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Prequalification Team Inspection services
WHO PUBLIC INSPECTION REPORT
(WHOPIR)
Bio-Equivalence Study

Part 1	**General information**
Organizationdetails	
Company information	
Name and Address of Clinical Research Site	Raptim Research Ltd A-226, T.T.C. Industrial Area, Mahape M.I.D.C., Navi Mumbai - 400 701, India
Name and Address of Bioanalytical Research Site	Raptim Research Ltd A-242, T.T.C. Industrial Area, Mahape M.I.D.C., Navi Mumbai - 400 701, India
Name and address Statistical Site	Raptim Research Ltd A-242, T.T.C. Industrial Area, Mahape M.I.D.C., Navi Mumbai - 400 701, India
Corporate address of Organization	Raptim Research Ltd A-242, T.T.C. Industrial Area, Mahape M.I.D.C., Navi Mumbai - 400 701, India
WHO product numbers covered by the inspection/ Product names/ Study numbers/ Study titles	**HA668:** Study no: BE/16/275 Tablets 300mg **HP009:** Study no: BE/15/114 Tablets 400 mg
Sponsor	1- Beximco Pharmaceuticals Limited 2- Strides Shasun Limited
Inspection details	
Dates of inspection	23-27 October 2017
Type of inspection	Routine
Introduction	
Brief summary of the activities	The facility had the capacity to perform bioequivalence / bioavailability in healthy subjects / patients and in-vitro bioequivalence / biowaiver studies.

General information about the company and site	Raptim Research, Ltd. started in 2004-2005 by Dr. Rajen Shah, Ph.D., Owner and Director, consisted of three buildings, dedicated to various activity areas, and a main office in Navi Mumbai, India. The company has a representative office in the US, New Jersey, mainly to handle the local customers in North America.
History	The CRO was subject to numbers of authorities' inspections, recently inspected by US FDA in January 2017. The inspection report was not yet provided. However, the previous EIR received on 22 Feb 2016 was available and reviewed. A complete list of details of Regulatory inspections as per 26 Sep 2017 was provided. The company was inspected by DCGI (India) 7 times, US FDA 8 times, NABL 3 times and ISP Chile one time.
Brief report ofinspectionactivities undertaken	
Scope and limitations	
Out of scope	N/A

Abbreviations		
	ADR	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
	CRA	clinical research associate(e)
	CRF	(electronic) case report form
	CRO	contract research organization
	CTM	clinical trial manager
	CoA	certificate of analysis
	CSR	clinical study report
	DQ	design qualification
	ECG	electrocardiogram
	GAMP	good automated manufacturing practice
	GCP	good clinical practice
	GLP	good laboratory practice
	GMP	good manufacturing practice
	HPLC	high-performance liquid chromatograph
	HPLC-MS/MS	liquid chromatography–mass spectrometry
	IB	investigator's brochure
	ICF	informed consent form
	ICH	international Conference on Harmonization

	(I)EC	(Independent) Ethics Committee
	IMP	Investigational medicinal product
	IQ	installation qualification
	LIMS	laboratory information management system
	LLOQ	lowest limit of quantification
	LOD	limit of detection
	MS	mass spectrophotometer
	MVR	Monitoring visit report
	NRA	national regulatory agency
	OQ	operational qualification
	PIS	patient information sheet
	PQ	performance qualification
	PQS	pharmaceutical quality system
	QA	quality assurance
	QC	quality control
	QRM	quality risk management
	SAE	serious adverse event
	SAR	serious adverse reaction
	SOP	standard operating procedure
	SUSAR	suspected unexpected serious adverse reaction
	ULOQ	upper limit of quantification
	URS	user requirements specifications

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

General section

1. Organization and management

A presentation was provided by the President of Raptim to give an overview of the activities of the organization. The third building which was dedicated to screening area was left out from the presentation.

The site did not have any accreditation at the time of the inspection for the screening area located at A-213, M.I.D.C., T.T.C., Industrial Area, Mahape, Navi Mumbai-400 701, Maharashtra, India. Only the correspondence with Indian Authority for accreditation was present. Approval of the National Regulatory Authority i.e. DCGI (The Drugs Controller General (India) was available for the other two sites. Certificate of Incorporation and Municipal Permission, DCGI approval was provided for:

Site Address: Raptim Research Ltd.
Clinical Operations: A-226, T.T.C. Industrial Area, Mahape M.I.D.C., Navi Mumbai-400 701, Maharashtra, India
Analytical Operations and Statistical Department: A-242, T.T.C. Industrial Area, Mahape M.I.D.C., Navi Mumbai-400 701, Maharashtra, India. Phone: +91-22-2778 188711889

Dr Rajen Shah was the director and founder of Raptim with broad research, regulatory and CRO experience. Mr Viraj Shah with experience in global equity finance and management experience was based in the US responsible for business development and marketing in the US.

