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

Part 1	**General information**
Inspected site	
Name and Address of inspected site	Clinical, Bioanalytical and Statistical site Panexcell Clinical Lab Private Limited R-374, MIDC, TTC Industrial area, Rabale Navi Mumbai – 400 701 India
Corporate address of Organization	Panexcell Clinical Lab Private Limited R-374, MIDC, TTC Industrial area, Rabale Navi Mumbai – 400 701 India
GPS coordinates	Latitude: 19,1409 Longitude: 73,0041
Inspection details	
Dates of inspection	24 – 27 July 2018
Type of inspection	Routine
Introduction	
Brief description of activities performed at the site	The CRO has the capacity to perform the clinical phase, bioanalytical and statistical analyses of bioequivalence / bioavailability in healthy subjects and/or patients' studies.
General information about the company and site	Panexcell is a CRO which provides Clinical, Analytical and Statistical Services. The clinical site having 82 beds and a 2 bedded ICU to take care of any medical emergency. The Bio-Analytical facility has 11 LCMS/MS. The analytical department is also involved in services such as analytical method development and validation.
History	The company, was established in 1998 as the "Drug Monitoring Research Institute PVT. Ltd" in Sion, Mumbai. It was purchased by the current owners in 2011. Initially, the facility was handling only applications from companies for submissions to CDSCO to conduct local studies. In May 2014, the company changed name to "Panexcell Clinical Lab Private Limited", now located at R-374, TTC MIDC, Rabale, Navi Mumbai-400701

	A list of inspections performed by other authorities was provided which includes during the last 5 years, inspections from USFDA, AEMPS Spain, ISP Chile and the national medicines regulatory authority of India.
Brief report of inspection activities undertaken – scope and limitations	
Areas inspected	The Inspection team covered the study-related activities of the two studies included in the scope of the inspection. The company's history, clinical study performance, informed consent process, ethics committee approvals and correspondence, test article accountability, dispensing and storage, processing and handling of biological (plasma) samples collected during the study, equipment calibration, employee training, computer controls, were reviewed and a tour of the facility taken. In relation to analytical operations, the team covered confirmation of good practices, qualifications of personnel and procedures used during method validations and analytical testing. The clinical study data, analytical method validation, and analytical study data were reviewed, and the source data compared to the study reports.
Restrictions	N/A
Out of Scope	N/A
WHO product names covered by the inspection, study title, sponsor	**Study no: PCLPL-147-15** An open label, balanced, randomized, two treatment, two period, two sequence, single oral dose, crossover, bioequivalence study of Betrim Forte {Cotrimoxazole tablet BP 960 mg (Sulfamethoxazole BP 800 mg and Trimethoprim BP 160 mg), with Septrin® Forte tablet (Sulfamethoxazole BP 800 mg and Trimethoprim BP 160 mg) of Aspen Pharma Trading Limited, 3016 Lake Drive, Citywest Business Campus, Dublin 24, Ireland in normal, healthy, adult, human subjects under fasting condition. **Study no. PCLPL-110-17** Dolutegravir 50mg, Lamivudine 300mg & Tenofovir DF 300mg Tablets

Abbreviations	Meaning
DR	adverse drug reaction
AE	adverse event
ALCOA	attributable, legible, contemporaneous, original and accurate
BE	bioequivalence
BDL	below detection limit
CAPA	corrective actions and preventive actions
CC	calibration curve
CPU	clinical pharmacology unit
CRA	clinical research associate(e)
eCRF	(electronic) case report form
CRO	contract research organization
CoA	certificate of analysis
CS	calibration standard
CSR	clinical study report
CSV	computerized system validation
ECG	electrocardiogram
F/T	Freeze thaw study
GCP	good clinical practice
GLP	good laboratory practice
HPLC	high-performance liquid chromatograph
HQC	high concentration quality control standard
IB	investigator's brochure
ICF	informed consent form
ICH	International Conference on Harmonization
IEC	(independent) ethics committee
IMP	investigational medicinal product
IS	internal standard
ISR	incurred sample reanalysis
ISV	internal standard response variation
JD	job description
LC-MS/MS	liquid chromatography–mass spectrometry
LIMS	laboratory information management system
LLOQ	lowest limit of quantification
LOD	limit of detection
LTS	long term stability
MVR	monitoring visit report
OQ	operational qualification
P&A	precision and accuracy
PIS	patient information sheet

PQ	performance qualification
QA	quality assurance
QCs	quality control samples
QMS	quality management system
RT	retention time
SAE	serious adverse event
SAR	serious adverse reaction
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
ULOQ	upper limit of quantification
URS	user requirements specifications
WS	working standard

Part 2	**Summary of the findings and comments**

1. Organization and management

A presentation was provided detailing the activities of the organization.

