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

Part 1	**General information**
Organization details	
Company information	
Name and Address of Clinical Research Site	RA Chem Pharma Limited, Clinical Research & Biosciences Division Plot-No. 26 & 27, Technocrat Industrial Estate (TIE) Balanagar, Hyderabad-500037 India
Name and Address of Bioanalytical Research Site	RA Chem Pharma Limited, Clinical Research & Biosciences Division Plot-No. 26 & 27, Technocrat Industrial Estate (TIE) Balanagar, Hyderabad-500037 India
Name and address Statistical Site	RA Chem Pharma Limited, Clinical Research & Biosciences Division Plot-No. 26 & 27, Technocrat Industrial Estate (TIE), Balanagar, Hyderabad-500037 India
Corporate address of Organization	RA Chem Pharma Limited, Clinical Research & Biosciences Division Plot-No. 26 & 27, Technocrat Industrial Estate (TIE) Balanagar, Hyderabad-500037 India
GPS coordinates	17.47 latitude – 78.44 longitude
WHO product numbers covered by the inspection/ Product names/ Study numbers/ Study titles	**Study no. 053-16-WHO** Tablets 100 mg / 270 mg **Study no. 096-16-WHO** Dispersible tablets 100 mg **Study no. 039-15-WHO** Tablets 400 mg Follow up from previous inspection July 2016
Inspection details	
Dates of inspection	12 - 16 February 2018

Type of inspection	Routine
Introduction	
Summary of the activities	The facility has the capacity to perform bioequivalence / bioavailability and in-vitro studies in both healthy subjects and patients. Other services provided to the sponsors were regulatory filings, Ethics committee approval, medical writing, clinical phase execution, eCTD submissions, quality assurance and clinical trial co-ordination.
General information about the company and site	The CRO was established in 2007, as Clinical Research and Biosciences (CRBio), division of RA Chem Pharma Ltd, located in Hyderabad city of the state of Telangana in India. RA Chem Pharma Ltd. is a vertically integrated pharmaceutical company started in 2003, performing other pharmaceutical activities such as manufacturing of API and Formulations.
History	Previous inspections were carried out by various Regulatory Agencies, including DCGI, MoH Turkey, USFDA, UAE-MoH, MoH-Malaysia and UK MHRA. The CRO was last inspected by WHO in July 2016. Reports for inspections conducted by UK MHRA and US FDA in the years 2016 and 2017 were respectively reviewed.
Brief report of inspection activities undertaken	The inspection team covered the following study-related activities under the scope of this 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, and a tour of the facility. Regarding the analytical operations, the team covered good practices, qualifications of personnel and procedures utilized during the method validations and analytical testing. A review of the clinical study data, analytical method validation, and analytical study data was accomplished along with comparisons of the source data to study reports.
Scope and limitations	
Out of scope	Not applicable

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
CPU	clinical pharmacology unit
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
LC-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 CRO explaining the activities of the organization in detail.

The abbreviation CRBio was used as company's logo.

The CRO was a four-story building. The clinical facility covered an approximate area of 30,000 sq. ft. It was compartmentalised into Registration, Bioanalytical, Administration, Information Technology, Clinical Pharmacology Units (CPU), Pharmacokinetics and Statistics, Quality Assurance and Archive units.

The scope of accreditation by national authorities included conduct of clinical studies (all phases) on healthy population as well as patients, in accordance with the GCP and applicable GLP principles.

The CRO's had completed more than 500 studies in the last 10 years.

The Organizational charts were provided depicting key positions and the names of responsible persons. Organograms for each department were also provided. The CRO Master file was available.

Designated personnel from Biostatistics and Programming, Design of protocol and Clinical data managements were interviewed during the inspection. A list of employees was kept by the HR department.

An in-house ambulance was available to transport patients to a nearby hospital (4 km away) in case of an emergency.

Changes since last inspection i.e. 20 Jul 2016 till date were presented:

Facility/Layout Changes

- Head office shifted from 1st floor of this building to other location and entire building was dedicated for CRO Operations.
- Consent areas 1 and 2 of ground floor had been allotted to Bioanalytical Department for expansion of lab operations.
- Structural changes done in the bioanalytical area for ease of operations. QC staff sitting area was converted to processing area. Document storage area and BA Head Cabin was modified to additional processing area.
- Deep freezer room was expanded and an earlier washing area was changed to a segregation area
- Informed Consent area 1 at ground floor was modified to Fume hood and solvent storage, wash area of bioanalytical.
- Informed Consent area 2 at ground floor was modified to bioanalytical staff sitting area
- Clinical Informed consent areas were shifted from ground floor to first floor
- Clinical staff sitting (including HOD Cabins) shifted from second floor to first floor
- Sample collection rooms were modified on ground floor. New ambulatory sample collections areas were created
- Earlier Ambulatory room was changed to staff area
- Archival area was expanded in 2nd floor