Furthermore, the company was operated by the President - Dr. Sailendra Kumar Goswami, Clinical investigator, Head Bioanalytical and Head Quality Assurance. The company had approximately 200 employees led by the Heads of Departments.

The recent changes since performance of study were as follows:

- Clinical Facility Expansion: The bed capacity of clinical facility was increased from 104 beds to 170
- Scientific Data Management system: CRED-Bio Scientific Data Management system, version 1.0.2.215
- The procedure of printing analytical instruments output was shifted from hard copy print out to Cred-Bio Application, version 1.0.2.215, Scientific Data Management System
- SOP title: SOP for operation and security configuration of Cred-Bio Scientific Data Management System
- To accommodate more LC-MS/MS systems, layout of bioanalytical laboratory was changed.

2. Computer systems

The requirements for computer systems that were specific to BE studies were inspected to confirm the company's compliance.

Two electronic data systems were used in management of the data in studies under the scope of inspections:

1- Data Integration software, Analyst versions 1.4.2, 1.6.1, 1.6.2 and 1.6.3 by Sciex
2- Scientific data management system (SDMS) version 1.0.2.215 by Cred-Bio application

Analyst software version 1.6.2 was reviewed on LC-MS/MS-059 instrument for security configuration, audit trail full map and management of folders on the share Drive.

According to the SOP for allocation of security rights and its implementation, the system administrator was responsible to create different user IDs and passwords and passing on that information to the respective personnel. Administrator was also responsible to allocate the operational rights to the Analyst, group leader, QC reviewer and QA reviewer.

Annexure 01 was the operational rights of Analyst software, organized by each responsibility and the respective allocated access rights.

In the last updated version of the SOP, the Administrator was restrained from his rights to change Audit Trail settings. If required, then with proper justification and with management approval, the rights to change the settings of Audit trail would be given to the administrator. There was no incident of change of setting of Audit trail.

The full Audit map was on since the development of the data system and only administrator had access to the audit trail mapping.

Any rights to make changes to the audit trails were revoked from the administrator role.

The audit trail history for administrator role was reviewed. On 23 Oct 2017, the computers were set up to give the inspectors access rights as operator and in that context, a few functions were disabled. These options were accessed only by admin role. A full detailed Audit map was provided. All changes were checked to ensure the proper audit trail history. An Excel sheet was provided and reviewed. No further remarks were noted.

SOP for back up of Computer system was reviewed.

The log of the backup for Analyst was generated in the system by backup software, which would be verified by IT person. Data from analytical department was created on local computers and backed up in every 15 days ± 7 days on back up Drive in incremental order. This activity of manual back up was documented in the logbook of manual back up of computer system. All analytical computers which were connected to LC-MS/MS had hard disc mirror imaging to prevent data loss in case of hard disc failure. Back up data were stored in controlled temperature and humidity room, to prevent data loss.

The log of manual back up of computer system was reviewed for the period of the studies. The action was performed properly. Date of back up, the computer name was signed and approved.

Once the samples were injected in the auto-sampler, the data management system; Cred-Bio Scientific Data Management System (SDMS)would be used until the acceptance of the batch. All generated data by Analyst were also transferred to SDMS for storage.

Raptim Computer System Inventory List was also provided.

SOP Allocation of security rights and its implementation, and SOP for computer system validation were reviewed.

There were adequate systems in place to prevent the unauthorised logging into computer, and to prevent unauthorised data changing.

Concerns raised in relation to computer systems were addressed adequately.

Analyst Software validation:

Analyst software was used as a single-point controller for LC/MS/MS system as a chromatography data system and integrating software.

Performance verification of Analyst version 1.6.2 operated by Windows 7 with instrument ID INS/ANA/059 and attached API 2000 was reviewed.

Performance verification of Analyst version 1.4.2, operated by Windows XP with instrument ID INS/ANA/026 was also reviewed.

Protocol for performance verification of analyst software was reviewed. Protocol was used to validate analyst software with the API 2000, API 4000, API 5500 LC/MS/MS system and two workstation platforms (SDMS-PC, SDMS-PC02) for SDMS, installed at Raptim. This applied both to Analyst 1.4.2 and 1.6.2. Protocol correspondingly outlined the acceptance criteria for various experiments and tests and on basis of those acceptance criteria, results of specific experiments were accepted and conclusions were drawn.

According to the protocol for performance verification of analyst software, the software used in LC MS/MS systems, was validated by challenging its expected functionality and evaluation of the results. The results were evaluated and conclusions were drawn for the suitability of its usage.

