training documentation were verified.

12. Receiving, storage and handling of investigational drug products

Receiving, storage and handling of the investigational medicines for the two studies was comprehensively documented and the integrity of the investigational drug products well maintained.

The shipment, delivery, receipt, storage, dispensing, administration reconciliation documents were complete and correct.

The pharmacy was securely locked and accessible only to authorized personnel. Dispensing and handling of medicine involved the pharmacist and the principal investigator to identify products, one reading aloud the requirements/details and the other checking the sameness of details/information to the information being read. The surface was thoroughly cleaned by the pharmacist during the inspection.

The accountability records and remaining test and reference products of both studies were verified. Investigational test and reference products were handled separately during the inspection of the remaining study products.

Records evidenced comprehensive notes of activities at the time they were performed including doses dispensed and returned, cleaning and clearance of the area before dispensing and verification thereof.

The observation made with relation to the handling of investigational products was adequately addressed in the CAPA provided by the CRO.

13. Case report forms

Case report forms were randomly reviewed for studies in the scope of inspection regarding lab-results, ECGs and deviations of blood sample collection times.

14. Volunteers, recruitment methods

Prospective volunteers reported to the JSTL facility through word of mouth. New volunteers were registered in the volunteer database.

Volunteers were received at the gate-security where they were registered upon their arrival in a logbook for screening or study logbook respectively.

Initially volunteers underwent registration process by documenting the volunteer details, as well as confirming adequate literacy skills, in the volunteer registration form, after giving the volunteer consent for registration in the JSTL database. Volunteer's personal details were updated in the volunteer database and a unique six-digit volunteer registration number was allotted to each volunteer and volunteer photo identity card generated. Subsequent visits of volunteer to JSTL facility for any purpose would be identified by unique registration number in the old database, i.e. VIMS. VIMS was currently used only for verification of eligibility of volunteers already registered in VIMS through biometric device (left and right thumb and photo). The new software system was not completed yet. SOP for Registration of volunteers' ICF was reviewed. Screening validity (21 days window prior to the check-in period) and Project eligibility to avoid double participation were checked against validated Excel sheets provided by PIC consisting of information about subjects' participation in screening and/or project activities.

The VCPVS database was used to avoid cross participation in clinical studies. 19 other CROs were registered in this database to input volunteers project participation information.

Volunteers underwent the screening process after giving the consent for screening as prescribed in the respective SOP. During screening, the volunteer's medical information was verified and documented in respective forms as defined in relevant SOPs. Volunteers' data was maintained in a database with restricted access to only the concerned staff.

During screening activities, volunteers undertook study specific x-ray, ECG, protocol specific hematology, biochemistry, serology and urine tests 21 days prior to the check-in process.

Volunteers selected in the screening and reporting for study participation underwent the study informed consent process. Informed consent presentation was given in groups in vernacular language by the designated study personnel followed by a One-on-One presentation with the Clinical Research Physician and CRA to resolve medical/general study related queries. Volunteers were allowed to proceed for study specific activities only after having obtained their consent for study participation. Ample time was given to the volunteers to take a decision on their study participation. The Informed consent process (Group and One-on-one) was Audio-Video recorded. Concerned study personnel obtained the consent for study participation from volunteers. A photocopy of the signed consent document was issued to the subjects.

The observation made with relation to the recruitment was adequately addressed in the CAPA provided by the CRO.

15. Food and fluids

The preparation of food in accordance with the protocol requirements was supervised by a qualified dietician and outsourced to a caterer.

16. Safety, adverse events, adverse event reporting

Adverse events were documented in the Adverse Event Reporting form adequately according to the applicable SOP for both adverse events occurring during the study and post-study.

Concomitant medication was also captured on the form if relevant. The logbook for usage of medicines in emergency for the period of studies was reviewed.

Bioanalytical section

The inspection included auditing source documentation and raw data for validation of bioanalytical methods, and analysis of subject plasma samples as well as audit trails for electronic data capture (including instrument audit trail), and handling related to the PK study. Results of the calibration standards, quality control samples (QCs), subject plasma samples in analytical runs were verified along with the chromatograms generated from analytical runs. The preparation of analyte stock solutions, calibration standards, QCs and internal standards, and reagents was also audited.

Personnel assisting the inspection team with review of study-documents were knowledgeable, transparent and helpful. Project duty delegation was available and verified during the inspection.