Panexcell is an independent contract research organization providing clinical research support to the pharmaceutical and biotechnology industries in various drug development phases.

Panexcell Clinical Lab Private Limited had more than 20,000 sq. ft. built up property at Rabale, Navi Mumbai.

The Master Services Agreements with sponsors were reviewed.

Valid organization chart dated and signed on 09 Jul 2018 was provided.

The working hours is from 09:00 am until 5:30 pm. A second shift might be arranged when needed.

The organizational structure of Panexcell Clinical Lab Private Limited consisted of the following departments:

- Bio-availability/ Bio-equivalence studies
- Clinical Trials
- Bio-analytical
- Medical Writing
- Statistical Analysis
- Pharmacokinetic Studies with NDDS & NCEs
- Data Management
- Special Population Studies

2. Computer systems

A computerized system inventory list was provided.

Access control was provided by the IT-administrator. The overview of the access control to the restricted areas was reviewed.

There were three routes for providing backup of electronic data:

1- Raid 1 configuration which was the mirroring of the hard drive of the MS-instruments, located in the LC-MS/MS system, with 1 TB capacity.
2- Incremental back-up through Veeam software.
3- Keeping the daily back up on a LTO6 tape.

Incremental backup was performed by using Veeam Endpoint Backup Security Software, with a storage capacity of 4TB. The system software was server-based. Scheduled incremental backup was conducted every four hours.

Additionally, two tapes were provided for a monthly backup, one for onsite and the other for offsite archiving facility. The agreement with the offsite archiving facility (HDFC bank) was reviewed.

The backup procedures were implemented in the QMS, effective on 10 Jul 2018.

The data of the study in the scope of inspection was backed-up on the NAS system. The SOP applicable at the time of the study was provided, effective from 15 Jan 2016. The e-storage used was installed on the required computer for backup of the generated data.

The invoice for purchase of Veeam software dated Feb 2018 was provided. Additionally, the invoices for purchase of NAS (OLD MODEL) Seagate Central 3TB Personal Cloud Storage and NAS stcg3000100 were available.

Restoration of backup data was described in the SOP for Completion of data backup used in study conduction, effective 12 Feb 2018. Restoration should be performed once in every six months from server to ensure that the backup media was restorable.

The validation plan for laboratory computerized system was approved by QA manager on 10 Jul 2018. A list of all the equipment IDs and the model and application of software systems was provided in Annexure 1 attached to the validation plan for laboratory computerized system. Risk assessment was elaborated in the plan. This documentation was recently implemented in the QMS.

Validation documentation of LC-MS/MS instruments was reviewed.

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

3. Quality management

The CRO's quality management was described in the Quality Manual V02 dated 11 Jul 2018.

The CRO master (CROMF) file was reviewed.

The CRO's organizational chart was studied to confirm the QA -department independency. The QA manager was reporting directly to the director of the CRO.

The QA department was responsible for conduct of the audits including vendor-audits. Quality procedures and management of documentation, including archiving procedures were verified.

A list of SOPs was submitted. The following SOPs were reviewed:

- SOP for In-house audits. Audits were divided in three phases:
  a) In process audit
  b) Retrospective audit
  c) System audit
- SOP for Backup and restoration of electronic data, effective 10 Jul 2018.
- SOP Screening of volunteers, effective 10 Jul 2018. In the new version, the laboratory reference ranges annexures were removed. Subsequently, the investigator was only allowed to use the laboratory reference value in accordance with SOP for Evaluation of laboratory investigations after reviewing the reports.
- SOP for Evaluation of laboratory investigations effective date 17 May 2018.
- SOP for Document control

The request for the total number of templates required for each project was issued by the department.

