## WHO PUBLIC INSPECTION REPORT
### Bio-Equivalence Study

<table>
<thead>
<tr>
<th>Part 1</th>
<th>General information</th>
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<tbody>
<tr>
<td><strong>Inspected site</strong></td>
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<tr>
<td>Name and Address of Inspected site</td>
<td>Clinical, Bioanalytical &amp; Statistical site&lt;br&gt;Sitec Labs Pvt. Ltd. Mahape&lt;br&gt;PEE-DEE Infotech, Plot No. Gen-40, TTC MIDC, Near Nelco, Behind Millennium Business Park&lt;br&gt;Mahape - Navi Mumbai&lt;br&gt;400 710, India</td>
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<tr>
<td>Screening and pathology site</td>
<td>Sitec Labs Pvt. Ltd.&lt;br&gt;First floor, Jayashree Plaza&lt;br&gt;LBS Marg, Above ICICI Bank&lt;br&gt;Opposite R.R. paints&lt;br&gt;Bhandup (West)&lt;br&gt;Mumbai – 400078&lt;br&gt;India</td>
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<tr>
<td>Corporate address of Organization</td>
<td>Sitec Labs Pvt. Ltd. Mahape&lt;br&gt;PEE-DEE Infotech, Plot No. Gen-40, TTC MIDC, Near Nelco, Behind Millennium Business Park&lt;br&gt;Mahape - Navi Mumbai&lt;br&gt;400 710, India</td>
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<tr>
<td>GPS coordinates</td>
<td>Latitude 19,1409&lt;br&gt;Longitude 73,0041</td>
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<td><strong>Inspection details</strong></td>
<td></td>
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<tr>
<td>Dates of inspection</td>
<td>30 July – 3 August, 2018</td>
</tr>
<tr>
<td>Type of inspection</td>
<td>Routine</td>
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<tr>
<td><strong>Introduction</strong></td>
<td></td>
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<tr>
<td>Brief description of activities performed at the site</td>
<td>The facility had the capacity to perform bioequivalence / bioavailability and in-vitro studies in healthy subjects, contracting out the catering of the study volunteers and X-ray investigations.</td>
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<tr>
<td>General information about the company and site</td>
<td>Sitec is a CRO which provides various analytical services such as analytical method development and validation, pilot and pivotal clinical services, as well as bioanalytical services including bio-sample analysis.</td>
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### History
In the last 14 years, the organization was inspected by different authorities such as USFDA, MHRA, EMA, MCC and Malaysia. The CRO was inspected by WHO in 2014.

A list of inspections performed was provided.

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

#### Areas inspected
The following scope- and study-related activities of the studies were reviewed:

The company’s history, clinical study performance, informed consent process, ethics committee approvals and correspondence, test article accountability, dispensation and storage, processing and handling of biological (plasma) samples collected during the study, equipment calibration, employee training, computer controls were reviewed, in addition to a tour of the facility.

Regarding the Analytical operations, the team covered confirmation of good practices, qualifications of personnel, and procedures utilized during the method validations and analytical testing.

The clinical study data, analytical method validation, and analytical study data was reviewed, and the source data was compared to study reports.

#### Restrictions
N/A

#### Out of Scope
N/A

#### WHO product names covered by the inspection, study title, sponsor

<table>
<thead>
<tr>
<th>Study no: 14-11-107</th>
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<tr>
<td>A randomised, single dose, open label, four-period, replicate cross-over bioequivalence study comparing the test product, Artesunate suppositories 100 mg (Cipla Ltd., India) with the reference product, Artesunate suppositories 100 mg (Manufactured by Catalent [Eberbach, Germany] and packed and distributed by Scanpharm, [Birkerod, Denmark] on behalf of WHO-TDR [Geneva, Switzerland]), in healthy adult male human subjects under fasting conditions.</td>
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<tr>
<th>Study no: 15-05-100</th>
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<tr>
<td>A randomised, single dose, open label, four-period, cross-over replicate bioequivalence study comparing the test product,</td>
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</table>
Sofosbuvir 400 mg film-coated tablet (Cipla Ltd., India) with the reference product, Sovaldi 400 mg film-coated tablet (Gilead Sciences International Ltd., UK), in healthy adult human subjects under fed conditions.

**Study no: 15-03-040**
A randomised, single dose, open label, two-period, cross-over bioequivalence study comparing the test product, Tenofovir disoproxil 245 mg (containing 245 mg of tenofovir disoproxil as fumarate, equivalent to 300 mg tenofovir disoproxil fumarate) and Lamivudine 300 mg combination film-coated tablet (Cipla Ltd., India) with the reference products, Viread 245 mg film-coated tablet (containing 245 mg of tenofovir disoproxil as fumarate, equivalent to 300 mg tenofovir disoproxil fumarate) of Gilead Sciences International Limited, UK and Epivir® 300 mg film-coated tablet (ViiV healthcare UK Limited, UK) in healthy adult human subjects under fed conditions.

