### Part 1  General information

<table>
<thead>
<tr>
<th>Inspected site</th>
<th>General information</th>
</tr>
</thead>
</table>
| **Name and Address of the inspected site** | Bioanalytical & Statistical site  
Sun Pharmaceutical Industries Limited, Clinical Pharmacology & Pharmacokinetics (CPP)  
Plot No. GP-5, Sector 18, HSIDC  
Old Delhi – Gurugram Road  
Gurugram - 122 015  
Haryana  
India |
| **Corporate address of Organization** | Sun Pharmaceutical Industries Limited  
SUN HOUSE, CTS No. 201 B/1, Western Express Highway, Goregaon (E), Mumbai 400063  
India |
| **GPS coordinates of the inspected site** | Latitude: 28.4933  
Longitude 77.0574 |
| **Inspection details** | **11-14 September 2018** |
| **Type of inspection** | Routine |
| **Introduction** | Sun Pharmaceutical Industries Limited developed expertise in performing pharmacokinetic / bioequivalence studies to facilitate the introduction to generic or new drugs into the national and international market. Sun Pharma; Gurugram conducted bioanalysis of samples from studies. The site was also responsible for the statistical part of the studies. No clinical operation or manufacturing was undertaken by this Unit |
General information about the company | Sun Pharmaceutical Industries Limited established in 1983 and headquartered in Mumbai, India, is an international, integrated pharmaceutical company, with 45 global manufacturing facilities.

The CRO in India consisted of three units located in Gurugram, New Delhi and Vadodara.

| History | A list of inspections performed in the last five years was provided. The CRO was inspected by various authorities, including MHRA, ANSM, ANVISA, USFDA, Malaysia, MCC, Thailand, GCC, as well as CDSCO. The CRO was previously inspected by WHO in 2013.

### Brief report of inspection activities undertaken – scope and limitations

| Area inspected | The following scope and study-related activities were reviewed:

The company’s history, the analytical operations, including storage, processing and handling of biological (plasma) samples collected during the study, equipment calibration, employee training, computer controls, and a tour of the facility.

Inspection coverage was provided to firm practices, qualifications of personnel, and procedures used during the method validations and analytical testing.

A review of the analytical method validation, and analytical study data was conducted, along with the comparison of the source data to the study reports.

| Restrictions | N/A

| Out of scope | Since the site was only responsible for bioanalytical & statistical part of the studies, the inspection did not cover any clinical activities.

| WHO product names covered by the inspection, study title, sponsor | Study:

Single dose two-way crossover bioequivalence study on Dolutegravir tablets 50 mg in healthy adult human subjects under fasting condition

Study:

Single dose two-way crossover bioequivalence study of Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate tablets 50mg/300mg/300mg in healthy adult human subjects under fasting condition
**Study:**
A randomized, open label, balanced, two-treatment, two periods, two-sequence, single dose, crossover bioequivalence study of Abacavir and Lamivudine tablets, 600 MG/300 mg of Sun Pharmaceuticals industries Limited, India and the reference tablets

<table>
<thead>
<tr>
<th>Abbreviations</th>
<th>Meaning</th>
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<tbody>
<tr>
<td>ADR</td>
<td>adverse drug reaction</td>
</tr>
<tr>
<td>AE</td>
<td>adverse event</td>
</tr>
<tr>
<td>ALCOA</td>
<td>attributable, legible, contemporaneous, original and accurate</td>
</tr>
<tr>
<td>BE</td>
<td>bioequivalence</td>
</tr>
<tr>
<td>BDL</td>
<td>below detection limit</td>
</tr>
<tr>
<td>CAPA</td>
<td>corrective actions and preventive actions</td>
</tr>
<tr>
<td>CC</td>
<td>calibration curve</td>
</tr>
<tr>
<td>CPU</td>
<td>clinical pharmacology unit</td>
</tr>
<tr>
<td>CRA</td>
<td>clinical research associate(e)</td>
</tr>
<tr>
<td>eCRF</td>
<td>(electronic) case report form</td>
</tr>
<tr>
<td>CRO</td>
<td>contract research organization</td>
</tr>
<tr>
<td>CoA</td>
<td>certificate of analysis</td>
</tr>
<tr>
<td>CS</td>
<td>calibration standard</td>
</tr>
<tr>
<td>CSR</td>
<td>clinical study report</td>
</tr>
<tr>
<td>CSV</td>
<td>computerized system validation</td>
</tr>
<tr>
<td>ECG</td>
<td>electrocardiogram</td>
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<tr>
<td>F/T</td>
<td>Freeze thaw study</td>
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<tr>
<td>GCP</td>
<td>good clinical practice</td>
</tr>
<tr>
<td>GLP</td>
<td>good laboratory practice</td>
</tr>
<tr>
<td>HPLC</td>
<td>high-performance liquid chromatograph</td>
</tr>
<tr>
<td>HQC</td>
<td>high concentration quality control standard</td>
</tr>
<tr>
<td>IB</td>
<td>investigator’s brochure</td>
</tr>
<tr>
<td>ICF</td>
<td>informed consent form</td>
</tr>
<tr>
<td>ICH</td>
<td>International Conference on Harmonization</td>
</tr>
<tr>
<td>IEC</td>
<td>(independent) ethics committee</td>
</tr>
<tr>
<td>IMP</td>
<td>investigational medicinal product</td>
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<tr>
<td>IS</td>
<td>internal standard</td>
</tr>
<tr>
<td>ISR</td>
<td>incurred sample reanalysis</td>
</tr>
<tr>
<td>ISV</td>
<td>internal standard response variation</td>
</tr>
<tr>
<td>JD</td>
<td>job description</td>
</tr>
<tr>
<td>LC-MS/MS</td>
<td>liquid chromatography–mass spectrometry</td>
</tr>
</tbody>
</table>
Part 2 Summary of the findings and comments