Addition of Instrument's/Equipment's

- New instruments added in bioanalytical department
- New instruments included clinical department

Procedural changes

Bioanalytical department

- Method validation SOP: Method validation plan and trend analysis for batch failures was introduced.
- Repeat analysis SOP: Identification of out of trend samples was introduced.
- Project sample analysis and analytical batch acceptance: Subject sample analysis should be initiated only after signed validation report was available. Trend analysis for batch failures was introduced.
- LC-MS/MS systems were upgraded to Windows7 from Windows XP operating system.
- Pipette Calibration: Pipettes were calibrated before and after preventive maintenance.
- Incurred sample reanalysis: Select samples from each subject, from each period and from each analyte for ISR experiment.

- ❑ Investigations conducted during the study were incorporated in the bioanalytical study Report.
- ❑ Project specific excel calculations as well as instrument specific audit trails were archived along with source data.

Clinical department

- ❑ Subjects who had Hemoglobin value 12.5 g/dl and above shall be enrolled into the study and same was captured in inclusion criteria. This procedure was incorporated in the respective SOP.
- ❑ SOP was revised to incorporate the procedure to use most recent version of Drug literature.
- ❑ SOP for Operation maintenance and calibration of x-ray machine: Validity of X-Ray duration modified from 06 months to one year.
- ❑ SOP for Receipt, Storage, Accountability and Retention of Investigational Products was revised to incorporate procedural change pertaining to "If IPs having near expiry date, schedule the study in such a way that last period dosing should commence one day prior to expiry date of IPs".

Statistical department

- ❑ Applicable SOP was revised. SAS software was validated with real time bioequivalence data sets.

Archival department

- ❑ Network attached storage (NAS) device was installed in archives for archiving soft copies of source data

2. Computer systems

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

Server backup was maintained on a daily, weekly, monthly and yearly basis in a suitable storage media in two copies. One copy was kept at the onsite archiving facility with the other stored at an offsite location.

A designated back-up server was in use for all bioanalytical software systems, accessible by user roles as "Administrator". A back-up was scheduled for every 30 minutes.

Network attached storage (NAS) was a storage device, kept in another office of RA Chem. All generated data were securely stored in three sets of data-storage devices. The purchase order for the NAS was available. The system was adopted since it was faster and more reliable with better security measurements.

A periodic verification process (every 6 months) was carried out by random selection of data to ensure that they were secured against alteration, inadvertent deletions or loss.

The logbook for storage and retrieval of backup data to/from off-site archival facility was reviewed. On 12 Jan 2018, six projects were randomly selected to verify the safekeeping of the archived electronic data. All were verified successfully.

The retrieval request procedure for electronic data stored, related to the studies within the scope of inspection was reviewed.

Validation plan pertaining to SOP for Computer System Software / Hardware validation schedule, was available for scheduling the validation of applicable computer systems, Jan 2017 until Dec 2018.

Risk assessment reports of computerized system for LC-Quan Software for two different versions were reviewed.

Performance Qualification was performed. Screenshots were provided. The documentation was reviewed by the Assistant manager, BA Dept., IT admin and Sr Executive of QA Dept. and approved by Asst. General Manager BA Dept.

In a newly revised applicable SOP, it was outlined how to verify the qualification of instruments/equipment (IQ, OQ, PQ) according to the manufacturer specification. In this SOP, an attachment form (no. 1) was provided to be used for request of user requirements prior to the purchasing of a new instrument. This SOP was first implemented in June 2017; hence it did not apply at the time of acquiring the software systems used in the studies within the scope of the inspection. A user requirement specification was consequently not present.

IQ report was provided and dated 19 Jul 2010.

Permission levels for user groups in LC-Quan software were detailed in an SOP for Authorization in LC-MS/MS software, effective 2 Jun 2017. A correspondent SOP was also available for Analyst® Software.

SOP for usage of each software program, used in BE-activities was provided.

XP window program was still applied for software used for X-ray images. Since XP was no longer supported by the provider the CRO was recommended to apply other applications.

The VIMS database was used for registration of volunteers by means of their biometrics (finger print), name and photo. Subjects were primarily identified by finger print. A cross-check study participation was performed through VCPS system, covering south of India. A list of CROs registered in VCPS system was provided by the service provider. A harmonization process was being carried out to cover CRO’s volunteer data-pool throughout India, directed by CDSCO.

The audit trail functionality of VIMS was confirmed. Search in audit trail was possible both via subject and period of time.