**Study no: 15-10-180**
A randomized, single dose, open label, two-period, cross-over bioequivalence study comparing the test product, Zidovudine and Lamivudine 300 mg/150 mg tablet (Anhui Biochem Bio-Pharmaceutical Co., Ltd., China) with the reference product, COMBIVIR® 150 mg/300 mg film-coated tablet (ViiV Healthcare UK Ltd, UK), in healthy adult human subjects under fasting conditions.

**Study no. 14-12-122**
Artesunate 100 mg - Amodiaquine 270 mg FDC tablet – Fasting

<table>
<thead>
<tr>
<th>Abbreviations</th>
<th>Meaning</th>
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<tr>
<td>ADR</td>
<td>adverse drug reaction</td>
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<tr>
<td>AE</td>
<td>adverse event</td>
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<tr>
<td>ALCOA</td>
<td>attributable, legible, contemporaneous, original and accurate</td>
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<tr>
<td>BE</td>
<td>bioequivalence</td>
</tr>
<tr>
<td>BDL</td>
<td>below detection limit</td>
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<tr>
<td>CAPA</td>
<td>corrective actions and preventive actions</td>
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<tr>
<td>CC</td>
<td>calibration curve</td>
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<td>CPU</td>
<td>clinical pharmacology unit</td>
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<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>CRA</td>
<td>clinical research associate(e)</td>
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<td>eCRF</td>
<td>(electronic) case report form</td>
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<td>CRO</td>
<td>contract research organization</td>
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<tr>
<td>CoA</td>
<td>certificate of analysis</td>
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<tr>
<td>CS</td>
<td>calibration standard</td>
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<tr>
<td>CSR</td>
<td>clinical study report</td>
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<tr>
<td>CSV</td>
<td>computerized system validation</td>
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<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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<td>GCP</td>
<td>good clinical practice</td>
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<tr>
<td>GLP</td>
<td>good laboratory practice</td>
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<tr>
<td>HPLC</td>
<td>high-performance liquid chromatograph</td>
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<tr>
<td>HQC</td>
<td>high concentration quality control standard</td>
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<tr>
<td>IB</td>
<td>investigator’s brochure</td>
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<tr>
<td>ICF</td>
<td>informed consent form</td>
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<tr>
<td>ICH</td>
<td>International Conference on Harmonization</td>
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<tr>
<td>IEC</td>
<td>(independent) ethics committee</td>
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<td>IMP</td>
<td>investigational medicinal product</td>
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<td>IS</td>
<td>internal standard</td>
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<tr>
<td>ISR</td>
<td>incurred sample reanalysis</td>
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<tr>
<td>ISV</td>
<td>internal standard response variation</td>
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<tr>
<td>JD</td>
<td>job description</td>
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<tr>
<td>LC-MS/MS</td>
<td>liquid chromatography–mass spectrometry</td>
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<tr>
<td>LIMS</td>
<td>laboratory information management system</td>
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<tr>
<td>LLOQ</td>
<td>lowest limit of quantification</td>
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<tr>
<td>LOD</td>
<td>limit of detection</td>
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<tr>
<td>LTS</td>
<td>long term stability</td>
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<tr>
<td>MVR</td>
<td>monitoring visit report</td>
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<tr>
<td>OQ</td>
<td>operational qualification</td>
</tr>
<tr>
<td>P&amp;A</td>
<td>precision and accuracy</td>
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<tr>
<td>PIS</td>
<td>patient information sheet</td>
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<tr>
<td>PQ</td>
<td>performance qualification</td>
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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.

Sitec Labs Pvt. Ltd. is a Private Limited company established in 2004, taking over the previously existing, Medlar laboratories Pvt. Ltd. The Bioequivalence Division occupies a total area of about 26500 square feet, divided in Bioanalytical department and Bioclinical Section. The CRO is situated in Mahape, an industrial area of Navi Mumbai. However, the organization operates a separate site as a screening and pathology facility, located in Mumbai at the following address:

Sitec Labs Pvt. Ltd.
First floor
Jayashree Plaza
LBS Marg,
Bhandup (West)
Mumbai - 400078

Schematic diagram of site, as well as the organization’s organogram was available in the CRO MF.

The CRO’s laboratory was approved by the local authority as a contract testing laboratory with approval no. KD/Testing Licence/19/201 0. The CRO had an approval for conducting bioavailability and bioequivalence studies on healthy human volunteers. However, the DCGI accreditation for the facility was not available for the period between 15 Oct 2016 and 08 Jun 2017 due to re-accreditation process. The Quality Management System of the facility was certified according to the ISO 9001:2015.

The Master Services Agreement signed on April 2012 (the "Effective Date") between Cipla Limited, as "Sponsor" and Sitec as “CRO” was reviewed.