Test on access verification, control verification, mixed mode security configuration verification, hardware configuration, data acquisition, explore, audit trail verification, event log verification, quantitation table verification and printing verification. The reports were provided and were found to be adequate.

Prior to the validation, a protocol was prepared to set the user specification, also provided the methodology and acceptance criteria.

In the validation report; assessment of functionalities, and the status of the activities, whether passed or not, were recorded together with the screen shots.

CREDBIO application Software version 1.0.2.215 validation

The validation plan for CREDBIO application 1.0.2.215 dated 15 Jan 2016 was provided, containing all steps of validation. However, the content of the validation plan and pertaining documentation were not reviewed due to time constraint.

Performance verification of Analyst version 1.6.2, operated by Windows 7, as well as for Analyst version 1.4.2, operated by Windows XP was present.

3. Quality management

Company's Quality management was operated by the Head QA, according to their Quality Manual. The CRO had QA and QC systems with written SOPs to ensure that trials were conducted and data were generated, documented and reported in compliance with the applicable requirements.

Their Quality System consisted of three levels: SOPs (in hard copies), Working Instructions and templates to be in use. The QA Department was independent of the work they were quality assuring.

An overview of all SOPs in use, with effective dates and the date of next review.

The activities were audited categorized as internal audits, project audits and vendor audits. Annual plans were provided for vendor audits, such as Pathology lab, Emergency hospitals.

Two types of audits were performed by the QA personnel for activities pertaining the projects / bioanalytical studies:

- Audit during study activity or documentation (In-process): The in-process audit was carried out by QA during the actual conduct of the study/analytical activities to confirm that the activities were carried out as per the respective study protocol and SOPs.
- Audit post study activity or documentation: In the retrospective audit, the data/documentation was audited.
- The annexure 02 of the Audit plan SOP was the Template of QA audit plan

Audit plans for 2016 and 2017 were provided and were reviewed. Audit plan schedules were detailed indicating the time and extent of audit, as well as the name of the auditor. These audit plan schedules were prepared in December each year.

Procedures for adherence to sample processing time and temperature as specified by analytical method were included in the QA activities.

Following SOPs were reviewed and verified.

- SOP for preparation and implementation of SOP documents
- SOP for subject sample analysis
- SOP for operation, calibration and maintenance of micro balance
- SOP for operation, calibration and maintenance of piston-operated micropipettes and multi pipettes reviewed.
- SOP for Bioanalytical method development.
- SOP for training and evaluation of staff
- SOP for Quality review assurance
- Business Continuity Plan and Disaster Recovery Plan for all facilities, with doc no RRL_BCP-001 version 05 and dated 2 May 2016, authored by QA manager, approved by QA Head.

SOPs were in hard copies and softcopies and were provided if needed. SOPs were authored, reviewed and authorised by the designated personnel. Period of review were stated. Controlled samples were stamped as controlled copy, signed and marked with the effective date.

4**. Archive facilities**

The archive facilities on site were appropriately secured. Access to archive storage area was controlled and restricted to the authorized personnel.

The facility was equipped by fire extinguisher system, smoke detectors, and temperature and humidity monitor. Access to archiving room was restricted and equipped by a fire-resistant door. Min/max measurement of temperature was available and recorded daily. Access logbook, retrieval log book and archiving of study documents logbook checked by inspector and found to be adequate. Temperature log was randomly checked for several days. The archiving room had pest traps. A quarterly maintenance by a pest control entity was executed. The contract and visitors' logbook for pest control Company was verified for 2017.

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5. Premises

The facility was kept clean and had adequate lighting, ventilation.

The facility consisted of three buildings:

1- Clinical Facility consisted of
   a. CPU
   b. Emergency Care Unit (ECU)
   c. Dosing area
   d. Blood sampling area
   e. Pathology laboratory
   f. Pharmacy
   g. Dining area
   h. Washrooms

2- Screening area consisted of
   a. ICF room
   b. Physical exam room
   c. ECG room
   d. Blood and urine sample taking room
   e. Medical exam room
   f. Washrooms

3- Bioanalytical site and main office in three floors consisted of
   a. Store rooms
   b. Dark room
   c. Instrument rooms
   d. Balance room
   e. Deep freezers rooms
   f. General laboratory
   g. Personnel rooms
   h. Office area

Restricted access was provided, biometrically functional. Access was provided by IT. A list of personnel with access to the facilities based on role was reviewed.

The facilities were visited in several occasions. In the CPU, there were dedicated areas to male subjects and another for female subjects. The facility was equipped with tilt beds and alarm system which was tested. Subjects were differentiated by different uniform colours, as well as ID-cards and wristbands with their identification.