Issues raised during the inspection were resolved in the company CAPA.

3. Quality management

A Quality manual with effective date 21 Jun 2017 was available providing all quality procedures followed at CRO.

QA, with 15 employees, was divided in Clinical-QA, BA-QA and Documentation area. The department functioned independently and reported directly to Management. QA functioned as per own SOPs and was responsible for overall quality systems observed in the organization. All the procedures applicable to the activities performed in the organization were under the supervision of QA.

The CRO Master File was also provided and structured according to the requirements.

The CRO's internal audits were performed once in six-month periods to verify the functionality of the freezers, the equipment and instruments, and the validity of the labelling.

An in-process study audit was scheduled for each study by random selection of activities performed during the conduction of the study.

A retrospective study audit was also planned to audit the activities executed during the study after the completion of each study. The audit schedule included the activities from the initiation to the end of the study, based on a check-lists provided.

Examples of SOPs reviewed and verified during inspection:

- SOP for Preventive Maintenance for Micropipette and Multi-pipette, effective 6 Jan 2017
- SOP for Audit planning
  The audit schedules for 2016, 2017 and 2018 was available. For each month, one area was planned to be inspected. The scope of the inspection was not detailed.
  The retrospective audit report dated 13 Feb 2017 was reviewed. CAPA was requested. The response to the audit report was provided dated 14 Feb 2017, and found to be satisfactory. No remarks were made.
  The recent audit report for clinical system and facility was present dated January 2018. CAPA was not provided yet. The report seemed to be adequate.
- Audit of third party vendors: An audit plan for vendors for critical services was available to schedule monthly audit for the respective vendors. Audit plans for 2016-2017 and 2017-2018 were reviewed.
  List of outsourced services was provided.
- SOP for Archival, Retention, Re-storage of data

- SOP for Acceptance criteria for chromatograms
- SOP for Acceptance criteria for quality control samples
- SOP for Calibration and maintenance of equipment
- SOP for Computer system validation
- SOP for Development of bioanalytical method
- SOP for LC-Quan software usage
- SOP for Repeat runs
- SOP for Sample receipt, registration, storage, processing analysis

All concerns raised during the inspection with respect to their quality management system were addressed adequately and respective CAPAs were provided.

4. Archive facilities

The archive facility was located on the second floor accessed by authorized personnel with key cards. A list of personnel with access to the facility was provided. Maintenance personnel as well as Head of Operations were authorized to access the facility unsupervised. The inspection emphasized that it was essential to supervise any access to the study documentation and asked CRO to revoke all the unrelated admissions.

All Entry-Exit data was recorded specifically.

Inward and outward logbook for archiving documentation, as well as logbook for request for retrieval of documentation were reviewed. A complete archiving index in an Excel sheet kept the oversight of the documentation archived in the facility. The back-up process of the index was also confirmed.

The facility was equipped with fire proof archiving racks, chemical powder sprinklers and smoke detectors. Documentation to verify the fire proof nature of the entrance door and walls was not available.

Pest control was carried out every 14 days, documented in service provider report, kept by HR.

The process for handling of retrieval of documentation and retention period was described adequately and could be verified via the successful recall of study documentation and supporting records during the conduct of the inspection.

The issue raised in relation to this section was addressed satisfactorily

5. Premises

During the inspection, a tour of facility took place.

The premises comprised the under-listed:

- Security office at the ground floor and main entrance
- Volunteer registration area and screening
    - Blood and urine sample collection
    - Examination rooms
    - ECG
    - X-ray
    - Consent area
    - Change room

All clocks were synchronized, connected to the main server operated by GPS to document the exact time of study activities. Medical exam equipment was labelled properly for installation and calibration information.

Access to different facilities was restricted by key cards.

Temperature and humidity was monitored by digital thermometers and hygrometers.

SOP for Operating, Maintenance of diesel generator was verified. The power backup system consisted of 1 Diesel Generator - 500 kVa, 3 UPS devices each 40 kVa, 1 UPS device - 60 kVa, 3UPS x 12 kVa. The diesel generator was tested during the inspection. Logbook for the general maintenance records was verified.

Disposal of waste and other environment-friendly measures were also inspected. Waste was collected in separate container with different colour codes and were handed over to Bio waste handling agency or chemical waste. The activity was outsourced for proper disposal of the waste material. No remarks were made.

- Clinical Pharmacology Unit with a total of 5 clinics, had 114 beds. It consisted of the following sections:

    - Dosing and sampling area
    - Clinical wards post sampling area
    - Dining area
    - Sample processing area
    - Doctors’ and monitors’ room
    - ICU

The site had two intensive care units located on the clinical floors. Each unit was provided with three beds and equipment for the management of medical emergencies.