General section

1. Organization and management

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

In May 2015, Ranbaxy was acquired by Sun Pharma. Since Apr 2016, Dr. Arshad Khuroo is the Head of Clinical Pharmacology & Pharmacokinetics department (CPP).

The company consisted of three BA sites with two of them located in India (Gurugram and Vadodara) and one in Romania. All sites were required to follow the Global Quality Standards. Gurugram and Romania sites report to Dr Arshad as Head of the Department since 2016. The Head of Global Quality was based in the USA.

Analyses were performed in a laboratory with established QA systems with SOPs for the operation, use, calibration, checks and preventive maintenance of equipment. Records were maintained, and items of equipment used during the trial were identified to verify that they were appropriately qualified and calibrated.

The recent approval from DCGI was dated 21 May 2018 and it was noted that the study reports were accepted by the authority.

The organizational chart for Clinical pharmacology and pharmacokinetics department was provided, illustrating Dr Sanghvi as Global Head and Dr Arshad Khuroo as Head- Clinical Pharmacology & Pharmacokinetics (CPP). The chart was electronically signed and authorized on 12 Jul 2018 as version 24.

A list of employees and the delegation lists of tasks during each study were provided.
From the opening meeting discussion, it was noted that Sun Pharmaceuticals had not made any substantial changes to their existing facility since they acquired it from Daichi and Ranbaxy Laboratories Limited. Most of the senior and middle management personnel were associated with the company for more than 20 years.

2. Computer systems
The organization provided a list of software systems that were used within the organization. of them were selected

Following computerized systems were inspected and the generated and stored data were reviewed to verify the reliability of data systems:

1- Analyst® software system  
2- WinNonlin software system  
3- SAS software system  
4- NuGenesis SDMS software system  
5- BSMS software system

User accounts were predetermined by roles/functions and granted a limited access to the system functions by IT-department based on a request issued by the respective department in accordance with SOP for “Assigning User Accountability and Responsibility for Computer Systems associated with Laboratory equipment and Scientific applications”.

NuGenesis software system was used to store the bioanalytical activities-related documentation. Documentation could be directly stored in the system from LC-MS/MS software system and the templates could be completed and signed off in the software. The system was also used by statisticians for Quality control review purposes. It was noted that an independent chromatography review group was designated to review chromatograms based on the SOP for “Chromatographic acceptance criteria and verification of chromatograms”. All chromatograms were manually printed into this system from the LC-MS/MS software system in PDF format for only review and storage purposes.

SOP for “Backup restoration and archival of electronic data” effective 27 Dec 2017 was reviewed. The archived data media which was ten-year-old or older was tested by restoration of the data from selected archived media once in a year. The restoration of the data backup was provided, and the action was supported by evidence.
**LC-MS/MS computerized system**
The validation plan/protocol of the selected LC-MS/MS software system was provided, reviewed and approved for regulatory compliance on 7 Jun 2016. The protocol consisted of the scope, objectives, validation strategy and risk assessment plans.

The User specification of the software was approved for regulatory compliance on 25 May 2016. The user requirements were specified, consisting of business, data, performance, environmental, security and audit trail, documentation, service and report requirements, as well as the CFR part 11 requirements. Another documentation for Configuration Specification of the software system, approved on 28 Mar 2017 was available.

Qualification reports were also approved for IT compliance, respectively:

- IQ documentation was approved for IT compliance on 7 Jul 2016.
- OQ was approved for IT compliance on 24 Aug 2016.
- PQ – UAT (User Acceptance Test) was performed on Sep 2016.

Upgrading of the software and respective hardware started in 2016. According to the validation plan, a system release certificate would be released upon completion of upgrading of each system. A complete validation report was planned to be issued after completion of the whole project when entire system was upgraded. Since there was still one instrument left to be upgraded, the complete validation report was not available.