ECU (Emergency Care Unit) was visited. The unit was equipped with the necessary instruments, such as defibrillator, Oxygen concentrator, and ECG machine. The thermometer was calibrated on 11 May 2017. The daily max. temperature was recorded 28.3, and min 18.4 since the last read.

Agreements with Multi-speciality and Trauma Centre were signed on 01Oct 2014 for 5 years, as well as the Emergency hospital signed on 25 Dec 2016 for 2 years were verified. As per SOP they would notify the hospital before enrolment start. The email correspondence with hospitals for enrolment notification was verified for BE/15/114 and BE/16/275 studies.

Power backup process in the Clinical facility at A-226 was tested. There was power cut failure during the inspection, which was fixed properly.

- ✓ DG set capacity of 100 KVA was installed with a support diesel tank capacity of 200 Liters, capacities to support critical instruments.
- ✓ Stabilizer with 100 KV A capacities was installed to regulate the voltage fluctuations.
- ✓ The UPS system of 6 and 10 KVA was installed to provide uninterrupted power supply to computers, centrifuge machines and digital clocks.
- ✓ The backup for the UPS system was 30 minutes on full load capacity.

Power backup process in the Bio-analytical facility at A-242 was verified as follows:

- ✓ DG set of capacity 300 KVA was installed with 200 KV isolation transformers to handle the power failure in this facility with a support diesel tank capacity of 200 liters.
- ✓ Stabilizer with 200 KVA capacity was installed to regulate the voltage fluctuations.
- ✓ All computers, weighing balances, centrifuge machines and digital clocks were connected to UPS of 40 KVA, 30 KVA, 10 KVA and 20 KVA capacities.

The drug inventory list of ECU was provided. A number of medicines, such as Inj. Adrenaline, Inj. Aminophylline, Inj. Dexamethasone Sodium, Inj. Hydrocortisone Sodium, and Inj. Diclofenac Sodium were required to be kept cool.

6. Personnel

Organisation charts, valid at the time of the inspection was provided. Documentation was a part of CROMF as Annexure 11.

Once an employee stopped working for the CRO, a resignation was sent to the HR. A policy of two-month' notice applied. Documentation on Request Note for Domain Account was provided for 12 employees who had left in last year. All had signed this form and the "user account" was mentioned to be deactivated. The type of user was also recorded on the form, also the reason for revoking of the access.

The individual workload of people in activities seemed to be appropriate.

SOP for training and evaluation of staff was reviewed.

Training matrix for each SOP group was provided. The training matrix was missing categories recorded on the staff list such as Executive, Trainee quality control. Hence, there was no control on providing necessary training for categories, not mentioned on the training matrix.

Training documentation for SOP for Reviewing the quality of chromatograms was reviewed. A few staff required to be trained had failed to be trained on this SOP.

CVs and JDs for investigator, Pharmacist and Phlebotomist provided and assessed

Clinical section

7. Clinical phase

There were two separate clinical facilities dedicated to conduct clinical studies. The new one located in A-213, M.I.D.C., T.T.C., Industrial Area, Mahape, Navi Mumbai-400 701, was used for only screening-related activities.

There was a total of 170 beds in the facility. All the clocks were synchronised.

SOP for lab results abnormalities was reviewed.

Both facilities were visited. The screening area was generally well maintained.

During our visit of ECU, the medical skills of the ECU personnel were examined.

The medications available for medical emergencies were verified for expiration date, none of them found to be close to expiration date or expired. Medical emergencies equipment: oxygen device, defibrillator, ECG machine, suction machine and laryngoscope were inspected.

The dosing area was visited while subjects were receiving their respective study drugs. The dosing was performed according to the protocol and respective procedures. Blood sampling was also done in the same room.

Next area visited was the blood sample processing area. Process and pertaining equipment were investigated.

The process for investigation of haemolysed blood samples and pertaining instruction was reviewed.

Pharmacy area in the clinical facility was visited. The pharmacy was biometrically accessed by seven pharmacists.

Temperature monitoring of the facility and required equipment was assessed by the inspection team.

Handling of documentation in the pharmacy was investigated.

The randomization list was checked versus IP labels for both studies. It was a different storage conditions of IP on period I versus period II. No inconsistency between randomization list and IP labels was observed.

Cross participation of subjects and pertaining preventive measures to be taken using OVIS database system was discussed with the CRO.

Screening databases used were for internal purposes and OVIS for intra CRO search were visited. Both of them were using biometric identifications.

The blood and urine samples collection of the screening process were verified.

In the day of study inclusion, the specific inclusion and exclusion criteria would be verified and if additional investigation was necessary, it would be carried out.

In order to keep the screening steps hygienic, the bed covers should be changed after each subject. Disposable bedcovers were recommended.