17. Method development, method validation and study sample analysis

It was confirmed that selective and sensitive Bioanalytical methods for the quantitative estimation of drug(s) and / or metabolite(s) were developed using High Performance Liquid Chromatography (HPLC), Ultra High-Performance Liquid Chromatography (UHPLC) and LC/MS/MS techniques for each study in the scope of inspection. The methods were optimized up to the minimum quantifiable concentration (Lower Limit of Quantification-LLOQ) of the drug and / or metabolite in the plasma matrix which were generally 20-fold less than the reported / expected Cmax values. The linearity of the methods was established in the concentration range from LLOQ to a value greater than expected Cmax (at least two-fold the value of reported / expected Cmax). The Method developments were carried out to optimize extraction, chromatographic and spectrometric conditions to achieve the desired quantitation outcome followed by pre-method validation activity. The procedures were performed according to the in-house SOP for Bioanalytical Method Development. Bioanalytical method validations were carried out by using LC-MS/MS method according to the regulatory requirement and the in-house SOP for Bioanalytical method validation.

The analytical method validation work books reviewed provided a detailed description and record of how the bioanalytical methods for all three analytes were developed and conducted, and included copies of extracts of the relevant literature.

The analytical method validation was further verified by perusal of the audit trails of the specific instruments used as well as those of other similar instruments that were not used.

The analytical method validation was applicable for both studies, as the three analytes are the same, differing only regarding the quantity of efavirenz, i.e. 600 mg and 400 mg efavirenz respectively.

The analytical method validation was completed before the initiation of the analyses of the study samples.

Study number: 18-117

The analytes analysed in this study were Efavirenz, Lamivudine and Tenofovir disoproxil fumarate Tablets 600 mg / 300 mg / 300 mg, using appropriate ISTDs. CoAs of ISTDs, e.g. Tenofovir D6 and Lamivudine 13 C15N2 were found to be appropriate. Assay of Efavirenz, Lamivudine and Tenofovir was estimated using two different Bioanalytical Methods. Objective of the bioanalytical methods were "Estimation of Tenofovir and Lamivudine in presence of Efavirenz in Human K_2EDTA Plasma using LC-MS/MS Triple Quad 4500 mass spectrometer as per Method SOP No. MS-18-026, and Estimation of Efavirenz in presence of Tenofovir and Lamivudine in Human K_2EDTA Plasma using LC-MS/MS on API 4000 mass spectrometer as per respective Method SOP. The duration of storage of project samples was verified to be 65 and 58 days respectively. The long-term stability was tested to be 68 and 66 days in -70 and -20 °C.

Documentation regarding LC-MS/MS instruments used during method validation and during sample analysis was reviewed.

Preparation of Calibration Curve Standards and Quality Control samples was reviewed to be in accordance with the respective SOP. One set of CCs and QCs were used in each run. Each CC aliquot or QC was prepared in a quantity that was enough to be used for each run. One set of CCs was used at the start of each analytical run. QCs were interspersed between the samples in the run.

Documentation for preparation of spiking solutions, together with labelling were reviewed.
A reconciliation of QCs and CCS was performed against the available documentation since the CCs and QCs were discarded and recorded in the respective logbook. No discrepancy was identified. It was also verified that freshly made CCs were provided whenever required such as ISR analytical run.

Batch acceptance criteria, such as ISTD variation, baseline value, etc were assessed by the project-lead using a validated Excel sheet.

The complete information regarding the analytical runs were provided. The information pertaining to randomly selected runs were confirmed against the system audit trail.

Analytical run pertaining to subject no 6 (T+L) was repeated due to instrument malfunction, and subsequently failure in meeting the batch acceptance criteria in accordance with SOP for Sample analysis, data check and batch acceptance. All records were properly documented in the logbook for usage and maintenance.

Software mass spectrometer was hung during Analytical run for one of the subjects (T+L) which caused a batch stop. Adequate evidence was available.

Chromatograms and pertaining iteration parameters were also verified throughout the randomly selected runs for both analytes and ISTDs.

The chromatographic condition described in Method SOP for Estimation of Tenofovir and Lamivudine in presence of Efavirenz in human K2EDTA was reviewed and compared with results for one of the subjects and the respective repeat analysis. Repeat of analytical runs were performed in accordance with respective SOP:

Study number: 18-119

The analytes analysed in this study were Efavirenz, Lamivudine and Tenofovir disoproxil fumarate Tablets 400 mg / 300 mg / 300 mg, using appropriate ISTDs. CoAs of ISTDs, e.g. Tenofovir D6 and Lamivudine 13 C15N2 were reviewed. The assays of Efavirenz, Lamivudine and Tenofovir were estimated using two different Bioanalytical Methods, Namely "Estimation of Tenofovir and Lamivudine in presence of Efavirenz in Human K_2EDTA Plasma using LC-MS/MS Triple Quad 4500 mass spectrometer as per Method SOP No. MS-18-026, and Estimation of Efavirenz in presence of Tenofovir and Lamivudine in Human K_2EDTA Plasma using LC-MS/MS on API 4000 mass spectrometer as detailed in the respective Method SOP. The duration of storage of project samples (54 and 51 days respectively) was verified to be within the long-term stability period tested, i.e. 68 and 66 days in -70 and -20 °C.