Validation of transfer of data generated in LC-MS/MS software system from D: Drive to the backup server was provided and supported by proper evidence.

The IQ, OQ and PQ documentation for the hardware installation linked to the selected instrument LC-MS/MS was reviewed.

A third-party IT-service provider WIPRO was outsourced as End user support for cost effective and efficiency purposes. Functionally, WIPRO system administrators reported to Sun Pharma whereas administratively, they reported to WIPRO team. The agreement between the service provider and the CRO came into force in October 2016.

The WIPRO administrator was responsible to perform and monitor activities such as transfer of data from D: Drive to the backup server, hardware-related issues, backup of generated data, providing password and setting up of the privileges. The services agreement between Sun Pharmaceutical Industries Ltd and WIPRO Limited dated 21 Jun 2016 was discussed.
The checksum was enabled at the time of the inspection. A routine check to ensure the performance of the checksum functionality prior to use of the software was planned to be implemented.

Privileges given to various user-roles in the LC-MS/MS software system were defined in the Specific Configuration documentation in accordance with the applicable procedure.

**Computerized system validation of Bio-Sample Management System**

System Bio-sample Management System was developed in 2011. The qualification was performed using ISPE GAMP 4 Category 5. The validation summary report of the software was reviewed. It was noted that the system was in use by CPP Gurugram, Clinical facility (CPU) of Sun Pharma and CPP Terapia.

Observations made in relation to the computerized system were addressed in the CAPA plan provided by the CRO.

**3. Quality management**

The Quality Manual version 01, effective from 27 Nov 2017 was available stating the company's intentions for operating the processes within the quality management system.

The Quality Assurance activities were performed by an independent group of Quality Assurance personnel who directly reported to the senior management of the organization. The study-based audits (In process audits, Retrospective audits and Investigator-site audits) were performed at various stages of the study as defined in the Study Audit Program/Plan. Study protocols were reviewed by Quality Assurance (QA) team. The QA group audited study activities, raw data and study reports and issued QA audit certificate/statement.

Additionally, the QA group also conducted internal system audits, qualification/requalification audits of CSP, CROs and material suppliers. Sponsor oversight audits were also undertaken by the Quality Assurance group.

Their quality documentation was divided in three groups:

1. Global Policies for Clinical Research Operations
2. Global Quality Standards for Clinical Research operations

The fourth version of the CROMF was available effective from 16 Apr 2018. The quality management system was adequately described in their CROMF.
The QA personnel were independent of the work they were quality assuring, including conducting bioanalysis and reporting of pharmacokinetic and statistical analyses. The QA personnel were not directly involved in the trial-related activities.

The Global Head – Quality & Compliance directly reported to the Managing Director.

A complete list of SOPs was provided, divided in two groups:

1. Clinical Pharmacology and Pharmacokinetics SOPs
2. GCP Quality assurance

Following SOPs were reviewed and verified:

- SOP for Preparation, review, approval, distribution and control of SOPs, effective 8 Dec 2015
- SOP for Computerized system validation planning, reporting and release
- SOP for Computerized Systems Classification and Validation Master Planning, effective 13 Aug 2016
- SOP for Computerized Systems Periodic Validation Review, effective 12 Aug 2016
- SOP for Backup, transfer, restoration and archival of Electronic data, effective 27 Dec 2017
- SOP for Archiving of documents, effective 11 Sep 2018
- SOP for Scope and Responsibilities of GCP Quality Assurance in Clinical Studies (BAIBE and Phase - I), effective 14 Jul 2017
- SOP for Chromatographic acceptance criteria and verification of chromatograms
- SOP for Good Documentation Practices (GDP), effective date 30 Oct 2017
- SOP for Chromatographic acceptance and verification of chromatograms, effective date 17 Sep 2016 described the procedure for reintegration of chromatograms.
- SOP for Bio-sample management system, effective date 22 Jul 2018
- SOP for sample analysis and reporting of bioanalytical results, effective date 12 May 2018
- SOP for Incurred sample reanalysis (ISR) procedure, effective date 5 Jul 2018. Chromatographic reviewers were responsible for selection of ISR whereas study director / laboratory manager was responsible to review and approve the plan for ISR analysis. Basically, the procedure on ISR was aligned with the recommended EMA guideline.
- SOP for Repeat analysis, effective date 23 Aug 2018
The annual audit system schedules for year 2015 and 2017 were provided. The internal systems were audited once a year. Date of revision, reason for revision and the applicable approvals were noted on the form, signed and authorized, on March 2015 and Jan 2017, respectively.

The GCP Quality Assurance performed both in-process and Raw Data / report study audits and issued a QA statement for the final study reports.

The QA department was also responsible for review of SOPs, study protocols and validation of documents, as well as qualification audit of service providers.

All SOPs were electronically managed in Document Compliance Manager system designed to assist in creation and management of SOPs.