The Inspectors compared more than 300 ECGs for following studies:
BE/15/114
BE/15/117
BE/16/275
BE/14/102
BE/15/230

No identical ECGs were identified.

All concerns raised in relation to this section were addressed sufficiently, providing adequate CAPA.

8. Clinical laboratory
This part was not inspected.

9. Ethics
The BE/15/114 study and BE/16/275 study were approved by CBP Independent Ethics Committee.

All signed ICFs were verified to ensure that subjects signatures were obtained before any study-related procedure was performed.

Concerns raised were addressed adequately.

10. Monitoring
Monitoring for BE/16/275 study was performed on 28-29.01.2017 for period I and for period II on 04-05 Feb 2017. Monitoring reports were verified. Visitors' logbook was studied to verify the monitor's visits.

Monitoring for BE/15/114 study was performed. CV of the monitor was verified. Visitors log book verified for monitor visits.

The monitoring reports verified.

Issues raised were corrected.

11. Investigators
Investigators CVs were verified for both studies BE/15/114 and BE/16/275. PI and SIs are qualified by education, training and experience for conducting of clinical studies.

Training logs were checked versus the delegation logs. All study personnel were trained for the responsibilities delegated by the Principal Investigator.

12. Receiving, storage and handling of investigational drug products
The analyte and pertaining IS for study BE/16/275(standard products used in MV and method development) shipment record was reviewed. The receipt was confirmed.

There was an inventory list for return of study medication, recording the relevant storage information such as cabinet identification to be easily located.

The stability of standard products in ambient temperature was certified.

The temperature log for the period of study no BE/16/275 for thermometer INS/CLN/010 was reviewed and confirmed.

The issues raised pertaining to the handling of IMPs were addressed adequately.

13. Case report forms

CRFs for 6 random subjectswere verified for both studies. No inconsistencies observed.

14. Volunteers, recruitment methods

The video records of obtaining the ICF were reviewed.

The site used the local database for recruitment of the subjects.
The subjects showed up at the main gate of the screening site and after being registered in the visitors' logbook, they proceeded to pre-enrolment area. Subjects were verified in the OVIS for cross participation, prior to the execution of the physical examination, alcohol and drug abuse test, urine sampling, ECG and other protocol-related activities.

Subject participating in BE/17/160 study was verified in the OVIS for cross participation. Although it was at the period III of the current study, he was not blocked in the OVIS database as enrolled subject. It was explained that all the subjects were blocked only after the last visit of the study due the OVIS' specific set-up.

Observations made in relation to the process of recruitments and handling of volunteers were addressed adequately.

15. Food and fluids

Food supply was outsourced to the catering and an agreement was signed and dated 10 Apr 2017 valid until 9Apr2018.

The dining area was visited during subject's breakfast. The details of food intake were recorded by dietician accordingly, after the subject's identification was verified.

16. Safety, adverse events, adverse event reporting

All safety and adverse events reporting were reviewed.

No SAE reported in both studies:
BE/15/114
BE/16/275

Bioanalytical section

17. Method development

The method development included Literature review, determination of the physical properties of the analyte, selection of range of quantification, on basis of Cmax, including ULOQ and LLOQ, selection of analytical instrumentation, selection of mobile phase, followed by method optimization.

The peaks were reviewed for no interference before the method was established. Final parameters of method e.g. precision and accuracy batches, recovery, selectivity matrix effect etc. were experimented as per the requirements. All the parameters were documented.
Based on the optimization, the method validation protocol was drafted. Protocols were approved and released by the QA.

STP/ANA/251v 00 (Standard Test procedure of analyte in study BE/16/275 (bioanalytical method) was available with effective date 7 Feb 2017:
"The STP for quantitation of the analyte from K3EDTA based human plasma by LC method"

The calibration standard range used in study BE/16/275 was determined using the literature:
For LLOQ, 5 % of Cmax was used and quantification of upper limit was described in the method development.

The publications used in method development was documented.

Reagents were verified as follows:
Mobile Phase Acetonitrile: Water (850: 150 v/v) with 1 mL Acetic Acid (EXP: within 3 days of preparation)
Diluent Methanol: Water (50:50 v/v): (EXP: within 7 days of preparation)
Rinsing Solution Acetonitrile: Water (50:50 v/v): (EXP: within 7 days of preparation)
Extraction Method: Solid Phase Extraction

Preparation of spiking solution was tabulated in the STP which was compared with the records and verified.

The stock solutions preparation foranalyte in method validation for study BE/16/275 was as follows:

About 5.027 mg of analyte working standard was weighed and transferred into 2 mL volumetric flask. About 1 mL of Methanol was added and sonicated to dissolve the analyte. The volume was made up to 2 mL with Methanol. Final concentration of the analyte Stock Solution was calculated by considering weight taken and % purity of working standard.