The major changes implemented since the previous WHO inspection in 2014 can be summarized as:

- Pathology Lab was relocated from 3rd floor of Mahape to Bhandup site in 2015.
- The Bio-Clinical and Bioanalytical departments were expanded in 2017.
- Four new LC-MS/MS were procured since 2014.
- Three orbital shaking incubators for conduction of in-vitro BE studies were provided.
2. Computer systems

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

In addition, the CRO was registered in OVIS database for confirmation of cross participation of study subjects. A database system used for registration of volunteers was available at both the screening site and at the Bio-clinical department.

Any access to the available and applicable software for the employees was provided by IT-unit based on a requisition form from the respective department. The user specification was created in the software. Passwords would be changed within predefined intervals.

LC-MS/MS Software systems were connected to INS server. The software system provided an option which enabled the software to transfer the generated data directly to the Network’s server. The company had adequate means to retain, maintain and back up all electronic records obtained from HPLC and MS analysis.

The yearly-tapes were stored at the in-house storage facility, in fireproof cupboards, in the IT-room, accessed by only authorized personnel.

Restoration of the data was carried out based on the request from the user department. Upon the request from the user department, the respective data was restored, and the result of the restoration was reported to the respective user department.

SOP for Backup and restoration of electronic data (Netbackup server) was reviewed, effective from 6 Jul 2018.

MassLynx software was installed in full security mode.

The computerized system validation of the CRO’s computerized systems was not implemented adequately. For deficiencies see Part 3 of the inspection report.

The Analyst Software used for the LC-MS/MS systems were inspected for security configuration and checksum use. Administration role was allocated to five IT-staff with specific username. D: drive was solely accessible by IT-staff. However, only calibration wiff. files were stored on the D: Drive.

The time and time-zone on the computer could be changed by IT-staff.
Observations made in relation to the computerized system were adequately addressed in the CAPA provided by the CRO.

3. Quality management
The CRO’s QMS system with written SOPs was structured to ensure that trials were conducted, and data were generated in compliance with the protocol, SOPs and applicable local and international laws.

The CRO Master file and the Quality Manual was available and reviewed.

SOPs were divided in different categories such as SAP, SLP, SOP Bioanalytical, Bio-clinical, Pathology, Personnel, IT, Stores, Organization Procedure, Instrument Operating Procedure (IOP), Equipment Operating procedure (EOP), SOP personnel and SOP Engineering, General analytical Methods and GLP procedures.

There was an SOP for SOP to regulate the preparation and revision of the SOPs. A Change Control System was implemented.

The request for change was raised by the relevant department, prior to the QA approval. The SOP would be effective as soon as 80% of the staff to whom the procedure was applicable, completed the training.

Deviation from SOPs were reported to the QA-unit after root cause investigation, followed by grading of the findings. Deviations were graded either as major or minor. Correction of major deviations should take place within 3 days, while there was a 30-days deadline for minor deviations. Trend analysis was annually carried out.

The QA was an independent unit reporting directly to the CEO. In addition, every unit had an internal QC-team in place.

The QA-responsibilities in the clinical and bioanalytical operation was adequately described.

The CRO’s QMS were regularly monitored in accordance with a validity schedule. SOPs were updated every two years. Validity schedule was provided on a hard copy, date-wise, to be reviewed monthly to detect the expired SOPs.
A number of SOPs were reviewed during the inspection:

- SAP for Creation, utilisation, and operation of SOPs effective 23 July 2018
- SOP for Repeat analysis of bioanalytical samples effective 13 Jul 2018.
- QAP for Self-assessment, effective 26 Jul 2018
- SOP for Master validation plan effective 25 May 2018. The
- SOP for LC-MS/MS regarding usage of Analyst software, effective of 1 Sep 2015. The SOP was reviewed by QA-team on August 2017 and documented that no change was required.

The system audit of the CRO was performed twice a year. The schedule for vendor audit was adequately provided.

4. Archive facilities

The onsite storage facility was inspected and authorized access to the facility was reviewed. Safety measurements to protect the documentation, such as smoke detectors, fire extinguishers, rodent trap and temperature monitoring were implemented. Pest control was performed monthly.

All documents were kept in the onsite storage facility for a period of 6 months before being transferred to the offsite archive facility. Folders within the onsite facility were correctly arranged by alphabetical order (based on the project). The index was provided in a notebook. However, the CRO was recommended to re-arrange the index in an electronic way to facilitate the search option and keep a better oversight of the archiving documentation.

The archive processes were tested via the successful recall of study documentation and supporting records during the conduct of the inspection.

The agreement with Iron Mountain offsite archive facility valid until 30 Aug 2018 was provided.