Upon the initiation of the study at the respective department, an audit plan for in-process activities was prepared by the designated QA-auditor of Clinical-unit. The critical activities/areas were identified with reference to the Annexure 1 "Format of Clinical Audit Plan" of the respective SOP.

QA audit plan (clinical) for project PCLPL-147-15 was provided. Activities such as dispensing, check-in, dosing and blood collection, check-out, as well as a retrospective audit were covered. Audit reports were available and reviewed.

Audit plan for third party vendors covering the period of 2016 and 2018 was reviewed. The audit plan was arranged annually. The audit plans were signed and approved by designated staff.

The CRO provided a list of all studies performed in 2016 and 2017 which was thoroughly reviewed by the inspection team.

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

4. Archive facilities

The archive facility consisted of two different rooms located at the basement floor. The arrangement of the folders by alphabetical order was performed through an Excel sheet to facilitate the retrieval of documentation. The facility was accessed by authorized personnel, i.e. two archivists.

Safety measurements to protect the documentation, including smoke detectors, fire extinguishers (2 automatic and one manual), and temperature monitoring were implemented. A pest control company was outsourced to carry out a facility inspection once every 3 months. Rodent traps were available in the archive rooms.

The archive facility logbook for the Entry/Exit records was verified.

The access to the facility, as well as temperature and humidity records of the archive facility were checked by the Inspectors for three consecutive days.

The SOP for storage of documents was reviewed.

The retrieval of documentation for the inspection purpose was properly handled.

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

5. Premises

The inspection included a tour of the facility.

The clinical facility had three wards comprising of 82 beds, with 2 bedded ICU under supervision of fully trained and experienced medical officers, round the clock, to handle all emergencies in case of any adverse event and serious adverse event. It also had its own ambulance 24 x 7 ready with a resident driver to shift the subject/volunteer in case of serious emergency to a nearby affiliated hospital with ICU. All wards had CCTV surveillance with emergency alarm system attached to all beds, washrooms/bathrooms for subject safety.

The following departments were visited:

- Reporting & registration area
- Counselling room with audio-video recording facility
- Separate dining area with in-house kitchen
- Screening room
- Ambulatory room
- Phlebotomy area with separate matrix processing room
- Examination and monitoring rooms

Back-up generators and UPC were verified. Synchronized clocks were located throughout the facility to document the exact time study activities occurred.

The ICU was visited. The facility was equipped with 2 beds, vital sign machine, ECG machine, BP measurement device, Oxygen cylinder etc. All physicians were trained by external trainer to perform the paramedics measures in the emergency situations.

The maintenance logbook for defibrillator and oxygen cylinder was verified. A logbook was kept for the usage of the emergency medicines. An inventory log of the medications was also provided.

Pharmacy

Medications were stored in cabinets, three humidity chambers and refrigerators, depending on their storage conditions, all monitored by Eurotherm digital thermometers.

Alarms connected to the pharmacy freezers were tested.

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

6. Personnel

Key personnel from selected departments were interviewed and their CVs and Job Descriptions were reviewed and verified. The employees were trained as per their job responsibilities.

Delegation and responsibility log was verified.

The SOP trainings were performed in a timely manner before effective date of the SOP for applicable versions.

Clinical section

7. Clinical phase

The justification for subject size was requested. The literature used for this purpose was "*Co-trimoxazole 960 mg tablets, UK Licence No: PL 30684/0228 UK public assessment report (MHRA)*". PK parameters in this article was used in the SAS system to provide the subject size justification. 19 evaluable subjects were considered to be sufficient. However, taking 20 % dropouts and withdrawals into consideration, a sample size of 24 subjects could establish bioequivalence between the test and reference formulations. The matter was elaborated in section 15.4 of the protocol.

During the Informed Consent Process, ample time was given to the volunteer to read and understand the informed consent information. After the ICF presentation, responsible physician conducted one to one interaction with individual volunteer and obtained informed consent.

After obtaining the informed consent, screening personnel started the screening process. For that, screening personnel was performing height and weight measurements and BMI calculation. Personal details of the volunteer were also recorded.

During the screening process, medical examination along with vital sign measurements, medical history and a 12 Lead ECG examination were performed by qualified physician.