A periodic management review was performed on a quarterly basis, analysing all the audit findings, trends and evaluation of the quality assurance.

A Change request was raised through the DMS (Document Management system) when necessary by the author. The Change request was sent to the relevant staff responsible for review and approval, through the system. The request consisted of the reason for change and the elements to be changed in the SOP. After approval of the Change request and revision of the SOP, a training was arranged. An attendance sheet was issued outside the DMS system. The SOPs could be effective as soon as 80% of the applicable staff, based on the training matrix created in the LMS, were trained. The respective SOP would be then linked into the LMS system to generate a notification to the remaining staff to be trained. A quiz would also take place.

The LMS system was demonstrated and adequately described by the system users.

**Audit of third party vendors:**
A complete list of vendors, as well as the contract service provider audit schedule for year 2017 and 2018 with the respective details were provided. The courier services, language translation services, caterer and x-ray services were planned to be audited in 2018. Respective audits took place in accordance with the plan.

An annual assessment was provided for vendors provided various services. The last assessment was performed on 29 Dec 2017.

Observations made in relation to the quality management were addressed in the CAPA plan provided by the CRO.
4. Archive facilities
The archive facility was not visited due to the time constraints.

SOP for “Archiving of Documents” effective 11 Sep 2018 was reviewed and discussed. The company deployed Enterprise Document Archival Management system to manage archival, retrieval and re-archival of records, inventory of all documents archived and destruction of documents. Hence, the archival and retrieval of documentation was electronically managed. Each documentation was labelled with a unique number. The procedure was adequately described in the SOP.

Retrieving procedures were fairly described in the respective SOP, allowing the retrieved documentation to be returned to the archives within 20 calendar days. The archive processes were tested via the successful recall of study documentation and supporting records during the conduct of the inspection.

An offsite archiving was used for the older documentation. The agreement was reviewed. The facility was regularly audited by the company. The recent audit report and the respective CAPA plan was provided, documenting that the facility was audited for the safety measurements. Observations made were noted in the report. The audit took place on 27 Jul 2017.

Observation made in relation to the archive facility was addressed in the CAPA plan provided by the CRO.

5. Premises
During the inspection, a tour of the facility was conducted. This facility was clean, organised, tidy, and was well maintained. The building was equipped with CO2 gas flooding system, fire alarms, smoke detectors and fire proof doors. The CRO had procedures in place to manage the disasters.

The facility consisted of:

   The Ground Floor:
   • Pharmacokinetics & Statistics group
   • Quality Control group
   • Reports group
   • Quality Assurance department
   • IT support department
   • Electronic Media archival room
   • Electronic system control rooms
   • Administrative offices
The 1st Floor:
- Sample receipt & storage area
- Sample processing labs, LC-MS/MS Labs
- weighing & balance room
- laboratory supplies / store area

The 2nd floor
- Chromatography review room
- Central Pharmacy
- Freezer Room
- LC-MS/MS Lab for non-clinical purposes

The electronic key card was designed to provide privilege of access to specific areas in the facility depending on the individual's role.

Synchronized clocks were located throughout the facility to document the exact time study activities occurred.

SOP for “Backup power supply to GLP Test Facility” was reviewed. The changeover from electricity board to Diesel generator took place in case of failure. The changeover was automated by Programmable Logic Controller. The generators used for the electricity supplies were visited. Three generators were in operation. The procedures were investigated to be in accordance with the respective SOP. A daily check list in a logbook was provided to check the level of the fuel oil, leakage of coolant, oil, air etc. There were two UPS to supply the electricity for the laboratory with 250 KVA which was also visited. The generators and the UPS rooms were well-maintained. After an assessment made by the CRO, the generators’ rooms were required not to be locked in order to be easily accessible in the case of emergency. The access to the facility was supervised by the security.

6. Personnel
The list of the employees was provided in the CRO Master file and the training was well described. Annexure V in the CRO Master file consisted of the organograms including organogram of CPP with key-employees’ names and positions.

The CV and JDs of the analysts involved in the study-related activities, as well as IT-personnel’s CV and JD were selected to verify the qualification of the respective employees during the inspection.
The delegation lists were provided prior to the initiation of the study to designate the roles and activities. The delegation list for one of the studies in the scope of the inspection was reviewed. 6 analysts were assigned to perform the respective activities. The JD, CV and training documentation of all of them were requested and reviewed.

SOP for “Management of Training and Curriculum vitae and JD” effective 13 Jun 2017 was reviewed.

Training needs were identified per the employees’ job roles in consultation with functional supervisors and Head CPP. They were categorized accordingly, followed by creation of a Master Training Needs Matrix (MTNM). The training matrix was exported from LMS (electronic Learning Management System). The procedure was adequately elaborated in the SOP.

The training was categorized as follows:

- Induction training for new employees
- Ongoing training per the job role
- Others covering general, technical training etc.