Details reported in the study sample analysis section 12 of the Bioanalytical report, such as samples analysed, linearity ranges, system suitability, carry over, lack of interference, precision and accuracy, and individual sample concentrations were verified by reviewing the analytical records and perusal of the equipment audit trails.

The repeat analyses, re-injection details, lack of re-integration, incurred sample reanalysis and other aspects reported on in the Bioanalytical report, sections 13 to 19, were well documented, reviewed and verified.

18. Sample collection, storage and handling of biological material

The specification of the samples (plasma K2EDTA), sampling method, volume and number of samples were stated in the clinical trial protocol and in the information provided to the volunteers.

Collection, preparation, shipping and storage of samples were documented. Both aliquots from each study were separately shipped to the BA site. Blood sample collection time-point deviations were properly reported. Samples were controlled upon their receipt at the bioanalytical facility, and information about number of samples, missing samples, shipment condition were verified. Any discrepancy would be escalated to the Head-BA. The sample request for analysis was recorded in a logbook for operation and maintenance of Deep Freezer in accordance with respective SOP.

K_2EDTA human plasma for preparation of QC and CCs was purchased from Care Well Diagnostics Laboratory on 14 Jul 2018.

The observation made with relation to the handling of samples was adequately addressed in the CAPA provided by the CRO.

19. Data processing and documentation

QA maintained Document Control and Distribution as per the respective SOP. Master documents of Quality Manual, Site Master File, Study Protocol, SOP/Work Instructions, Records (Forms, Templates and Logs) were maintained by the QA department. QA issued controlled copies of SOPs/ Work instructions and study protocol to user department for reference and also controlled copies of Forms, Logs and CRFs to document the activity performed. A reconciliation of issued templates/forms was performed after the completion of the study.

A document to record the date and time of obtaining of study specific ICF was available and served as volunteers' enrolment list. Screening was performed as a general screening activity, including obtaining the screening ICF and other additional ICFs a few days prior to the obtaining of study specific ICF which was recorded separately.

20. Good Laboratory practices

JSTL had adequate equipment in place, not limited to, as mentioned below and maintained with its validation and calibration as per the relevant equipment SOP.

- Liquid Chromatography-Mass Spectrometry/ Mass Spectrometry (LC-MS/MS)
- Deep-freezer (-20°C and -70°C) for storage of biological samples
- Refrigerator (2°C to 8°C) for storage of Working/Reference Standard
- Analytical Balance and Micro Balance for weighing of standards and chemicals.
- pH Meter to measure the pH of the solution/mobile phase
- Eurotherm Data Logger to monitor the temperature recording of freezers and critical areas.

All Equipment was identified by a unique identification/ serial number and labelled in accordance with the SOP. The Equipment List and Master calibration of equipment plan were attached to the CROMF**.**

The calibration certificates and/or documentation of randomly selected equipment, as well as temperature mapping of storages used for the studies in the scope of inspection were verified. Repeatability, operating range, off center load, linearity curve and calibration summary were performed monthly for balances.

The Bioanalytical Laboratory was seated at First floor of the building with separate dedicated areas for each activity. It consisted of the following areas:

- Documentation room
- Deep freezer room
- Balance room
- Sample processing room 1
- Sample processing room 2
- Fume Hood area for handling of solvents evaporation
- Washing area
- Instrumentation rooms

Deep freezers' temperatures were monitored using an appropriate software system.

The Calibration of a micropipette was successfully demonstrated.

Recording and consumption of columns use for mass spectrometry was carried out in accordance with SOP for Receipt and handling of analytical columns. Columns used for projects 18/117 and 18/119 were properly recorded in the respective logbook.

The observation made with relation to the data processing was adequately addressed in the CAPA provided by the CRO.

Pharmacokinetic, statistical calculations and reporting section

21. Pharmacokinetic, statistical calculations

Pharmacokinetic and statistical analyses were performed using licensed software, i.e. Phoenix WinNonlin and SAS respectively.