The blood and urine sample collection was performed by designated personnel for evaluation of laboratory parameters.

Chest X-ray examination was carried out at the site (if applicable).

During the screening, the volunteer was compensated for taking part in the activities, but he/she would not be included if found not to be eligible for screening.

On the basis of the screening documentation (including Laboratory reports, ECG and X-ray report (if applicable) eligibility of the volunteer was evaluated by Principal Investigator / Clinical Investigator for enrolment in the study.

<u>Check-in Process</u>

After obtaining the consent for the study, volunteer was proceeding for the further activities. Qualified and trained physicians were performing the medical examination and vital sign recording. Principal Investigator/ Clinical Investigator was declaring the volunteers' eligibility based on the inclusion and exclusion criteria evaluation and protocol compliance.

The volunteer's cross participation was avoided through biometric and OVIS verification on the check-in day prior to the breath alcohol test and urine scan for drug-abuse test.

After that, volunteers were guided for "Body and Baggage check procedure". In body and baggage check area, the study staff provided uniform, sanitary kit, slippers and a locker to the volunteers. At the same time, a subject number was given to the volunteer.

After that, the volunteer was checked in to the clinical ward and guided to the assigned bed.

Dinner was provided to the volunteer as per schedule time and approved meal plan. During the housing period, physician and custodian were remaining available in the facility.

In the morning, pre-dose activities like intra venous cannulation, pre-dose blood sample collection, pre-dose vital sign measurement and pre-dose ECG (if applicable) were performed by the designated and qualified staff.

Pre-dose restriction compliance was checked by the study staff before the dosing procedure.

Volunteers were dosed as per protocol and the randomization schedule under supervision of Principal Investigator. Before dosing, dosing instructions were given to the volunteer.

As per protocol requirements, activities such as blood sample collection, vital measurement, ECG recording etc. were performed by the designated qualified study staff.

On the day of check-out, qualified staff were performing the check-out medical examination and vital signs measurement, as well as collection of post study safety samples as per protocol requirements.

During the study period, compensation was provided to the volunteer as per compensation break up.

Agreement with Criti-Care ICCU, MULTISPECIALITY & TRAUMA CENTRE existing under the laws of India, was signed for handling of the emergency situations.

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

8. Clinical laboratory

The pathology laboratory used for the studies in the scope of inspection was Spectrum. At the time of the study, the CRO also had an agreement with Pathology Laboratory iGenetic Diagnostics Pvt. Ltd., in case re-test of the laboratory results was necessary. The CV of the Head of laboratory was available, dated 27 Apr 2016.

At the time of inspection, the clinical laboratory used by the CRO was Neocare diagnostics Pvt. Ltd with an agreement valid until 7 May 2019. The agreement was dated 16 Oct 2017.

During the inspection, the deviations from normal laboratory ranges of "healthy volunteers" were discussed. It was noted that all the subjects included in the study PCLPL-147-15 had, on average, more than five individual laboratory value deviations outside of the normal ranges.

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

9. Ethics

The CBP Independent Ethics Committee reviewed and approved the Protocol No. PCLPL-147-15 (version 01) and Informed Consent (Version 01) dated 4 Mar 2016 (English), (Version 00) dated 5 Mar 2016, (Hindi, Marathi) on 11 March 2016.

The CRO was working with following ECs:

- Ethicare Ethics Committee
- Suraksa Ethics Committee
- CBP Ethics Committee - provided approval for study

An audit was conducted on 28 Apr 2016 at CBP Ethics Committee.

The Insurance Policy for the period of 19 Aug 2015 – 18 Aug 2016 was verified.

10. Monitoring

Monitoring reports for study no. PCLPL-147-15 were verified. The reports were consistent and detailed. The visits of monitor were verified in the visitor logbook:

- Monitoring Visits performed on 28 Apr 2016 – 02 May 2016 for period I
- Monitoring Visits performed on 09 May 2016 – 13 May 2016 for period II

11. Investigators

The CVs and JDs for the investigators were reviewed.

The investigators had appropriate qualifications, training and sufficient experience in performance of BE studies, as confirmed by their CVs.

12. Receiving, storage and handling of investigational drug products

The Pharmacy was located in the basement of the facility.