ICU I

The medication available for emergencies was randomly verified for expiration date and found compliant.

Medical emergency equipment: oxygen device, defibrillator, ECG machine, suction machine, laryngoscope was verified. The defibrillator and laryngoscope procedures were discussed with ICU personnel with medical responsibility. Defibrillator functionality was checked. No issues were observed.

The Oxygen cylinder and defibrillator log book was verified.

ECG device was checked. It was concluded by the inspector that no changes related to equipment settings could be done.

Pharmacy

Pharmacy was located on the first floor with limited access to only authorised personnel for receipt, storage, and retention of drug products.

The records of Exit/Entry were logged in a logbook and found adequately.

The pharmacy was equipped with adequate space and three stability chambers. It was kept in good hygienic condition. The chambers were connected to a digital thermometer. Temperature and humidity records were downloaded daily and filed.

Logbooks for storage and accountability of IP, receipt of medication, last shipment record for Reference and Test product, together with the pertaining dispensation was available and reviewed. The data logger ID was recorded properly.

Adequate measured were put in place to rectify issues raised by the inspectors and these were found to be satisfactory.

6. Personnel

Approximately 120 employees were working in different shifts in the company, involved in different activities based on their roles described in respective job descriptions. According to the CRO Master File, periodical health check-up was done to ensure the safety of the employees and all the applicable employees were vaccinated. All the employees were covered by either ESI Scheme or private insurance policy for all medical and health related issues. All the employees were covered by Group personal accident policy (GPA). A list of employees was provided in the CROMF which was updated regularly. The employees were insured through an insurance company, until March 2018, according to the agreement provided.

CVs and JDs were randomly selected to be checked. The Job Description of Data Manager in section 3 of the CRO Master File was not available.

Personnel joining the organization were provided with induction training and briefed on the organization and activities of CRBio. The personnel were trained on SOPs and given job specific training. They were trained on study specific procedures such as protocols, method SOPs etc. In addition, GCP/ GLP /cGMP training was given to all the applicable personnel as required by their job description.

Biometric access for entrance was initially provided for monitoring purposes. The access key card was issued with respect to the employee's job description, upon a request from HR and authorized by Head CRBio.

A separate request form for access to the computer systems was required following the same process.

An overview of the access rights that the various levels of staff had was available. Upon employees' termination of duties, a certificate from each department was required to ensure deactivation of all activities. In case of unannounced leave, the Head of department would provide the termination form.

SOP for Training matrix was present. The matrix was organized by each department and arranged by role categories and SOPs applicable to each category.

The training documentation on SOP for Safety in laboratory was provided for 44 employees in BA. Training documentation was verified.

Clinical section

7. Clinical phase

There were five units with a total of 114 beds to accommodate the subjects in CPUs. Inspectors visited the clinical facilities. The working area was well maintained.

All clinics had separate dosing, dining, phlebotomy and medical monitoring areas, as well as separate sample processing areas for centrifugation and storage before analytical processing.

X-Ray was performed in screening phase on site when required.

Study 053-16 WHO
Delegation log was verified. It was noted that the PI authorized 50 people from the site personnel with different qualifications to conduct the ICF process and obtain consent. However, the site personnel obtaining subjects' consent should be qualified by education, training and experience in order to fulfil this task.

Study 096-16-WHO
SOP for Protocol training and delegation of study activities available.
As per the SOP, the delegation should be done according to designation, training and experience. 65 people from the site personnel were delegated to perform 16 different types of activities.

Subjects' belongings were kept in lockers in the changing room where the amenities such as uniforms and wristbands in respective colour codes were handed over to the subjects for their use, before being directed to the CPUs.

At the entrance, the volunteers signed a record for their belongings, such as cell phone. Fire alarm for pharmacy was activated and the alarm system was installed in the security room. A mock Emergency call was conducted. The site staff were informed and reacted appropriately. The Entry/Exit logbook for volunteers was reviewed kept by security. Volunteers were logged into the visitor-log upon their arrival and before heading to the pre-screening area.

During the facility tour, alarms on bedsides and showers were tested.

All issues raised, pertaining to the clinical phase of the study, were addressed adequately.

8. Clinical laboratory Clinical/Pathology lab
Medcis Pathlabs India Pvt Ltd, accredited by NABL was contracted for diagnostics purposes for both studies in the scope of the inspection. A service agreement, dated 19 Nov 2016 valid for 36 months was available.

The lab reports were sent by contracted laboratory to the site in paper form in an envelope. The CRO had also access to the results on-line with site-specific username and password, accessed only by physicians.