Observations made in relation to the archive facility were 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, looked professional and well maintained. The facility consisted of check-in area, changing rooms with lockers, physical examination and blood collection area, analytical research department, microbiology unit and four CPUs and bioanalytical laboratory.

Restricted access was provided by key-card. Access was granted by the IT-department. A list of personnel with access to the facilities based on their role was available.
The temperature of the different units of the facility was monitored by digital thermometers connected to the wireless datalogging and alarm system with light indicator. A hooter alarm was in the security room for 24-hours monitoring. A notification was sent as a text message to the designated personnel in case of temperature fluctuations out of the acceptable range. Alarms were tested during the inspection. A list of all triggered alarms for the last 2 months was provided.

The digital thermometer used for the monitoring of the freezer temperature which was connected to OceaSoft database-system was tested during the inspection.

There were three backup generators located at the main facility with individual capacity of 500 KVA, 320 KVA and 100 KVA respectively. One additional backup generator was available in the screening facility having 62.5 KVA power supply.

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

Screening area and the pathology laboratory were located at a separate location with the following address. The facility was visited by the inspection team:

Sitec Labs Pvt. Ltd.
First floor
Jayashree Plaza
LBS Marg,
Bhandup (West)
Mumbai – 400078
India

The screening and pathology laboratory was spread across 6000 sq./ft. area comprising of the areas for volunteer registration, screening, physical examination, ECG, blood and urine sample collection room, canteen, training room and pathology laboratory area.

Volunteers were received at the gate-security where they were registered upon their arrival in a visitor logbook. Volunteers’ details were recorded in a customised volunteer database. Additionally, the OVIS database was used to avoid cross participation of volunteers. The volunteer database was inspected to be fit for the purpose.

Barcodes, used for the identification of the volunteers, were generated in the volunteer database system after general review of the ICFs.
Volunteers were provided a requisition form for physical examination, ECG and sample collection.

At the day of the inspection, seven volunteers were registered at the site. The payment log was reviewed.

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

6. Personnel
Approximately 450 employees worked at the CRO at the time of the inspection.

Randomly selected CVs and JDs and training documentation was reviewed.

The structure of their SOP was built in a way that each and every staff was required to be trained on their respective department’s SOP. The SOPs which applied to the all employees, were categorized as SAP. Hence, the structure of their SOP-system could be considered as a training matrix.

The documentation of resignation of one of the employees dated 13 Apr 2018 was reviewed.

7. Clinical phase
Clinical Pharmacology Unit:
The second floor consisted of CPU- 1 (40 beds), CPU- 2 (36 beds), CPU- 3 (18 beds) and CPU- 4 (18 beds). Each bed was equipped with a locker for keeping utility kits. Each CPU was connected to washrooms/showers, phlebotomy room, centrifugation room for sample processing. All bed alarms, toilets and shower alarms were tested during the inspection.

There was a 3-bedded fully equipped Intensive Care Unit (ICU) with required emergency equipment and medicines, dosing and recreation area, pharmacy, principal/clinical investigators room, CPU staff rooms, nurse/doctor restroom. An emergency lift dedicated to the study volunteers, in case of emergency, was available. Sitec had its own ambulance 24 x 7 ready with a resident driver to shift the volunteer in case of serious emergency to a nearby affiliated hospital with an ICU. The CRO had a contract with Sai Snehdeep Hospital. The hospital was properly informed about the study commence. Communication with the hospital was verified. The
Agreement with SAI SNEHDEEP HOSPITAL covering the periods between 13 Jan 2014 and 12 Jan 2017, as well as 13 Jan 2017 and 12 Jan 2020 were verified.

Central monitoring with CCTV was installed.
The dosing area was equipped with a drug administration chamber for dosing of orally inhaled drug products. The chamber was maintained by a continuous cycle of air circulation to avoid the erroneous drug inhalation by the dosing supervisor.

While the subject was seated upright, one tablet of either the test product or the reference product was administered orally with 240±2 mL of water. After administration of the IMP, a mouth check was performed under supervision of Quality Control (QC) personnel to assess the procedure compliance. A duplicate label packed with the polybag was affixed to the case record form (CRF) to confirm administration of the correct IMP allocated.

**Study no:** 14-11-107  
All 80 signed ICFs were verified.

The existence of the first 50 subjects was verified in the visitor log book.