The pharmacy area, with restricted access (only to authorized pharmacists), was used for receipt, storage, dispensing and archival retention of study medications. All entries and exits of pharmacy should be recorded in a logbook.

The facility was equipped with functional temperature and alarm controls.

A logbook for IMP receipt form was used to record all the applicable information. Datalogger ID number was recorded on the receipt of the courier which was checked during the inspection (last shipment received). Upon the receipt of the shipment of the IMP, the medicines were checked in accordance with the SOPs and the packages were identified to be randomly selected for dispensing purposes.

The drug accountability for both Betrim Forte (Sulfamethoxazole~ BP 800 mg and Trimethoprim BP 160 mg) and Septrin® Forte tablet (Sulfamethoxazole BP 800 mg and Trimethoprim BP 160 mg) was verified.

13. Case report forms

Randomly selected CRFs of the study no. PCLPL-147-15 were verified.

14. Volunteers, recruitment methods

A complete body check of volunteers / study participants was carried out upon their arrival at the gate, by the security personnel

Afterwards, the volunteers were guided by the security personnel to the screening area, followed by registration of the volunteer's personal details in the "volunteer Entry/Exit Logbook for Registration/Screening".

Volunteers were registered in the volunteer registration database (VIMS), with option for fingerprint-identification.

Once registered in the VIMS, the volunteer was guided to proceed for the screening process.

For the Registration process, the DOB (Date of Birth), address proof and/or age proof and photo ID proof of volunteer were verified. After verification process, screening personnel was providing the Informed Consent document for registration process to the volunteer as per his/her vernacular language. Screening personnel was also performing the literacy check of the volunteer.

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

15. Food and fluids

The dietician qualification was verified.

16. Safety, adverse events, adverse event reporting

There were no deaths or other serious adverse events and withdrawals due to AE, during conducting the study PCLPL-147-15.

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 selected laboratory staff competently assisted the inspection team during review of the bioanalytical documentation. Their CVs and JDs were reviewed.

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

SOP for Guidance on bioanalytical method development with effective date 27 Feb 2017 and the method development documentation for study no. PCLPL-147-15 were reviewed.

SOP for Validation of bioanalytical methods with effective date 11 Apr 2017 was also considered in review of the bioanalytical data.

The clinical department prepared pooled plasma samples from individual patients. Each individual sample and the respective amount was recorded on an acquisition form. The pooled plasma was distributed in 10 ml aliquots stored in the freezer and logged in the logbook. The anticoagulant used for the study no. PCLPL-147-15 was K_2EDTA. The usage of the plasma was

also kept in the logbook. The matrix ID was reported on the form for preparation of spiked CC and QC samples, mentioning each individual plasma used for preparation of the pooled plasma.

The origin of the pooled plasma used for preparation of stock solutions was verified. Summary of Blank Matrix was given on a form issued by the Clinical department to the BA department on 23 May 2016. The date of collection, lot no., storage condition, expiry date and quantitation were given on the form. For each lot, there was an ICF, signed by the respective volunteer with allocated centre ID number which matched the screening number recorded on the CRF and the laboratory result from the pathology laboratory.

At the time of conducting of the studies in the scope of the inspection, the chromatogram integration settings used in analytical runs were mentioned in the method validation without considering any acceptable range for Retention Time (RT) shifts or any other iteration variation. However, in their current practice, all integration settings and their respective acceptable range would be mentioned in the method SOP.

<table>
<tr><td colspan="2">Study no. PCLPL-147-15</td></tr>
<tr><td colspan="2">Method development</td></tr>
<tr><td>COAs were reviewed.
• Trimethoprim Sulfamethoxazole
• Sulfamethoxazole-D4</td><td>Analyte determined: Sulfamethoxazole, Trimethoprim
Internal standard Sulfamethoxazole-D4 – Same IS for both analyte
Method of detection LC-MS/MS
Matrix Human plasma
Anticoagulant K_2EDTA</td></tr>
<tr><td>Method validation: MV-136-15
The instrument used for the sample analysis was verified.</td><td></td></tr>
<tr><td>Preparation of IS stock solution for use in the method validation was provided and reviewed dated 24 Dec 2015.