The following ECGs from different studies were checked and found compliant:

- Study 026-16-US
- Study 039-16-MA
- Study 114-16-EM
- Study 096-16-WHO
- Study 053-16-WHO

9. Ethics

Ethics Committee's approval of the screening ICF, registration ICF, ICF for changes in personal information and additional Informed Consent document was available and reviewed.

Issue raised in context with the ICF versioning was corrected satisfactory.

The signed ICFs from study 053-16 WHO and study 096-16-WHO were verified by using the subject specimen signature sheet. All ICFs were personally signed and dated by the subjects.

Video-recording of the ICF process was verified for some subjects in the study.

Study 053-16-WHO
Insurance policy issued by United India Insurance limited company with a period of insurance from 30/09/2015 till 29/09/2016 was verified.

Study 096-16-WHO
Insurance policy issued by United India Insurance limited company with a period of insurance from 30/09/2016 till 29/09/2017 was verified.

The approval and minutes of the meeting of the Ethics Committee used for 053-16-WHO was reviewed and found to ensure the presence of approval prior to the start of the study procedure.

10. Monitoring

CVs and qualifications for all monitors were verified.
The monitoring reports for studies 053-16-WHO and Study 096-16-WHO were reviewed.

The visitor's logbook was verified for monitoring visits conducted. No issues were observed.

Monitoring plan for both studies 096-16-WHO and 053-16-WHO for all study periods was verified.

The monitoring visit reports were accurate and well developed. CAPA to monitors observations were implemented accordingly.

11. Investigators

CV of PI and other applicable investigators were checked.

Training logs for the investigators were verified and found to be adequate. PI and SIs were adequately qualified by education, trainings and experience to conduct clinical studies.

The CAPA provided for the finding raised during inspection was adequate

12. Receiving, storage and handling of investigational drug products

The shipment of the investigational medicinal product was controlled adequately. Activities were logged in their respective logbooks.

Randomization schedule was provided by PK Statistician and hard copy was retained by the pharmacist. After receipt of the randomization list, labels were provided on an Excel sheet, followed by QC check.

Dispensing of Test and Reference IMPs was done independently, starting with line clearance procedures. As soon as the dispensing of doses was complete, IMPs were stored in the chambers, properly segregated and delivered to the clinic 30 minutes prior to the dosing process.

Remaining IMPs was retained, following the respective process for retention of IPs.

The shipment documentation for Studies' IMPs was reviewed. An excursion of temperature of several hours occurred during the shipment of the IMPs in both studies.
The temperature was recorded above 30 °C for 2 hours for study # 053-16. An email was submitted to the CRO by sponsor, verifying that the excursion would not have any impact on the product since the product would be stable in temperatures up to 40 °C ± 2.

Stability documentation for all IPs was provided. IP labels were verified versus randomization list for both studies 096-16-WHO and 053-16-WHO.

Working standards were not shipped under monitored condition. Documentation from USP dated November 12, 2017, signed by Global QA, stated that USP reference standards were not customarily shipped on ice or under refrigerated conditions, unless it was indicated as "COLD SHIPMENT REQUIRED".

All concerns raised regarding the handling of the IMPs during the inspection were addressed adequately

13. Case report forms

Study 053-16-WH

CRFs for six subjects were verified.

14. Volunteers, recruitment methods

Recruitment and Registration

Volunteers who were referred to the CRO were registered in the visit log prior to registration in an internal database (VIMS). Access to the database was password controlled to protect the volunteers' confidentiality. Subjects' personal data, height and weight were registered. BMI was calculated automatically. Volunteer's identification was ensured by checking their ID, photo and finger prints. A unique ID number was generated by the system for each volunteer registered in VIMS.

Issue raised pertaining to the registration of volunteer was adequately addressed in the provided CAPA plan.

Screening procedures

After registration, the volunteers were led to the informed consent (IC) area where the details of the specific ICF were explained to the volunteers. A copy of the ICF was provided to them. In addition, the general screening forms for HIV, X-ray, and registration of volunteer into the volunteer database were provided.

Following confirmation of enrolment, the volunteer would have a one-on-one meeting, which would be recorded. The volunteer could raise any concerns on the study with the medically qualified personnel (i.e. investigator).

Following consent, the volunteers proceeded for study specific tests such as drug and alcohol tests and physical examination. The medical examination process was observed. Discussion with the clinician on the screening of subjects and tests required were conducted.

The clinical laboratory was responsible for collection and transfer of blood and urine sample collected during the screening phase. The Lab personnel were present to collect and transfer the samples to the outsourced laboratory.

Their new ECG GE machines were operating according to the requirements. Three GE ECG machines were under installation. It was noted that the old ECG machine was retired during the inspection.

The X-ray facility was visited. The lead door and lead vest was available.