Both weight taken and the purity and molecular weight of the working standard was checked. The preparation of stock solutions was carried out independently for CCs and QCs, performed on 7 Feb 2017

The calculation and processing was checked and they were all according to the applicable STP.

However, the print outs from the balances were thermal papers where the recorded data was erased. It was very difficult to confirm the weight recorded on the documentation. It was claimed that the paper quality was changed to lasting paper.

The analyte in study BE/16/275was evaluated for metabolite interference. The molecule weight and MRM of the analyte was provided and compared with the metabolites, with different molecular weights. It was concluded that it couldn't be any metabolite interference with the analyte in human plasma during the method validation or sample analysis. Literature was provided from Rugbank.

The same investigation was done for metabolites of the analyte in study BE/15/114. Documentation was provided.

18. Method validation

SOP for Bioanalytical method validation explained the implemented procedures. It could take up to 8 weeks to carry out all related activities. Once the validation activities were completed and reported, the analytical part, sample analysis, was started.

No manual integration was allowed per respective SOP for reviewing of quality of chromatograms.

Study no. BE/16/275

Following documentation was reviewed and verified:

- Preparation of spiking solutions for both CCs and QCs performing on 7 Feb 2017 Number of aliquots prepared were 20
- Pipettes used in the sample processing, calibration certificates
- Refrigerator used for storage of analyte.
- The calculation, figures used in the preparation of solutions used in method validation.
- Date of preparation of working solutions
- The copies chromatograms for all runs
- Within-run accuracy run was carried out with 6 samples at 5 concentrations starting 58.93 to 6904.21 as HQC
- From 10 within-run accuracy, including the rejected run, the between – run accuracy was provided / calculated and verified on 26 Jan 2017
- Carry over result was reviewed:

Batch ID 200117ASC01.dab was analysed on 20 Jan 2017 (Audit trail checked). Preparation of pertaining Stock solutions was started at 18:15 20 Jan 2017. An Excel sheet was provided to prepare the spiking solutions for CC (STD). Spiking solutions were prepared on 20 Jan 2017, stored at 22:00. Batch processing documentation, showed that the biological matrix was retrieved at 18:30. Aliquots were prepared at 18:55 and the IS was added at 19:40. Auto sampler loaded at 21:17

- Matrix effect analysis was reviewed. The spiking solutions for QC was made on 20 Jan 2017. Samples were analysed on 23 Jan 2017. The run was failed because STD I failed. Analysis was repeated on 25 Jan 2017 and results were within the acceptable range. Stock solution prepared on 20 Jan 2017 was reviewed and verified.
- Anticoagulant used in this study was K3EDTA.

Study no. BE/15/114

Following documentation was reviewed/verified:

- Raw data forms for preparation of CC standards and QC samples of the analyte and metabolite of RRL-ANA-MV-337
- The Smoothing factor used for analytical run was set up as 10, which was too high.
- Preparation of stock solutions and pertaining process, for both fresh and with 4 days stability for both analyte and IS. The sample analysis was carried out on 13 Apr 2015.
- 5 days stability in biological samples, performed on 16 Apr 2015. Samples were stored in -20 °C from 9 Apr 2015 to 15 Apr 2015, for fresh and stored LQC and HQC level.
- 5 freezing/thawing cycles were provided for test procedures.
- Preparation of Human plasma stock solutions to be used for the stability tests. 6 lots were provided from the vendor. 300 ml plasma was provided to be used in MV with specific batch number Pooled Plasma on 9 Apr 2015. LQC and HQCs were provided from this batch for stability purposes.
- The long-time stability for 113 days. Date of storage was in the period of 9 Apr 2015 to 1 Aug 2015. LTS stability was accepted.
- Receipt of Human plasma with following lot numbers sent from Sai Baba Health care sent on 6 Apr 2015: P0922, P0923, P0924, P0925, P0926, P0927
- H016 for haemolysis samples collected on 23 Aug 2014
- L020 Lipemic samples collected on 21 Sep 2014
- Pathological report submitted verifying that plasma samples were free for malarial parasite, test negative antibodies against HIV I and II and HP C, syphilis and HP B surface antigen when tested.
- All plasma samples were collected on 29 Mar 2015

- Selectivity process, with acquisition start date on 9 Apr 2015 with anticoagulant K3EDTA for both the analyte and its metabolite. Results were within the acceptable range. Samples were traceable.

19. Sample collection, storage and handling of biological material

Once the clinical study was performed, the samples were transferred to an icebox – equipped with the data logger, with all the information regarding the samples and number of samples, as well as number of haemolysed and missing samples.