Preparation of stock solutions for sulfamethoxazole and trimethoprim was reviewed, each separately weighed and prepared on 24 Dec 2015.</td><td>Matrix effect
The sample processing and assessment of the run was provided. The run was met the acceptance criteria.

Sensitivity
RUN 17-11-14 P&A, Sensitivity, & ULOQ
Sensitivity was evaluated by preparing 6 LLOQ & 6 ULOQ samples</td></tr>
</table>

The re-integration of chromatograms was described and adequately defined in the respective SOP.	Precision and accuracy Preparation of Sensitivity LLOQ and ULOQ took place on 28 Dec 2015. Selectivity & Carry over Sample processing was reviewed and verified. The batch met the acceptance criteria. Dilution integrity & P&A IV Dilution integrity was evaluated by preparing quality control samples having concentration 162079.774ng/mL and 4925.l 71ng/mL for sulfamethoxazole and trimethoprim, respectively. The sample was diluted to ¼ and ½ of the original concentration and analysed against the calibration curve. Documentation dated 30 Dec 2015 was reviewed. Interference factor Accuracy in the presence of concomitant medication i.e., in presence of Paracetamol, Caffeine, Diclofenac, Aspirin, Ibuprofen, Ranitidine and Omeprazole was determined by preparing three LLOQQC samples and analysing them with the calibration standard prepared in the absence of concomitant medicines.
Precision and Accuracy	Five runs were provided on two different days. Documentation was reviewed and verified.
Stability: Preparation of the freshly spiked calibration curve and LQC and HQC for comparison was verified.	Freeze/Thaw The performance of the four cycles for DF -70 ºC, together with the preparation of fresh CC prepared on 1 Jan 2016 were verified.
Analysis of samples	
The delegation list dated 23 May 2016 for project authorization, personnel and instrument allocation was reviewed.	The analytical runs for randomly selected samples were reviewed.

Samples were organized properly in accordance with the respective plan. Preparation of the QC and CCs for both analytes and the respective IS solution, including the record of the usage of the Working Standards (WS) in the logbook were reviewed. Furthermore, the preparation of stock dilution, working solution and aqueous samples dated 24 May 2016 was reviewed. Preparation of spiked CC and QC dated 25 May 2016 was reviewed. Total of 34 sets of CCs and 148 sets of QCs, and 19 SST (for System suitability test) was prepared. The QCs and CCs were prepared from separate stock solutions. The acceptable range for RT, mass parameters, the Quantitation parameter including bunching factor, number of smooths, noise threshold and area threshold was mentioned in the method validation plan. These parameters could only be changed by project manager in accordance with the applicable SOP.	
The Repeat analysis was defined in the respective SOP.	The repeats analyses were reviewed. The reasons for repetitions were adequately verified.
Re-integrated chromatograms	There was no re-integration of the chromatograms during the study.
ISR	Number of sampled used: ISR1 – 37 samples – 8 Jun 2016 ISR2 – 39 samples - 8 Jun 2016 ISR3 – 33 samples - 9 Jun 2016

	Approval of selection of samples and SOP for Incurred sample re-analysis of 05 Aug 2016 were reviewed.
Back calculations	The back calculations were performed automatically by the software.
Acceptable ranges fulfilled	E-tools such as validated excel sheet was used to ensure the acceptance criteria were met.

18. Sample collection, storage and handling of biological material

The collection of blood samples was documented on the corresponding CRF page, including the anticoagulant used, dosing time-point, scheduled time of the sample collection, actual time of sample collection and initials /date of phlebotomist responsible for sample collection. The process was conducted under hygienic conditions.

After blood samples were collected at each time point, in pre-labelled tubes, these were sent to the sample processing room for centrifuging and freezer-storage. Samples were centrifuged according to the time, speed and temperature established in the respective protocol. It was noted that the charter for grading of potential haemolyzed samples in the laboratory was not available.

The Deep Freezer room was visited. There were five -75 ºC freezers and four -20 ºC freezers in use. There were also two refrigerators, one used for storage of the WS. The temperature was monitored by Eurotherm digital thermometers. The sensor for the freezer was tested. The alarm was connected to the security personnel which responded adequately to the alarm.