The issues identified in relation to screening procedures were addressed adequately.

15. Food and fluids

CV and training certificate for dietician qualified as Clinical Nutrition were verified.

The contract with the Caterers dated 07 Feb 2015, valid for 3 years was verified.

Vendor audit report dated 04 Jan 2018 was reviewed. No observations were made.

16. Safety, adverse events, adverse event reporting

Study 096-16-WHO

There were no adverse events reported. No SAEs or deaths were reported.

Study 053-16-WHO

Only one adverse event, (vomiting of mild intensity) was reported on 16 Jun 2016 for subject 17.

Bioanalytical section

The inspection included an audit of source documentation and raw data for validation of bioanalytical methods, analysis of subject plasma samples, audit trails for electronic data capture and data 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, internal standards and reagents.

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

Study number: 053-16-WHO	
Method development	
Detailed description of the method development, including copy of publications used, was documented in the method development notebook. The data for all four analytes was reviewed. Three calibration curves with specific slope and intercept were provided to determine the LLOQ and ULOQ of each analyte.	**Method of detection** LC-MS/MS **Extraction method:** Liquid-liquid extraction **Dilution Solvent** Methanol:Water (50:50) **Mobile phase** 10mM Ammonium Formate **Auto-sampler temperature** 5 °C ± l **Matrix Anticoagulant** K2EDTA Smoothing factor was allowed up to 10 according to the procedures. However, in this study, the factor used was below 5.

Method validation	
CoAs for all analytes and their pertaining ISDs were reviewed. The preparation of the stock solutions for the analyte and pertaining CCs (10 different concentrations of CCs) and 5 different concentrations of QCs on 1 Jun 2016 with project no. MV-011-16 was reviewed. SOP for Stock solution preparation was verified. Documentation related to standards acquisition and shipment was reviewed. 26x150ml of plasma was purchased from Janani Laboratories on 27 Jul 2016 and received by the site on 07 Sep 2016. There were 7 plasma lots of 150ml used for study 96-16-WHO on 15 Sep 2016, and 6 plasma lots of 150 ml for 053-16-WHO study on 30-31 Jan 2017 Logbook was verified versus shipment documents and invoices. No discrepancies were noted.	
Analysis of samples	
The analytical batch were organized in the following sample order: i. Un-extracted highest standard. ii. Mobile Phase/ Reconstitution solution/Elution Solution iii. Un-extracted lowest standard. iv. Extracted highest standard. v. STD Blank vi. STD Zero vii. CC Standards viii. Quality Control Samples	
	There was a total of 25 runs for System suitability for the analyte. Folder Sub_08_22082016 was erroneously created, since sub no 8 had only participated in period I. Subject 8' samples were hence analysed in other batch together with sub 13, 24 and 36. SUB21-29082016 was failed due to consecutive CC failure. The repeat batch was reported.

	SUB01_15092016 was repeated due to the QC failure. Repeat was performed on 28 Sep 2016
Repeat analysis	Reinjection details for two analytes: RUN ID IDREP-II 12092016 was reviewed There was a stoppage at 19:44 on 12 Sep 2016 due to obscure in probe compartment. The batch was reinjected from the beginning namely un-extracted ISTD 10 RI to subject 23207RI. Run ID REPEAT-III was repeated due to the ISTD variation over 20 % (52 %). It was reported. All the reasons for the repeat analysis for the analyte, together with the pertaining ISTD trend analysis was reviewed and verified. ID REPEATS-IV_ 170920 16, number of samples quantified in the batch was reported as 2 in the study report, whereas there were 12 samples of 5 different subjects. However, an erratum was made to correct this as it was a typographical error. Subjects no 3, 9, 16 and 22 were among others repeated in Analyst for the analyte / metabolite, due to either QC or CC failure. However, the repeated batches again failed due to the same reason. An investigation was carried out to assess the root cause: As a part of investigation, the tune was adjusted for both analyte and its metabolite. During the tuning, compound dependent parameter declustering potential value for both analyte / metabolite was changed from 110 to 85 and 140 to 80. By using the new tune parameters, the un-extracted highest STD was injected. The response was hence increased and remained stable.