Upon the sample arrival at the bioanalytical facility, the data logger was printed out and controlled. The samples were divided in two aliquots, one main and the other one labelled as replicate samples, with different colour codes. Samples were counted and stored in different freezers, separately. Logs were kept and recorded respectively.

The company was operational 24/7 and transfers outside normal workdays/hours were communicated with the site, but not documented.

Samples were registered by unique sample identification; Subject – period – time point

Handling of samples by custodian, and request of samples by analyst were investigated.

Biological samples receipt and storage for samples collected for study BE/16/275:

Samples from 28 subjects, each 22 time-points, from two periods were received on 7 Feb 2017 at 21:25. Total number of samples received was 1186, 3 samples were missing. The reason was recorded properly. Data logger was confirmed to have the proper temperature during transport from clinical facility to the bioanalytical site.

Receipt and shipment record of replicate samples on 10 Feb 2017 were also reviewed and verified

The sample storage time was also confirmed.

All the refrigerator and freezers were linked to an alarm system, which were connected to the security. The Falken system which was data-logger, was used.

The room temperature was monitored manually daily and a log was kept.

The label on samples was checked to verify the pertinence of the samples. No particular check was performed to verify the origin of the samples, since the samples were provided by the company clinical unit.

Number of freezing/thawing cycles that the samples were exposed to, was documented and reviewed. Samples were required to be stored at ±20 °C

Once the analysis completed, the analytical samples were returned to the custodian, who kept a log of that before disposal.

All samples were stored until an inspection took place. The length of storage was employed in the agreement with the sponsor.

Concerns raised during the inspection were addressed adequately.

20. Analysis of study samples

Manual integration of the chromatograms was not allowed per their procedures.

The following parameters were reviewed and verified for number of subjects in both studies:

Integration, chromatograms, smoothing factor and pertaining factors, Modifications made, acquisition times, Use of CS and QC and pertaining calculation, audit trail, IS area average calculation. Metric plots pertaining to each run were studied to verify the acceptable range. It was verified that no result above ULOQ were ignored.

Study no BE/16/275

37 samples out of 1185 subject samples were identified for Repeat Analysis under the categories as equipment related issues category (1 sample) and consecutive QC failures (36 samples). The pertaining raw data was reviewed and verified.

The reinjection of Run ID batch 090217sub01,02&03 was due to poor chromatograph. The results were reviewed and verified.

Sample analysis for three subjects, on 11 Feb 2017 was also verified.

Based on the Cmax values, 24 subject-samples were randomly selected to be reanalysed under inspectors' observation. These samples were as follows:

Subject no	Period	Time points
5	Period I Period II	2.25, 2.50, 3.00 1.75, 2.00, 2.25
7	Period I Period II	0.50, 0.75, 1.00 0.50, 0.75, 1.00
21	Period I Period II	0.50, 0.75, 1.00 1.00, 1.25, 2.00
24	Period I	2.00, 2.25, 2.50
27	Period II	1.00, 1.25, 1.50

The whole process from issuance of the forms, delegation of analyst, equipment assignment, balance calibration, solution preparation, accuracy test of stock solution to the performance of the STP (Standard Test Procedures) steps were followed. In the final results, all QCs failed and the batch ID 261017SST01 was consequently rejected.

The day after (last day of inspection) another random batch was selected, consisting of 9 samples from subjects 11, 12 and 13. The process underwent under the observation of the inspector. The results were provided, and all values were within the acceptable range.

Study no. BE/15/114

Changes in integration parameters were documented on the form for "Change Integration Details" parameters. It was verified that the re-integrated parameters were used for the whole batch per equipment per the respective SOP.

21. Data processing and documentation

Electronic raw data and paper raw data, including notebooks and logbooks were reviewed during the assessment of trials' conduct. Documentation regarding all trials selected for inspection was organised and labelled properly and an Index including all documentation was available for inspection.

The company had plans to paperless data management in a few months.

22. Good laboratory practices

The bioanalytical laboratory facilities were visited. There were two rooms dedicated to deep-freezers all equipped with digital thermometers to be monitored centrally. For more details, see section 7.

The calibration certificate for Deep freezer was reviewed.

Performance of requalification of Freezer –20 °C, Acceptance criteria ±2 was carried out on May 2016, validated by Unique services – valid until 10 May 2017 –covering the whole period of analyte used in study BE/16/275 was reviewed and verified.

Temperature log of all Deep freezers for period of study BE/16/275 was reviewed and confirmed.

The lab was also equipped by refrigerators for storage of products in range of 2-8 °C.

The balance room was equipped by sodium vapor lamp. Logbookfor daily calibration for one of the balances was reviewed.