Each employee was provided with copies of the qualification certificates, filed and maintained by QC Unit, stored in NuGenesis.

The training Matrix was arranged by department, designations, job name, categories and activities.

**Termination of the employment:**
Termination of the employment was handled by e-Clearance system.

The process of revoking the access to the IT-systems was outlined in the applicable SOP. The process was illustrated in a flowchart. Upon change of responsibilities or termination of a user, a “User account Management Form” was issued by the user’s supervisor to change the access or deactivate the user’s account.

The termination record for the statistician who had left the company on 27 Dec 2016 was reviewed and verified.
Bioanalytical section

The inspection included auditing of source documentation and raw data for validation of bioanalytical methods, as well as of the electronic data, audit trails for electronic data capture and handling related to the PK study.

Results of calibration standards, quality control samples (QCs), subject plasma samples in analytical runs were inspected along with the chromatograms generated from analytical runs. The preparation of analyte stock solutions, calibration standards, QCs and internal standards, and reagents were also audited.

The inspection team was competently assisted by selected laboratory staff to review the bioanalytical data records in the software and in paper form.

17. Method development, Method validation & Analysis of study samples
Following SOPs applicable during the conducting of the studies and/or in current practice were considered during the inspection of the study-related analytical activities:

- SOP for Bioanalytical method development
- SOP for Bioanalytical Method Validation
- SOP for Chromatographic acceptance criteria and verification of Chromatograms
- SOP for Preparation of Calibration Standards and Quality Control Samples; Analytical Run Organization and its Acceptance Criteria
- SOP for Repeat Analysis
- SOP for Sample analysis and reporting of bio-analytical results

SOP for Bioanalytical method development, effective 4 Jul 2016 was extensively discussed.

Bioanalytical method validation procedures and their respective change history were reviewed.

Back calculations were automated by the LC-MS/MS software system.
**Study I**

**Method development**
The literature from NIH Public Access was used for the optimization of this method. Method development was completed on 11\(^{th}\) July 2016 and synopsis and relevant raw data were available on the Electronic Notebook.

Certificates of Analysis of the working standards were reviewed. The copies of HPLC chromatogram, MS spectrum and NMR along with the certificate of analysis were provided by the supplier.

**Method validation:**
The instrument used in the method validation was verified. As part of the validation, three P&A batches, selectivity, signal to noise ratio, carry over matrix effect, recovery, ruggedness, short term stability for analyte and internal standard and other experiments were performed.

The LC-MS/MS software system was verified to confirm that the integration parameters used for method validation were consistent.

The internal standard variation was also verified for P&A batch 1 and noted that Dolutegravir D6 was very stable throughout the run.

While reviewing the software system, it was noted that “Sample Type” was changed from Standard to Sample or to Solvent / Blank etc. However, this change was captured in the audit trail result.

The applicable method validation SOP was reviewed. The documentation for Long-term stability study in human plasma, stored below -50\(^{\circ}\)C was reviewed. The run was compared against the freshly prepared QCs and results were found within the acceptable limit.

**Analysis of samples**

Total of 42 subjects were enrolled in the study, whereas 38 completed both periods.

A complete list of the project runs was provided and verified.

The LC-MS/MS instruments used in the analytical runs were verified and the randomly selected logbooks for the usage of instruments were reviewed.
The Analyst system was inspected and noted that the internal standard response was also found within the limit. The integration parameters used for CCs, QCs and subject samples were the same throughout the run.

There was no modified record and CCs and QCs were within the acceptable limits. Significant variation for the internal standard was not observed and the results were found within 40% and 180% of mean of internal standard area.

System suitability, acquisition time, IS area sets of QCs and use of CCs, interspersing of QCs, chromatograms and pertaining factors across the batches, for the randomly selected sample analytical runs, were checked.

<table>
<thead>
<tr>
<th>Repeat analysis</th>
<th>Not applicable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Re-integrated chromatograms</td>
<td>Not applicable</td>
</tr>
<tr>
<td>ISR</td>
<td>Three ISR runs were carried out. The records were properly documented.</td>
</tr>
<tr>
<td>Acceptable ranges fulfilled</td>
<td>Properly documented</td>
</tr>
</tbody>
</table>

**Study II**

**Method development**

The literature search was adequately performed, and the documentation was available.

Certificates of Analysis of working standards (WS) were reviewed. The logbooks for the usage of Abacavir, Abacavir D4 and Lamivudine Working standards in MV and Sample analysis were verified. The records were properly noted.
Method validation of Lamivudine and Abacavir in human K₃EDTA plasma using Lamivudine-13C 15N2 and Abacavir-D4 as internal standards.