Generation of the randomization schedule was carried out in accordance with the respective SOP and on email from pharmacist with randomization request. The printer used to print out the schedule was user specific password operative. However, the randomization schedule was not securely transferred to the pharmacist and could be accessed by unauthorized personnel.

The Biostatistician received the information about the availability of concentration data in specific folder with secured controls from bioanalytical department. The Biostatistician copied the data and arranged the data for PK analysis in accordance with SOP for Estimation of PK parameters using Phoenix WinNonlin software. The Biostatistician sent the arranged data to QA for verification. After QA clearance, the Biostatistician performed the PK analysis through WinNonlin and followed the statistical analysis through SAS software.

Upon completion of PK and statistical analysis, the data (final parameters, summary tables and SAS outputs) generated using Phoenix WinNonlin and SAS were submitted to the clinical study report author. SAS software was used to combine the concentration data and time point deviations.

Data lock was performed after PK analysis by printing out the merged concentration data and audit trail, dated and signed off by the QA-designated team.

The necessity of rationalization of the sample size was discussed with the CRO to avoid unnecessarily subjecting volunteers to medication and invasive procedures. It was noted that for the determination of the sample size SAS program; The power procedure equivalence test for paired mean ratio was applied.

22. Study report

Study report procedures, including templates and SOP for Handling and data lock of concentration data for PK analyst were investigated. Data entries were made directly from source documentation and reports were quality controlled by QA-team before submission to the sponsor.

Protocol deviations reported in study report were verified.

The observation made with relation to the study reports was adequately addressed in the CAPA provided by the CRO.

Miscellaneous	
Samples taken	14 bio-samples from different time points and period I & II, belonging to study 18/117 were randomly selected and retrieved for re-analysis purposes under inspectors' supervision. Observers from CDSCO were asked to oversee the whole processing procedure. Freshly made CCs and QCs were prepared. The batch met the acceptance criteria in accordance with the applicable procedure. Only one sample (subject no 32 hr 2:00, period I) slightly failed to meet the acceptance criteria.
Assessment of the CRO master file	BA site JSTL-SMF-001, dated 21 Feb 2019, version 01 CL site: JSTL-SMF-002 dated 21 Feb 2019; version 01
Annexes attached	Not applicable

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 study was considered to have been conducted at an acceptable level of compliance with WHO GCP guidelines at ***Jeevan Scientific Technology Ltd (JSTL)*** located at the following 2 addresses are considered to be operating at an acceptable level of compliance with the guidelines and standards of WHO:

Clinical site:
No. B-17, TIE, Phase II
Balanagar, Hyderabad-500 037, India

BA site:
Plot No. 1 & 2, Sai Krupa Enclave,
Near Lanco Hills, Golconda Post,
Hyderabad - 500 008, Telangana, 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 3 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***
   http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex09.pdf

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://www.who.int/tdr/publications/documents/gclp-web.pdf

3. Guidelines for good clinical practice for trials on pharmaceutical products. *WHO Expert Committee on Specifications for Pharmaceutical Preparations*. Thirty-Fourth Report, Geneva, World Health Organization, 1995 (WHO Technical Report Series, No. 850), pp. 97–137.
   Short name: WHO GCP
   http://apps.who.int/medicinedocs/en/d/Js5516e/19.11.html

4. WHO guidance on good practices for desk assessment of compliance with good manufacturing practices, good laboratory practices and good clinical practices for medical products regulatory decisions. *WHO Expert Committee on Specifications for Pharmaceutical Preparations*. Fifty-Second Report, Geneva, World Health Organization, 2018 (WHO Technical Report Series, No. 1010), Annex 9.
   Short name: WHO TRS 1010, Annex 9
   https://www.who.int/medicines/areas/quality_safety/quality_assurance/TRS1010annex9.pdf?ua=1

5. 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

6. 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/ethics/publications/9789241502948/en/

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***
   http://apps.who.int/medicinedocs/documents/s18683en/s18683en.pdf

8. 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***
   http://www.who.int/medicines/publications/44threport/en/

9. Glove use information leaflet, Patient Safety, Save lives clean your hands. Geneva, World Health Organization, 2009 (revised).
   Short name: Glove use information leaflet
   http://www.who.int/gpsc/5may/Glove_Use_Information_Leaflet.pdf

10. WHO guidance on good data and record management practices. *WHO Expert Committee on Specifications for Pharmaceutical Preparations*. Fiftieth Report. Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 5.
    Short name: TRS 996 Annex 5 or ***WHO GDRMP guidance***
    http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex05.pdf

11. 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
http://apps.who.int/medicinedocs/documents/s23245en/s23245en.pdf