	One precision and accuracy batch was performed by using the new tune parameters and acceptance was evaluated per the applicable SOP. The Q1 Mass and Q3 Mass were constant through the analysis of batches. However, DE and CE parameters for declustering (tuning parameters) could be modified when the instrument did not show results within acceptable ranges. The system suitability runs were reviewed in Analyst®. SUB07_19092016 failed due to QC failure repeated which was reported properly. LLOQ and ULOQ for randomly selected subjects were reviewed to be verified against the study report. A plan deviation was raised for SOP "Repeat analysis", for not repeating the Pre-dose samples of clinical periods 2, 3, and 4 for the analyte. The concentrations obtained in respective periods for the analyte were above 5 % of max concentration of their respective period, due to long half-life reported for the analyte.
Re-integrated chromatograms	None
ISR For two analytes: SOP Investigation of high internal standard variability in subject samples was reviewed to verify the ISTD response area variation for all samples with the analyte A. If the percentage difference between the average IS area of accepted known samples (CC and QC) and the subjects accepted unknown samples was not within 20 %, and such type of batches were less than 20 percent of the subject population then additional samples from such batches	Number of samples: 2216 ISR REPEATS_17092016 ISR-III-15092016 ISR-II_1409206 ISR-IR_16092016 ISR-IV_16092016 ISR-V__16092016 ISR-I_14092016 Acceptance criteria were met.

were to be identified for ISR. It was noted that selection of the additional samples to be included in the ISR was according to the ISR sample selection in the respective SOP.	
Back calculations	N/A
Acceptable ranges fulfilled	To ensure that the criteria for batch acceptance was fulfilled, a check list named Project Data check-up was used, where all the criteria were noted to be ticked off whether they were fulfilled or not.
Trend of ISTD variation	Trend of ISTD variation for the analyte's analytical runs was reviewed. 12 batches were out of acceptable range and they were re-run due to prevailed reasons such as failure in QC and/or CC. ISTD trend analysis was performed adequately.

Study number: 096-16-WHO	
Method development	
	Method of detection: LC-MS/MS (software LCQuan) **Extraction:** Liquid-Liquid extractin **Data generation** LC-MS/MS - LCQuan **Matrix:** Blood plasma **Anticoagulant**: K2EDTA
Method validation MVR-00217	
	Matrix effect Performed on 7 Jan 2017 with RUN ID ME_07072017 was reviewed and verified. **Sensitivity & Dilution integrity** Run ID DI, sensitivity 10012017 was reviewed. Sensitivity run was performed using 6 LLOQ concentrations. The run was successfully performed. However, the Dilution integrity failed due to failure of 6 Diluted QC. Another run was performed using

	the second set of DQC and it passed on 11 Jan 2017. The stock solution was prepared on 6 Jan 2017 with ID MV-002-17-DIstock-01-070117 Both Carry over and selectivity validation was also performed.
Precision and Accuracy	Performed according to the procedures.
Evaluation of stability was carried out properly. The QC samples were analysed against calibration curve obtained from freshly spiked calibration standards. Obtained concentrations were compared to the nominal concentrations.	**Freeze/Thaw** RUN ID FT, INT, BFT_110117 5 cycles were provided for this test. HQC and LQC from ID no 175 – 180 were used in this run eventually, last retrieved on 12 Jan 2017, starting 7 Jan 2017. Freshly spiked CC ID FSCC02 was used. The record in the paged logbook was organized by project. And the samples for each project were stored in an identified freezer with unique ID number recorded. The analysis was run on 11 Jan 2017. Preparation of stock solution and spiking solution used for purpose of stability run was reviewed. Preparation of stock solution for concomitant medication was reviewed.
	Bench Top The stability test was performed.
	Long term stability stock solution LTSS_07012017 Performed on 11 January starting at 3:26. The documentation was reviewed and verified.
	Long term stability of analyte in matrix Performed on 13 Feb 2017 for 37.13 days. HQC and LQCs were stored at -77 °C and -25 °C starting on 7 Jan 2017. The freezer log was reviewed. The form for Long Term Stability

	was reviewed, confirming that the CC was spiked freshly.
Analysis of samples	
	Samples from subjects 2, 4, 6, 9, 10, 11, 13, 16, 20, 21, 24, 25, 26, 27, were repeated. With ID IDREPEAT_09022017
Analytical run	Due to time constraint, a random selection of the analytical runs was reviewed for only study # 053-16 WHO
Trend of ISD variation	Documentation for assessment of trend of ISD variation was provided and reviewed.
Repeat analysis	Reasons for reanalysis of the samples and criteria to select the value to be reported were adequately defined in the applicable SOP.
Re-integrated chromatograms	There were no re-integrated chromatograms in this study. Chromatograms were randomly selected to be verified.
ISR	Documentation was not reviewed due to time constraint.
Consistency of the report with raw data / verification of audit trail	The raw data were randomly selected to be verified. Audit trail of Analyst® was reviewed to investigate any content where the data was changed / modified / edited / change of audit trail setting / mapping / disabled. No observation was made. Generic Administrator user name was only used in 2014, in setting up of the printer.

Issues identified in relation to this section were resolved satisfactory.