Following documentation was verified:

- The retention times for analytes and their respective internal standards
- Matrix IDs used for bulk spiking to prepare calibration curve standards and quality control samples in normal human plasma.
- Haemolyzed matrix IDs
- Lipemic matrix IDs
- Storage and independent preparation of QC solutions
- Preparation of stock solutions used for the method validation of Lamivudine and Abacavir, as well as the respective IS solutions
- Preparation of samples for Matrix effect experiment, as well as the respective analytical run
- Review of data in the LC-MS/MS software systems on analytical runs performed for Matrix factor, Sensitivity, Selectivity in presence of concomitant medication, Dilution integrity, Carry-over and Interference factor

Precision and Accuracy experiments were performed in accordance with the applicable procedures. The P&A III was carried out along with the recovery test.
Stability:
The stability of the samples was tested both for Autosampler processing and for the during the extraction of sample processing. The documentation was reviewed, and the length of the stability was verified.

The Autosampler temperature was confirmed for the period of the time the samples were kept in the Autosampler waiting to be analysed.

Freeze/Thaw stability
The analytical run was conducted on samples which had undergone three cycles. The documentation, together with the record of samples in the BSMS were reviewed.

The run was performed together with the Autosampler stability, Bench Top stability, and bench top stability during extraction. The whole sample processing together with the respective result table in the software and the respective audit trail were reviewed.

The batch met the acceptance criteria. Documentation for batch acceptance was recorded in the NuGenesis system.

The CCs were spiked freshly in accordance with the applicable procedures.

Analysis of samples
Acquisition time, IS area, sets of QCs, interspersing of QCs and use of CCs of randomly selected runs, as well as their respective audit trail and file information were verified.

Checksum functionality was not enabled at the time of the study.

Chromatograms and pertaining integration parameters across the batch were randomly selected and inspected.

The security configuration for the project was verified.
Optimization runs were conducted in accordance with SOP for scanning and optimization of mass spectrometer parameters prior to the first sample run in each study to optimize source/gas dependant parameters and compound dependent parameters to obtain the desired sensitivity and consistent response for a specific ion or ions.

Matrix screening runs were carried out in accordance with SOP for “Procedure for procurement and preparation of biological matrix, matrix screening and spiking / bulk spiking.”
Sample processing documentation for presence of the concomitant medication for biostudy was reviewed.

Pooled plasma sources, use and record of the lots were reviewed. The respective invoice and the shipment documentation with the record of the datalogger ID to verify the shipment condition were available.

The records for System suitability & IC were verified in the software to be in chronological order.

The reason for reinjection of selected runs was properly reported and recorded in NuGenesis. Repeat analyses were also properly reported.

<table>
<thead>
<tr>
<th>ISR</th>
<th>Lamivudine:</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISR I 15 Mar 2016:</td>
<td>48 samples</td>
</tr>
<tr>
<td>ISR II 6 Apr 2016:</td>
<td>134 samples</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ISR</th>
<th>Abacavir:</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISR I 15 Mar 2016:</td>
<td>38 samples</td>
</tr>
<tr>
<td>ISR II 6 Apr 2016:</td>
<td>113 samples</td>
</tr>
</tbody>
</table>

ISR runs were carried out for both analytes as one run. However, since some of the samples for Abacavir were BLQ (below lowest quantity), they were not counted in the calculation.

ISR III 6 Apr 2016 and respective audit trail were reviewed.

All ISR results met the acceptance criteria in accordance with the applicable procedure.

| Acceptable ranges fulfilled | Performed properly. |
Study III

Method development
In September 2011, Tenofovir alafenamide / Lamivudine / Emtricitabine was optimized and validated. Then Tenofovir disoproxil fumarate (MV505/11) was validated alone in 2011.

The laboratory notebook was maintained. This method was used for subject sample analysis, but it failed. In June 2017, the analytical method for Tenofovir alafenamide / Lamivudine / Dolutegravir was validated. The subject samples for Lamivudine and Dolutegravir were analysed using this method. Lamivudine and Dolutegravir method was used for the subject sample analysis however it did not cover Tenofovir and hence it was redeveloped and revalidated.

From 8 Aug 2016 onwards, the laboratory started maintaining issuance of method development number logbook.

The balance printouts, copies of excel sheets, certificate of analysis of reference substances etc. were maintained.
### Method validation

#### Method validation of Tenofovir in Human K3EDTA Plasma using Tenofovir-D6 as an Internal Standard:

The validation requirements for the analytical method described in the protocol and the LC-MS/MS instruments used for the method validation were verified.

The records of weighing of the working standards (Tenofovir d6 and Tenofovir) for preparation of CCs and QCs were reviewed. Pipettes used for the activities were also properly identified and recorded.

Certificates of analysis of Tenofovir and Tenofovir D6 were verified. The copies of the respective MS spectra, NMR spectra and UPLC printout were available.

9 lots of normal matrix, 2 lots of each haemolyzed and lipemic matrix were used for the method validation study.

The certificates of analysis of the human plasma, provided from the service provider in the USA were available. K3EDTA Lipemic plasma and K3EDTA haemolyzed plasma were purchased from the service provider in India. The material transfer agreements between these service providers were in place.