**Study no:** 15-03-040  
All 32 signed ICFs were verified vs. the subject signature log.

**Study no:** 15-05-100  
All 60 signed ICFs were verified.

**Study no:** 15-10-180  
All 60 signed ICFs were verified.

The procedure of enrolment of volunteers into the CPU for the participation in the study was investigated. The volunteers planned to be screened, were informed to report to the clinical facility on the check-in day for the study. Upon volunteer reporting to the facility for the study admittance, a wristband was assigned to the volunteer containing volunteers’ details including screening no, VB no, initial, and reporting time. The same details were recorded in the list of volunteers completed for the study. The volunteer was afterwards identified by finger impression scanner in the volunteer database as well as in the OVIS database. Provided that the volunteer was confirmed for screening participation, an ICF form in the language that he/she could understand i.e. English, Hindi or Marathi was provided. Volunteers were asked to read the informed consent form. The study information was explained to the volunteers verbally by principal investigator/clinical investigator individually in the language that was non-technical and understandable. All questions
were answered to the satisfaction of the volunteers. If the volunteers were willing to participate in the study, they were asked to sign and date the informed consent form. An audio-video recording of the informed consent process of individual volunteer was done. Volunteers were given a copy of signed consent form.

Prior to the check-in process, the volunteers were tested for:

- Beta Human Chorionic Gonadotropin (HCG) test for females if any
- Breath alcohol test
- Urine test for drugs of abuse amphetamines, barbiturates, benzodiazepines, cocaine, tetrahydrocannabinol [THC] and morphine /opiates
- Vital signs examination and enquiry of well-being

Volunteers found eligible were checked for visible injury/abnormality and a locker was allocated (containing uniform and footwear) for the storage of personal belongings. Individual subject study numbers were allocated as per the rank order of the reporting time of the volunteer to the facility and identity cards were issued. Volunteers were checked-in to the clinical facility at least 12 hours prior to the dosing and remained at the facility until 24 hours after dosing or as per protocol. An evening meal was served at a specified time to allow a fasting period of at least 10 hours before dosing. In the morning of the dosing day, vital signs were checked within 120 min prior to dosing and an intravenous cannula was inserted to facilitate blood sample collection. The pre-dose (0.00 hour) blood sample was collected within 120 minutes prior to dosing.

After dosing, a series of blood samples were collected as per the protocol into labelled vacuum blood collection tubes containing anticoagulant.

Observations made in relation to the clinical phase were addressed in the CAPA plan provided by the CRO.

8. Clinical laboratory
Clinical/Pathology lab
Lab accreditation was issued by the National Accreditation Board for Testing and Calibration Laboratories dated 9 Oct 2014.
9. Ethics

- Protocol No. 15-10-180 (version 01) was approved by CBP Independent Ethics Committee registered by IRB00010057 on 05 Nov 2015.
- Protocol No. 15-05-100 (version 01) was approved by CBP Independent Ethics Committee registered by IRB00010057 on 18 Jun 2015.
- Protocol No. 15-03-040 (version 03) was approved by Ethiwell IEC on 12 Apr 2015.
- Protocol No. 14-11-107 (version 03) was approved by Ethiwell IEC on 25 Jan 2015.

10. Monitoring

Monitoring reports were verified for following studies:

- Study no: 15-10-180
- Study no: 15-03-040
- Study no: 15-05-100

All monitors’ visits were verified in visitor’s logbook.

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

11. Investigators

CV and job descriptions of investigators involved in the studies were verified.

Delegation and authorisation log was verified for Study no: 14-11-107.

12. Receiving, storage and handling of investigational drug products

Pharmacy

The Pharmacy was located on the 2nd floor and well controlled and compliant with access records for each visit. The visitors’ logbook was kept in a neat built-in cupboard at the entrance. The facility was biometrically accessed only by three authorized personnel.

The IMPs were stored, dispensed and reconciled in the pharmacy. There were two walk-in humidity chambers maintained at 23±2°C and 45±5% relative humidity and one refrigerator with temperature maintained at 2-8°C in the pharmacy area. IMPs were stored after verification of the availability of the documents as per the relevant SOP/Protocol. The IMP’s were stored in the
chambers maintaining the required storage conditions mentioned on the label/pack insert or as specified by the sponsor.

The humidity chambers were monitored digitally for both humidity and temperature. Additionally, the pharmacy was equipped with a hood used for Line Clearance procedures, balances and freezer for storage of medication required to be stored cold. The datalogger was printed out monthly and verified. The last week datalogger was requested and reviewed.

The digital thermometer used for the freezer (connected to a software system) was tested. The notification was received by the pharmacist properly. In general, the facility was equipped with functional temperature and alarm controls.

A logbook was applied as IMP receipt form to record all the applicable information. Datalogger ID number used for the shipment was recorded on the receipt of the courier. The provision to record the datalogger ID number was foreseen in the new logbooks provided to the site. Upon the receipt of the shipment of the IMP, the medicines were checked per the applicable SOPs and the packages were labelled to be randomly selected for dispensing purposes. The CRO generally asked for 5 times the required quantity to be supplied by the sponsor of the pivotal studies.

The labelling of the IMP was also described and documented according to their procedures.

The Line Clearance procedure was inspected during control of the drug accountability for the retained IMP belonging to the study no. 15-05-100. The reconciliation of the Reference IMP was successfully demonstrated.