18. Sample collection, storage and handling of biological material

The receipt, storage, retrieval, re-storage and transfer of Biological samples, was described by the custodian as per applicable SOP.

Request from analyst for retrieval and re-storage of CCs, QCs and subject samples was appropriately recorded. Project number, the QC set IDs, subject number, name of requester, time of retrieval and re-storage, temperature, freezer ID and the number of subject samples restored were all recorded and verified.

Labels were prepared as per the applicable SOP.

A reconciliation list of the pooled plasma used for preparation of the stock solutions used in sample analysis for both studies were verified.

In the BA facility, receipt, storage and re-storage of samples for individual projects were recorded. The data for study # 053-16 WHO for all 4 periods was reviewed including the date of receipt and storage. Subject sample details including date of receipt, subject and period number, time points, transfer box temperature, missing samples, time and temperature of storage was recorded, with Freezer ID, rack ID, box ID. All records were quality controlled.

According to the service agreement with the sponsor, dated 11 August 2014 (valid for 5 years) the biological fluids of subjects should be retained for a period of 6 months in case of pivotal studies. The CRO was to notify the sponsor 30 days prior to the expiry of free storage period for a decision on the future handling of the samples. Documentation for discard of aliquot 1 and 2 was provided for study # 053-16 WHO.

19. Data processing and documentation

Two check points were put in place to ensure the integrity of data in data-entry process from the source data to the computerized systems. Data extracted from the paper source-data was directly recorded in the integrated report. The report was quality controlled by the Clinical QC-team with the finalized study report, authorized by the QA department.

All discrepancies between the source documentation and the report would be reverted to the respective team for rectification.

Logbooks were kept with controlled pagination, and required information.

20. Good laboratory practices

The Bioanalytical laboratory facility, consisted of the following sections:

- Deep freezer room
- Documentation room
- Solvent storage room
- Separate Equipment/Instrument room, such LC-MS/MS
- Sample weighing area

The facility had one -25°C, one -65 °C and eight -75 °C freezers. The automatic alarm system for one of the freezers was tested for its functionality. Security reacted immediately by notifying the department about the out of range temperature. Daily temperature monitoring and alarm checks were documented.

The temperature mapping report for one deep freezer was reviewed. Temperature distribution check at -80 °C and 24 hrs mapping was done (dated 5 Apr 2016). The result was satisfactory.

The hygienic conditions were adequate. Logbooks for usage of instruments, Preventive maintenance of instruments, receipt, storage and re-storage of biological samples and other relevant logbooks were available.

The weighing room was a separate area with a micro balance and one analytical balance. Balances and other measuring balances were periodically calibrated.

SOP for safety and working norms in the BA department was reviewed. Training documentation was reviewed.

Stock solution labelling was verified and found compliant.

List of equipment and instruments used in the studies was provided in the applicable SOP and was verified through the documentation review.

The instruments were labelled with calibration dates and validity information. Procedure for calibration of instruments was described in the SOP for Management of Instruments/ Equipment, effective 26 Jun 2017.

When visiting the laboratory facility, it was observed that there was water in the upper compartment of the refrigerator used for storage of working standards. A root cause investigation was performed involving the in-house engineer. Service report was made by Care Biosystems India Pvt. Ltd. It was reported that the water condensation in the chamber was caused due to blockage in the drain line. Hence, the refrigerator was defrosted to clean the drain line. It was confirmed that the refrigerator was in good working condition. The details were satisfactorily

recorded in the log book for preventive maintenance of instruments/equipment during the inspection.

Labelling of chemical was done properly.

CAPA provided on matters raised on Good Laboratory practices were acceptable.

Pharmacokinetic, statistical calculations and reporting section

21. Pharmacokinetic, statistical calculations

Interviews were conducted with biostatisticians responsible for biostatistics and programming activities such as writing the statistical methodology sections of protocols and statistical analysis plans of clinical studies.

Both biostatisticians reported directly to the Head of Operations.

Randomization

SAS software was used to create the randomization list. Site had two licenses for SAS. The SAS was not server based.

Randomization request was received from the pharmacist via email based on the protocol requirements. The randomization list was printed, signed and quality controlled by the designated personnel. The randomization was provided by the biostatistician, verification by QA and submitted to the PI.

Sample size was determined based on the molecule, past studies and literature available.

PK analysis was performed using the software system Phoenix. The results from Bioanalytical laboratory were stored on the server. After running Phoenix, the results were printed and transferred to the QA department for verification. Following verification, the statistician generated the results. Internal data verification was performed by QA department.

22. Study report

This part was not inspected.

Miscellaneous	
Samples taken	N/A
Assessment of the CRO master file	CRO Master File was provided.
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:

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Hyderabad-500037 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 GxP computerized 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.
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
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