A new balance was under installation with specific ID number.

LC-MS/MS instruments used for study BE/16/275 and study BE/14/115 were confirmed to be installed during the study performance.

The facility had a total of 3 HPLC systems, 16 LC-MS/MS systems and inductive coupled Plasma Spectrometer.

Calibration certificates for Microbalances, Micropipettes, and refrigerator for the period of Lamivudine study was reviewed and verified, as well as SOP for the operation of the Sonicator, effective 21 Oct 2017.

Water qualification test was outsourced to be performed once a year. The test report was provided, dated 16 Feb 2017 by Envirocare labs pvt ltd in India.

Another test was performed on 16 October 2015, certificate of analysis was performed by Unique Pharmaceutical Laboratories.

Pharmacokinetic, statistical calculations and reporting section

23. Pharmacokinetic, statistical calculations

Inspectors performed a discussion with the Biostatistician. He is using SAS version 9.4 server based and Phoenix 6.4.

Adequate CAPA was provided for the concern raised during the inspection.

Study no BE/16/275

CC and QC concentrations, as well as subjects' plasma concentrations were provided in an Excel sheet and were investigated for all out of range concentrations and above ULOQ. No concern was raised. Report of repeat analysis was verified.

Study no. BE/15/114

CC and QC concentrations, as well as subjects' plasma concentrations were provided in an Excel sheet and reviewed and were investigated for all out of range concentrations.

166 Samples were identified with back-calculated concentrations above ULOQ. Repeat Analysis as per the respective SOPs (effective date 3 Jul 2015) were conducted and the pertaining results were reviewed.

24. Study report

Batch ID 180715SUB 49 & 50; 180715SUB 53&54; 200715sub 60 & sub09 (P I&III) were re-integrated and the re-integration was reported and justified, as well as changing the parameters for the whole batch. However, this was not reported in the bioanalytical study report V01, which was submitted to the WHO.

Miscellaneous	
Samples taken	N/A
Assessment of the CRO master file	It was reviewed without any remarks.
Annexes attached	N/A

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 CRO **Raptim Research Ltd, A-226 and A-242, T.T.C. Industrial Area, Mahape M.I.D.C., 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

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

5. WHO Handbook on Good Laboratory Practice/OECD Series on Principles of Good Laboratory Practice and Compliance Monitoring, Number 1: OECD Principles on Good Laboratory Practice (as revised in 1997). Organization for Economic Co-operation and Development. ENV/MC/CHEM(98)17. 26.Jan, 1998.
Short name: WHO GLP
http://www.who.int/tdr/publications/documents/glp-handbook.pdf

6. The Good Automated Manufacturing Practice (GAMP) Guide – A risk-based approach to compliant GxPcomputerized systems (GAMP5). ISPE – International Society for Pharmaceutical Engineering, December 2009.
http://www.ispe.org/gamp-5

7. Guidelines on Bioanalytical Method Validation EMEA/CHMP/EWP/192217/2009 Rev.1 Corr.* Committee for Medicinal Products for Human Use (CHMP), 1 February 2012.
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/08/WC500109686.pdf

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

9. Good Practices for Computerised Systems in Regulated "GXP" Environments, PIC/S Guidance, Pharmaceutical Inspection Convention Pharmaceutical Inspection Co-operation Scheme, PI 011–3, 25 September 2007.
http://www.picscheme.org/pdf/27_pi-011-3-recommendation-on-computerised-systems.pdf

10. US FDA Code of Federal Regulations Part 11
http://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=11&showFR=1

11. EU guidelines to Good Manufacturing Practice and Medicinal Products for Human and Veterinary Use Annex 11, Computerized systems
http://ec.europa.eu/health/files/eudralex/vol-4/annex11_01-2011_en.pdf

12. Handbook – Good Laboratory Practice (GLP): quality practices for regulated non-clinical research and development – Annex I: The OECD Principles on GLP, 2nd ed., 2009. This document will be referred to as "GLP".
http://www.who.int/tdr/publications/documents/glp-handbook.pdf

13. Model guidance for the storage and transport of time-and temperature-sensitive pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 9.
Short name:WHO TRS No. 961, Annex 9
http://apps.who.int/prequal/info_general/documents/TRS961/TRS961_Annex9.pdf

14. Guidelines for the preparation of a contract research organization master file, WHO Technical Report Series, No. 957, 2010, Annex 7
Short name:WHO TRS No. 957, Annex 7
http://www.who.int/medicines/publications/TRS957_2010.pdf

15. 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

16. WHO Good Clinical Laboratory Practices (GCLP)
http://www.who.int/tdr/publications/documents/gclp-web.pdf