The retention and destruction of the IMPs took place in accordance with the respective protocol. The investigational product stock record for Reference product Sovaldi 400 mg tablets Batch no SCVSD for study number 15-05-100 was reviewed.

13. Case report forms
Randomly selected CRFs from study no. 15-03-40 were reviewed and verified.

14. Volunteers, recruitment methods
Volunteer recruitment was done by recruitment coordinators. Volunteers were visiting the facility for registration along with a document for confirming information such as date of birth, name, sex, address, contact number. Language skills were checked and confirmed by the volunteers by filling the volunteer data sheet. Registration of volunteers was done in volunteers’ database system. Subsequently, volunteer’s fingerprint impression and photograph were also captured in the biometric software to complete the volunteer registration in the database.
The audit trail for the volunteers’ database system was verified. All changes were properly captured in audit trail.

**Screening and Consent Process:**
Upon volunteer reporting for screening procedures, he/she was first identified in the biometric software to be verified in the volunteers’ database and OVIS. Subsequently, volunteers were given and explained the screening volunteer consent form (VCF) along with consent form for HIV test in the language he/she understood (English, Hindi or Marathi). After obtaining the consent, height and weight measurements were recorded and BMI calculated. Provided that the volunteer was found eligible at this point, he/she was sent for medical examination, ECG, blood and urine sample collection and chest X-ray. The results were reviewed by principal/clinical investigator and eligibility status was confirmed. Screening eligibility was valid for 21 days from the date of the screening. Approximately 60% of the volunteers had laboratory results out of the reference normal range values and were evaluated as clinically non-significant.

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

**15. Food and fluids**
A dietician from Gagangiri Hospitals & Occupational Health Services was contracted. The contract was verified by the inspectors as well as his qualification and job description.

The contract between Sitec and OM SAI FOOD SERVICES was verified.

The observation made in relation to the food and fluids was addressed in the CAPA plan provided by the CRO.

**16. Safety, adverse events, adverse event reporting**
No SAE reported.
Bioanalytical section

The inspection included audit of source documentation and raw data for validation of bioanalytical methods, and analysis of subject plasma samples as well as audit 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 selected laboratory staff competently assisted the inspection team during review of the bioanalytical documentation.

17. Method development, Method validation & Analysis of study samples
SOP for Method development dated 13 Oct 2017 and the method development documentation for study no. 14-11-107 were reviewed.

The audit trail of the analytical runs in the software used was quality controlled by the QC-team of the BA-department. A checklist for verification of chromatograms was used. Among others, Quantitation audit trail, project audit trail, instrument audit trail and quantitation method were verified. The verification of the instrument audit trail was requested to be demonstrated by the QA-staff.

The IA-team (Internal Assessment), also verified the print-outs of the Quantitation method and the type of the analyte integration (base to base) and IS integration.

The repeat of analysis was predefined in the respective SOP.

(Study 14-11-107)
The method development data laboratory notebooks for Artesunate and Dihydroartemisinin (DHA), including the literatures and run results were available. The anticoagulant used in this method was sodium fluoride + potassium oxalates whose use was justified in the literature: “A liquid chromatographic-tandem mass spectrometric method for determination of artesunate and its metabolite DHA in human plasma by Faculty of tropical medicine, Mahidol University, Bangkok 10400 Thailand”. The method development activities were recorded in the logbooks. The logbooks were appropriately document controlled and paginated.
A pilot study with protocol number 15-01-002 was run on the same product (Artesunate and DHA in suppository form) by the same sponsor to rationalize the sample subject size of the pivotal study.


SOP for Validation of Bioanalytical methods, effective 29 Sep 2017 was reviewed.

The validity of the Working Standards was verified. The logbooks for recording of the usage of WS were appropriately indexed and managed.

The CRO was using a logbook for the record of preparation of stock and working solutions. The records were reviewed. The calculation of nominal concentrations for CCs and QCs were performed manually, in accordance to the applicable procedures. Later the Excel spreadsheet was used for verification of the calculation. Recalculation of the concentration for stock solution used in this study was requested and provided.

Matrix effect sample processing documentation, as well as use of plasma lots were reviewed.

**Sample Analysis:**

Instrument used in analytical runs were verified to be the same instruments used for the method validation process.

Randomly selected sample analyses and the reason for repetitions and reinjections, if any, were reviewed.

SOP for Processing and evaluation of chromatographic data was reviewed to ensure the pre-definition of the changes to the chromatograms.

**(Study 15-05-100)**
The Method validation protocol with number BIO-AMVP-08/15 was available. The full validation was reported in the report with no. BIO-AMVR-10/15.

Precision and Accuracy test (P&A) was carried out. Five P&A batches were prepared for this purpose.
Sample analysis:
Randomly selected sample analyses and the reason for repetitions and reinjections, if any, were reviewed.