The logbook and documentation used for receipt and handling of the blood samples, in particular for the last shipment from clinical department, were reviewed. The process was performed in accordance with the SOP for Receipt, storage, issuance and disposal of samples. The missing and haemolyzed samples were also recorded properly. Replicate I and II of the samples of the study no. PCLPL-147-15 were stored separately, in provided Deep Freezers.

The subject sample transfer record dated 24 May 2016 was reviewed. The receipt of both samples from period I and II and aliquot I and II was properly recorded. The samples were stored at -20 ºC in the clinical department's freezer.

The total of 1070 samples of the study PCLPL-147-15 for both period I and II were discarded on 18 Nov 2017. The requirement was to keep them 3 months after the study completion.

The discard of unused CC and QC and SST vials was recorded in a requisition form for disposal of samples (Blank Matrix, CC/QC and subject samples) for each project.

19. Data processing and documentation

The data from the CRF was transferred to the database by clinical staff, followed by QC and later QA verification.

The LC-MS/MS instruments in the BA department were visited. The analyst did not have the right to change the date and the time on the computer attached to the instrument. The delete option was also disabled. The software was accessed by four staff with administrator rights, each with individual username.

At the time of the study PCLPL-147-15, the logbook used to record the usage of the instruments was study specific. The operational log of the instrument could not provide a consistent overview.

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

The results of analyses were traceable.

Observation made in relation to the data processing was addressed in the CAPA plan provided by the CRO.

20. Good laboratory practices

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 instrument list dated July 2018.

Randomly selected calibration certificates, together with the SOP for calibration of LC-MS/MS were reviewed. The temperature mapping of randomly selected Deep Freezers was reviewed.

Observations made in relation to the equipment qualification and calibration were addressed in the CAPA plan provided by the CRO.

Pharmacokinetic, statistical calculations and reporting section

21. Pharmacokinetic, statistical calculations

The randomization list was provided using the SAS software, recorded in the logbook and submitted to the pharmacist in hard copy after PI's verification.

The generation of the randomization list was requested by the designated pharmacist.

Once the study was completed, the clinical and bioanalytical data were submitted to the statistician via email in an Excel sheet with read-only access. PK parameters were verified by the QA-Unit to be consistent with the approved protocol for time points, period, sequence, treatment and time deviation and concentrations. The results were quality controlled by designated staff.

QA responsibility was to review the study report and compare the report with the raw data.

22. Study report

The study report was provided. QA statement was issued on the project PCLPL-147-15, indicating the audited activities, date of audit, type of audit and date of report. The statement included the verification of method validation raw data, result tables, logbooks and method validation report, addendum-01 and study raw data forms, CRF, ICF and regulatory binders. The statement was signed and dated 15 Jul 2016 by Head QA.

Miscellaneous	
Samples taken	Not applicable
Assessment of the CRO master file	The CRO master file was available.
Annexes attached	Not applicable

Part 3	Conclusion

Based on the areas inspected, the people met, and the documents reviewed, and considering the findings of the inspection, including the observations listed in the Inspection Report, as well as the corrective actions taken and planned, the study was considered to have been conducted at an acceptable level of compliance with WHO GCP and GLP at the following site:

Clinical, Bioanalytical and statistical site
Panexcell Clinical Lab Private Limited
R-374, MIDC, TTC Industrial area, Rabale
Navi Mumbai – 400 701
India

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

This WHOPIR will remain valid for 3 years, provided that the outcome of any inspection conducted during this period is positive.

Part 4	List of guidelines referenced in the inspection report

1. Guidance for organizations performing in vivo bioequivalence studies. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fiftieth Report* Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 9
   Short name: WHO BE guidance
   http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex09.pdf

2. Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability. In: *Expert Committee on Specifications for Pharmaceutical Preparations. Forty-ninth report*. World Health Organization, Geneva. WHO Technical Report Series, No. 992, Annex 7, 2015, pp. 347–390
   Short name: WHO multisource guidance
   http://apps.who.int/prequal/info_general/documents/TRS937/WHO_TRS_937__annex7_eng.pdf

3. Guidelines for good clinical practice for trials on pharmaceutical products. WHO Technical Report Series, No. 850, 1995 (pp. 97–137)
   Short name: WHO GCP
   http://apps.who.int/medicinedocs/en/d/Js5516e/19.11.html

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