Tenofovir bioanalytical method was validated as per respective SOP version 5.0. The experiments performed as part of the validation were reported within limit and the validation was completed on 11 Sep 2017 with exception to the long-term stability.

Duration of the storage of the solution was established and was supported with long-term stability data performed on 18 Dec 2017 with preparation of bulk spiking on 5 Sept 2017 (total of 104 days).

#### Method validation of Lamivudine and Dolutegravir

The validation requirements for the analytical method described in the protocol and the preparation of stock solutions, together with procurement of human plasma were reviewed and verified. The certificates of analysis for Lamivudine, Lamivudine 13C15N2, Dolutegravir and Dolutegravir D6 were reviewed. The bulk spiking preparation and long-term stability records were properly documented and verified. The integration parameters used for Lamivudine and Dolutegravir, across the analytical runs were reviewed in the software system.
Analysis of samples

The Lamivudine & Dolutegravir subject sample runs’ documentation was reviewed. The total number of the subjects participated in the study was 66 whereas 62 had completed the study. All timepoints of the randomly selected subject sample collections were verified. Three LC-MS/MS instruments were used for the subject sample analysis.

Same integration parameters were maintained for all the injections. The internal standard response of Lamivudine 13C-15N2 for randomly selected runs was verified and found stable.

The linear regression was manually (excel sheet) calculated for Lamivudine analyte and compared against the back calculated concentration which was reported in the study report. The calculated concentrations were not found to be different.

Observations made in relation to this section were addressed in the CAPA plan provided by the CRO.

18. Sample collection, storage and handling of biological material

Samples were collected at the clinical facilities and stored in the designated deep freezers. After completion of each period, plasma samples were shipped to the CPP facility in packed insulated containers with dry ice. Periods were segregated with different cap-colours and different aliquots were stored in different freezers.

The shipment was received and the shipment condition, number of samples, including the haemolysis and missing samples were verified. The documentation for the recent shipment, as well as the respective logbook for the freezer was reviewed.

There was a total of twelve 50 ºC deep freezers (DF) and three walking Cold Rooms (CR) in the sample storage facility. The temperature was monitored by Eurotherm Monitoring System software system. SOP for Operation, maintenance and calibration of monitoring systems used for monitoring temperature and relative humidity, dated 26 June 2018 was in place to take appropriate action when the temperature exceeded the limit. Eurotherm digital thermometer and the alarm were connected to the security room. The alarm notification for one of the deep freezers was tested. An email was generated to the custodian’s email box. Additionally, Deep freezers’ thermometer was equipped with a CO2 container to provide CO2 in case of increased temperature.

The storage facilities were adequately labelled with calibration data and unique ID number.

The deep freezer room was supervised by custodians with access rights.
The procedure for receipt, log-in/replacement, log-out/retrieval, transfer, bulk movement and disposal of samples were well-described in the respective SOP. Retrieval of the samples for analysis purposes was requested by lab-analyst through the NuGenesis. Samples were prepared based on the request and logged in the respective freezer’s logbook, verified by the analyst. The restorage of the samples was also verified through the same route. The analyst did not have access to the room and the samples were delivered through a window.

BSMS system was used for management and handling of samples prepared at the site, namely CCs and QCs. All spiked CCs and QCs were barcoded at the laboratory upon their preparation and handed over to the custodian for system registration and storage. The system was traceable through the respective audit trail.

The bio-samples were required to be retained at least 6 months after completion of concentration data.

Observations made in relation to the handling of bio-samples were addressed in the CAPA plan provided by the CRO.

19. Data processing and documentation
Integration settings of the analytical runs were randomly reviewed. Smoothing was kept the same throughout the runs.

Full audit trail was activated on the analytical instruments used for the study in the scope of inspection.

Internal Standard Variation (ISV) was trended and used as part of the verification of result validity. The calculation of ISVs for all runs was requested and randomly reviewed.

The CRO used paper forms, as well as e-forms stored in the NuGenesis system.

The electronic notebooks (ELN) were used to document the activities of method development. The data was printed along with data file information in NuGenesis. Results for method qualification were calculated and reported through Excel worksheets.

Raw data were generally documented in a manner that enabled the traceability with respect to sample and equipment identification and time and date of activity and the respective delegate. Logbooks were consistently used to record the activities and usage of equipment throughout the organization.
The procedure for issuance of templates was described by the QC-team and the related documentation for one of the studies in the scope of inspection was reviewed. The issuance of the templates was chronologically recorded in a logbook. In addition, there was a compilation form with the list of all templates for a specific study, prepared after completion of the study as a part of the TMF. The list consisted of number of forms, specified for different purposes, together with the number of unused forms. The unused forms were annulled and kept with the rest of the documentation. For reconciliation purpose, a checklist was provided in the NuGenesis to be used by the QC-team.