(Study 15-03-040)
Preparation of CC and QC stock solutions for some of the runs used in the method validation, each independently, took place on 21 May 2015. The corresponding documentation was reviewed in the logbook for Tenofovir (Lamivudine) method validation.

The CC and QC were freshly spiked for the respective stability runs on the day of performance, using the stock solution prepared on 21 May 2015. The documentation was reviewed. The stability of the stock solution was determined using the system suitability samples. Explanation was provided in detail, by the BA-head

Separate method validation was provided for Tenofovir and Lamivudine.

Freeze/Thaw stability of was reviewed. The preparation of stock solution properly took place.

The stability of the CC and QC prepared freshly on 21 May 2015 was tested, using the Main Stock solution stored in the refrigerator. The samples were identified as MSSRF (Main Stock Solution refrigerator). The stability run was performed on 2 Jun. The run met the acceptance criteria.

The record of F/T cycles (3 consecutive cycles) in the Deep Freezer logbook were reviewed and verified.

The raw data of the method validation were reviewed.

(Study 15-10-180)
The method validation applied to both analytes used in this study.

Long term stability (LTS) of analyte in the matrix was tested on day 40 (LTS-35 days) for both -25 °C and -70 °C. The respective documentation was reviewed.

Post-operative stability test for Lamivudine and Zidovudine after 74 hours of storage in the refrigerator at 2 °C – 8 °C was performed. The sample processing took place on 8 Jan 2016. The sample processing and the whole procedure, including the evaluation of the chromatographs, conducted on 8 Jan 2016 was reviewed and verified.
Sample Analysis:
Randomly selected sample analyses and the reason for repetitions and reinjections were reviewed.

180 samples were selected for ISR runs. The documentation was reviewed.

IS-variation calculations for all batches for both analytes in an Excel sheet were provided and reviewed. The process was carried out in accordance with the documented procedures.

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

18. Sample collection, storage and handling of biological material

Blood/Sample Processing area:
Each CPU was equipped with separate blood/sample processing area. Four cooling centrifuge machines and four deep freezers were available. Immediately after blood collection, the tube was inverted gently several times to ensure the mixing of tube contents and placed upright in a rack which was kept in iced water bath at 4 - 8°C before centrifugation. The blood samples were centrifuged at 2-6°C and 3000 revolutions per minute (rpm) for 10 minutes to separate plasma within 45 minutes after blood sample collection.

Each plasma sample was separated into two aliquots (i.e., main and reserve) with equal amounts of plasma in the main and reserve tubes. Information included on the label tubes were including the name of the CRO, short study title, Protocol No., Subject No., period and time point and main as A / reserve as B with a color code. All plasma samples were stored upright in a deep freezer at a - 70±10 °C until completion of analysis.

Samples were afterward packed in the insulated box filled with an adequate amount of dry ice while being transferred to the bio-analytical department. A datalogger was placed in the insulated box to confirm whether the temperature during the transit and records were maintained.

The Deep Freezer room was visited. The custodians were interviewed.

The samples were received frozen and investigated for any discrepancies to be communicated with Bio-clinical site. The missing time points were checked against provided missing time points list. The required details on the document sent by Bio-clinical department, e.g. Received by, Date and time of receipt of samples to Bioanalytical department, was recorded in the respective log. The study samples were stored in the deep freezer followed by an appropriate
entry in the deep freezer logbook for storage of samples, as well as in the log of receipt of subject samples from Bio-clinical department.

After completion of 180 days of storage from the date of last sample analysis, study samples would be disposed. Fifteen days prior to disposal date, a communication would be sent to the sponsor to get approval for the same. Only after the approval from sponsor study samples should be disposed as per the applicable SOP.

The documentation for receipt of the samples for study no. 14-11-107 from the clinical unit was reviewed dated 26 and 29 Jun 2015 respectively for Batch A and B, as main and reserve samples. Number of samples (3057), missing and haemolyzed samples were recorded and verified.

The freezer logbook was reviewed to verify the storage of the samples. All samples for both batch A and B and both aliquots were stored in the same freezer, but different racks.

Temperature log for one of the Deep Freezers was requested to be reviewed. There was an out of range temperature for a short period of time.

SOP for temperature and humidity monitoring effective 23 Jul 2018 was provided to implement their new practice. In their new practice, the temperature was measured/read through the datalogger every 30 minutes and in case of out of range temperature, the alarm would be going off immediately.

Different aliquots were shipped separately and labelled with adequate information by different colours. The subject number and timepoint was recorded on the label.

In their new practice and SOP, two logbooks were in use:
1- Logbook for record of the individual plasma lots provided by clinical unit, recording the ID number, anticoagulant, type of matrix, date of collection, receipt, expiry date and disposal as Index, referring to the specific page number for the usage of the plasma lot for each project with the exact amount.
2- Logbook for record of pooled plasma, the usage details such as date, bottle no., volume used, volume remaining and project name and protocol number.