The GCP QA Audit report verified that complete study report was reviewed along with associated data.

Observations made in relation to the data processing were addressed in the CAPA plan provided by the CRO.

20. Good laboratory practices
The bioanalytical laboratory was located on the first floor. Another facility was designated to MAP (Metabolism and Pharmacokinetic) laboratory on the second floor.

The laboratory was well-equipped and well-organized, with adequate safety measures such as the availability of shower and eye-wash station and a binder with Material Safety Data Sheet (MSDS).

Currently, there were 20 LC-MS/MS instruments available at the facility, whereas two of them were located at the MAP laboratory to be used for non-clinical purposes.

The CRO had a mature system in place for the maintenance and calibration of equipment, including a Master list of equipment and pipette inventory log which were made available. An SOP for Equipment Qualification and its Lifecycle Management was presented.

The temperature mapping documentation for randomly selected storage facilities was reviewed. The process was carried out in accordance with the respective SOP. The activity was performed to ensure that the entire storage area was uniformly cold, instead of identifying the hot spot. The practice was properly performed and documented.

The calibration documentation of one of the LC-MS/MS instrument performed on 12 Oct 2016 and 5-6 Oct 2015, and the pertaining audit trail was reviewed. The service report from Sciex and the documentation for preparation of the solvent used in the calibration were also available.
Working standards were kept in the weighing room in the designated refrigerators and desiccators. The room was equipped with temperature monitoring-system, three refrigerators, one freezer box (0 – minus 20 ºC) and both micro and analytical balances.

The working standards were recorded in the logbooks in alphabetic order with information regarding the quantity, usage and expiry date.

Observations made in relation to the Good Laboratory Practice were addressed in the CAPA plan provided by the CRO.

### Pharmacokinetic, statistical calculations and reporting section

#### 21. Pharmacokinetic, statistical calculations

**Randomization**
Randomization schedule was generated based on a request from the Clinical department through an email. A copy of IC-approved protocol was also submitted via this email. The email related to the randomization schedule for one of the studies, dated 11 Jul 2017 was verified. The randomization list was produced using SAS software system. The schedule was printed into the NuGenesis for quality control by another biostatistician before it was sent to the requester and the pharmacist by email.

**Statistical data**
The bleed sheet for one of the studies was shared by the Clinical department to the biostatisticians, on 8 Aug 2017. It was noted that the bleed sheet was shared through the shared folder as the size of the files was above 5 MB.

The clinical data such as actual blood collection timepoints, number of dropouts and withdrawals was received by the statistician on the bleed sheet.

Transfer of clinical data to the SAS program was executed using copy-paste option from Excel spreadsheet. The statistical report was quality controlled by designated QC-staff and signed off in the NuGenesis.

Phoenix software system provided by Pharsight was used for PK-calculations by importing the bioanalytical data from the respective study folder.

CV and JD and training documentation of the biostatistician was verified.
Observation made in relation to this section was addressed in the CAPA plan provided by the CRO.

22. Study report
In addition to the source data, the CRO provided the reports of analytical method validation and the reports for subject sample analysis.

SOP for preparation and release of study reports stipulated that original and reintegrated chromatograms were required to be reported.

<table>
<thead>
<tr>
<th>Miscellaneous</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Samples taken</strong></td>
<td>Not applicable</td>
</tr>
<tr>
<td><strong>Assessment of the CRO master file</strong></td>
<td>The CRO master (CROMF) file was available to provide brief description about the infrastructures and systems / processes of various sites / departments / units involved in conducting BA/BE studies at SPIL, Gurugram India.</td>
</tr>
<tr>
<td><strong>Annexes attached</strong></td>
<td>Not applicable</td>
</tr>
</tbody>
</table>

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 and GLP at the following site:

Bioanalytical and statistical site
Sun Pharmaceutical Industries Limited, Clinical Pharmacology & Pharmacokinetics (CPP)
Plot No. GP-5, Sector 18, HSIDC
Old Delhi – Gurugram Road
Gurugram - 122 015
Haryana
India
All the non-compliances observed during the inspection that were listed in the complete report as well as those reflected in the WHOPiR, were addressed by the CRO, to a satisfactory level, 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**

   
   **Short name:** WHO BE guidance  

   
   **Short name:** WHO multisource guidance  

   
   **Short name:** WHO GCP  
   http://apps.who.int/medicines/docs/en/d/J5516e/19.11.html

   
   **Short name:** WHO TRS No. 996, Annex 5 WHO GDRMP guidance  
   http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex05.pdf

   
   **Short name:** WHO GLP  


**Short name:** WHO TRS No. 961, Annex 9 http://apps.who.int/prequal/info_general/documents/TRS961/TRS961_Annex9.pdf

**Short name:** WHO TRS No. 957, Annex 7 http://www.who.int/medicines/publications/TRS957_2010.pdf