SOP for Procurement, storage and usage of blank plasma/blood/serum effective of 31 Jan 2018 was reviewed. The SOP was newly implemented and did not apply to the time of performance of studies in the scope of inspection.
The disposal of the samples from study no. 14-11-107, together with QC, CCs and pooled plasma was reviewed.

Observations made in relation to this section were adequately addressed in the CAPA 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.

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 observation made in relation to this section was adequately addressed in the CAPA provided by the CRO.

20. Good laboratory practices
The bioanalytical laboratory was located on the third floor.

The laboratory was well-equipped and well-organized, with adequate safety measures such as the availability of an Emergency Kit, shower and eye-wash station.

The deep freezer room was equipped with eleven -70 °C freezers and one -20 °C freezer, all of them equipped with the digital thermometers connected to the data logging system.

The CRO had a mature system in place for the maintenance and calibration of equipment within both the clinical and analytical facility, including a Master list of equipment 2018 which was made available.

The temperature mapping documentation for one of the Deep Freezers, performed in 2015 and 2016 was reviewed. The process was done in accordance with the applicable SOP and the template for temperature distribution study of deep freezer was completed. The activity was outsourced to the Company Care Biosystems India Pvt. Ltd. located in Mumbai. The temperature
was controlled as fully loaded, partially loaded and empty with placement of temperature probes in different location in the DF as illustrated. The documentation was adequate.

The software system for operating automated liquid handling system was visited. The system was in use since 2008, but not used for any of the studies in the scope of the inspection.

The balance room was equipped with 2 micro- and 1 analytical balance that were calibrated daily. The refrigerator and freezer for storage of the WS were also located in this room.

The BA-unit was equipped with 16 LC-MS/MS instruments divided in three rooms. All the instruments used in the studies in the scope of inspection were verified to be labelled by ID-number, and date of calibration.

The observations made in relation to Good Laboratory Practices were adequately addressed in the CAPA provided by the CRO.

**Pharmacokinetic, statistical calculations and reporting section**

21. Pharmacokinetic, statistical calculations

Randomization

Randomization list was prepared in accordance with the SOP for Generation of randomization code, after completion of the protocol meeting and receipt of the respective approvals by the statistician using SAS software system.

The ability of the alteration of the data after receipt of the data by statistician was inspected.

Bioanalytical results were submitted to the statistician through password protected email. The clinical data such as actual blood collection timepoints, number of dropouts and withdrawals were received by the statistician. The statistical report was quality controlled by designated QC-team and signed off prior to the submission to the sponsor and the CRA.

Software WinNonLin was used for PK-calculations by importing the bioanalytical data from the respective study folder.

The observations made in relation to this section were adequately addressed in the CAPA provided by the CRO.

22. Study report

Study reports were provided and used during the inspection.
The observation made in relation to the study report was adequately addressed in the CAPA provided by the CRO.

<table>
<thead>
<tr>
<th>Miscellaneous</th>
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<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>It was provided.</td>
</tr>
<tr>
<td><strong>Annexes attached</strong></td>
<td>Not applicable</td>
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</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 sites:

**Clinical, Bioanalytical and statistical site**
Sitec Labs Pvt. Ltd. Mahape
PEE-DEE Infotech, Plot No. Gen-40, TTC MIDC
Near Nelco, Behind Millennium Business Park Mahape
Navi Mumbai; 400 710
India

**Screening and pathology site**
Sitec Labs Pvt. Ltd.
First floor, Jayashree Plaza
LBS Marg, Above ICICI Bank
Opposite R.R. paints
Bhandup (West)
Mumbai – 400078
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

<table>
<thead>
<tr>
<th>List of guidelines referenced in the inspection report</th>
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   **Short name:** WHO BE guidance  
   **Short name:** WHO multisource guidance  
   **Short name:** WHO GCP  
   **Short name:** WHO TRS No. 996, Annex 5 WHO GDRMP guidance  
   **Short name:** WHO GLP  
   [http://www.ispe.org/gamp-5](http://www.ispe.org/gamp-5) |

8. WHO Operational guidelines for Ethics Committees that review biomedical research (7).
   WHO, TDR/PRD/ETHICS/2000.1
   http://www.who.int/entity/tdr/publications/documents/ethics.pdf?ua=1


11. EU guidelines to Good Manufacturing Practice and Medicinal Products for Human and Veterinary Use Annex 11, Computerized systems

    **Short name:** WHO TRS No. 961, Annex 9

    **Short name:** WHO TRS No. 957, Annex 7

14. Glove use information leaflet, Patient Safety, Save lives clean your hands, WHO, revised August 2009
    http://www.who.int/gpsc/5may/Glove_Use_Information_Leaflet.pdf

15. WHO Good Clinical Laboratory Practices (GCLP)